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COMPREHENSIVE REVIEW

Human vulnerability and variability in the cold: Establishing individual risks for cold weather injuries

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ABSTRACT

Human tolerance to cold environments is extremely limited and responses between individuals is highly variable. Such physiological and morphological predispositions place them at high risk of developing cold weather injuries [CWI; including hypothermia and/or non-freezing (NFCI) and freezing cold injuries (FCI)]. The present manuscript highlights current knowledge on the vulnerability and variability of human cold responses and associated risks of developing CWI. This review 1) defines and categorizes cold stress and CWI, 2) presents cold defense mechanisms including biological adaptations, acute responses and acclimatization/acclimation and, 3) proposes mitigation strategies for CWI. This body of evidence clearly indicates that all humans are at risk of developing CWI without adequate knowledge and protective equipment. In addition, we show that while body mass plays a key role in mitigating risks of hypothermia between individuals and populations, NFCI and FCI depend mainly on changes in peripheral blood flow and associated decrease in skin temperature. Clearly, understanding the large interindividual variability in morphology, insulation, and metabolism is essential to reduce potential risks for CWI between and within populations.

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Introduction

After spending most of their evolutionary time in the African Savanna, humans acquired key morphological and physiological adaptations to efficiently dissipate heat in warm, dry climates (furless bodies, large density of eccrine glands, long appendages). However, as they migrated to northern, colder regions of the globe, such warm-climate adaptations did little to prevent excessive heat loss (H_{loss}) in colder temperatures. Consequently, this migration northward required major improvements in cold protection technologies (i.e. insulated shelters and clothing, mastery of fire) and cold-adapted behavioral strategies (i.e. collaborative work) that allowed populations to thrive in cold environments. Nevertheless, even today with substantial advancements in cold protection technologies and materials, human tolerance to the elements is still extremely limited and depends on severity of the conditions (time exposed, temperature, humidity, wind, and contact with cold surface), the insulative properties of their clothing, the level of physical activity and individual morphology. In this context, extended civilian expeditions, work assignments, or military deployments in cold climates require extensive planning to ensure proper resources are available to prevent the development of cold weather injuries (CWI) namely hypothermia as well as freezing (FCI) and non-freezing cold injuries (NFCI). However, regardless of whether adequate planning and preparation are achieved, living and working in extreme cold climates such as the Arctic remains extremely challenging and exposes individuals to harsh conditions that can lead to substantial CWI. Even armed forces

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accustomed in operating in cold climates face tremendous challenges in mobilizing ground forces to cold environments given the high interindividual diversity in morphological, physiological, and psychological preparedness. For example, in 2016 alone, a joint Arctic military exercise including the Canadian and U.S. armed forces reported frostbite rates at ~20% of the 215 reported medical injuries from the average −44°C wind chill [1]. Clearly, in this context, accurately identifying vulnerable individuals prior to cold weather exposure would prove a key asset to maximize operational readiness and reduce risks of CWI.

The present manuscript highlights current knowledge on the vulnerability and variability of human cold responses and associated risks of developing CWIs. Firstly, we define and categorize cold stress and CWI. Secondly, we present cold defense mechanisms including biological adaptations, acute responses, and acclimatization/acclimation [2,3]. Finally, we propose CWI mitigation strategies. The body of evidence presented here clearly indicates that all humans are highly at risk of developing CWI without adequate knowledge and protective equipment.

Defining cold stress

Cold stress and associated physiological consequences are highly variable and depend on the medium of exposure (water vs air), level (temperature and humidity gradients), and duration of exposure (min vs days). This stress could be considered as any environmental exposure that increases H_{loss} and elicit heat preservation mechanisms. From this point on, the body activates a number of cold-protective mechanisms aimed at attempting to maintain core temperature (T_{core}) at ~37°C. Any potential change in T_{core} occurs when the heat stored in the body (heat storage) either decreases if H_{loss} is greater than the rate of heat production (H_{prod}) or increases if H_{loss} becomes lower than H_{prod}. The H_{loss} to the environment: 1) is the main driving force to modulate quickly a metabolic increase in H_{prod} [4] and 2) is determined by physical heat exchange mechanisms (i.e. evaporation, radiation, conduction, and convection) [5]. These four pathways of heat exchange are influenced on one hand by environmental conditions, by the work rate and by the protective equipment available and, on the other, by the physiological, metabolic, and morphological characteristics distinct to each individual. Consequently, under the same environmental conditions wearing the same protective garments and performing the same tasks, variations in cold stress are determined primarily by interindividual differences in physiology, metabolism, and morphology. Contact cooling is also a substantial risk factor for peripheral cooling and CWI when touching or gripping cold objects (at work or during military duties). Physiologically, initial cold-defense mechanisms include the activation of peripheral vasoconstriction to prevent excessive H_{loss} to the environment and, to redistribute warm blood toward the core and vital organs. Figure 1 illustrates the wide range of biological, environmental, psychological, and sociological factors that influence afferent and efferent cold response in a given individual and between populations. While not include in Figure 1, it is important to indicate that some medical conditions may influence heat transfer and effector responses. This may in turn acerbate the risks of developing CWI [6].

In most daily environmental conditions, vasoconstriction is sufficient to maintain thermal balance, and in physiological terms the body remains in its thermoneutral zone [7]. However, when vasoconstriction alone is not enough and whole-body skin temperature (T_{skin}) decreases further, cold-effectors are also activated to increase metabolic H_{prod} in an attempt to prevent any decrease in T_{core} or hypothermia due to the increase in H_{loss}. If this increase in metabolic H_{prod} is sufficient to compensate fully for H_{loss}, the level of cold exposure is defined as *compensable*. Remaining in compensable cold conditions will be determined by metabolic capacity of each individual to sustain H_{prod} and/or by the individual incapacity to prevent a progressive increase in H_{loss} [8–10] (see Figure 2).

Presently, what limits H_{prod} in the cold is unclear at best but does not seem to be related to glycogen availability as for exercise and/or fatty acid availability [10–12]. Instead, individuals can generate heat using multiple pathways that compensate for one another when required [13]. This high flexibility in heat generating processes is

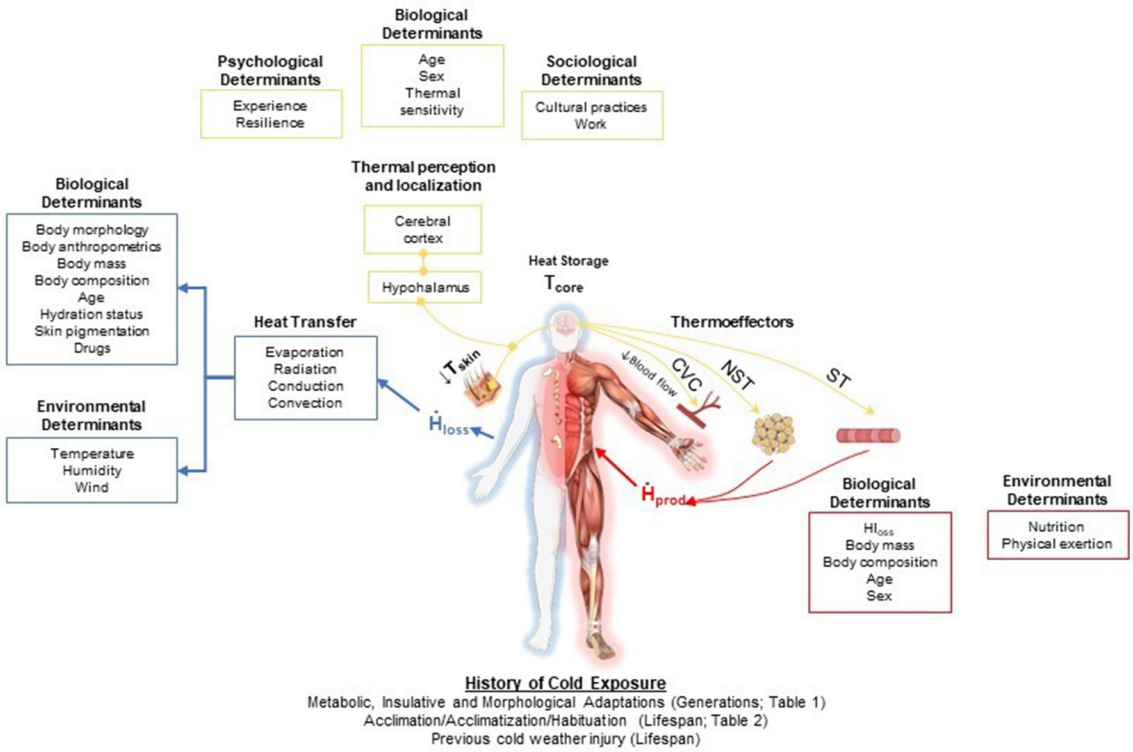

Figure 1. Conceptual illustration of thermoregulatory pathways involved in heat loss (Hloss, in blue) and heat production (Hprod, in red). Changes in temperature are detected by thermal receptor at the skin (Tskin) and in the preoptic area of the hypothalamus (Tcore). Neural integration of these afferent signals (in yellow) coordinates thermoeffector responses to reduce Hloss (peripheral vasoconstriction, CVC) and to increase Hprod (non-shivering thermogenesis, NST, and shivering thermogenesis, ST). Determinants of cold perception, Hprod and Hloss are also presented.

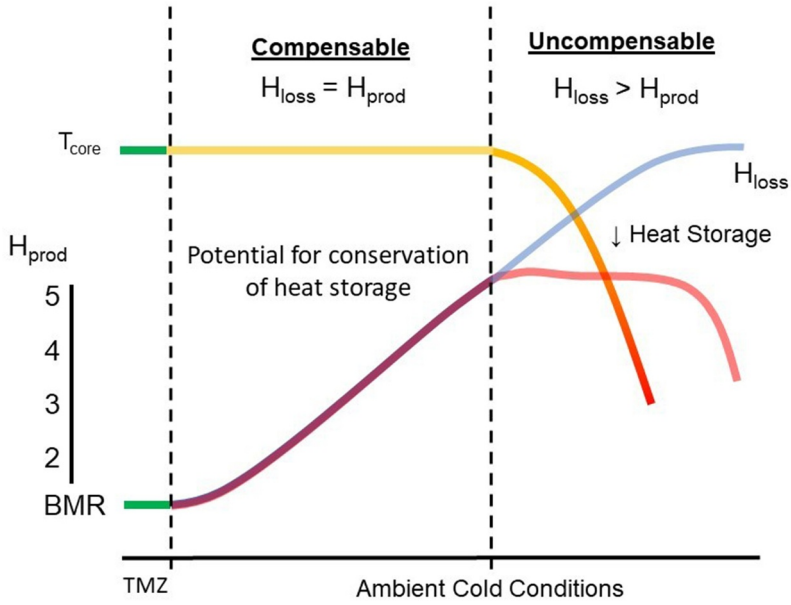

Figure 2. Conceptual representation conditions leading to risks of hypothermia. Potential of conservation for heat storage by increased tissue insulation (e. g. lower skin temperature and increased metabolic response).

likely due to the low metabolic rates reached even during maximal H_{prod} which are ~60% lower than what is found during exercise. However, this substantial metabolic flexibility comes at the cost of

a lower capacity to generate sufficient heat as cold intensifies making the compensable cold protection window fairly narrow in humans.

When H_{prod} becomes insufficient to counterbalance increases in H_{loss}, cold conditions are deemed as *non-compensable* and result in a progressive decrease in T_{core} at a rate determined by the extent of the difference between H_{loss} and H_{prod}. If left untreated, a T_{core} decrease below 35°C may affect cognitive and metabolic functions and may eventually prompt failure of multiple organs and systems [14]. As such, cold water immersion, below 20°C, poses the greatest non-compensable risk for hypothermia due to substantial increases in cooling rate. With a heat capacity more than 4 times higher than air, water increases H_{loss} by as much as 2 to 5 times compared to air; as it takes more heat to heat up the water boundary layer *vs.* the air boundary layer [15]. For cold water immersions ranging from 18°C to 7°C, body cooling rate has been shown to range on average between 0.5°C and 2.5°C/h, respectively [11,16,17]. In addition, survival times were reported to be limited to 1 to 9 h in light clothed individuals immersed in 5°C and 15°C, respectively [18–24]. If T_{core} continues to fall, H_{prod} progressively decreases and is suppressed when T_{core} reaches 31°C [25]. Under such advanced stages of hypothermia, T_{core} falls rapidly and rewarming is not possible without an external heat source [26]. Clearly, all humans are extremely vulnerable to cold and require a high level of cold protection compared to other mammals of similar size. In fact, recent work has shown that cold tolerance is extremely limited even when physiological and metabolic limits are far from being reached. In cold accustomed large men (~100 kg) exposed to 7.5°C in a thermal chamber for up to 24 h, Haman *et al.* showed that only half of the participants could withstand the full day of exposure even when provided a thick cotton overall, shoes, mitts, a wool hat, buddied-up, kept busy with tasks and fed survival rations every 3 h [27]. On average, T_{skin} only decreased by ~6°C and T_{core} plateaued below normal values (~0.8°C). This thermal stress resulted in an 50% increase in baseline H_{prod} in the first 6 h and was sustained until the end of the exposure. While these conditions are abnormal and difficult, they are still far from being beyond reaching physiological limits. Such a study exemplifies the difficulties for human cold survival even in large individuals (~86 to 128 kg and ~1.76 to 1.85 m tall) selected for their occupational cold exposure experience (i.e. Search and Rescue operators, offshore workers) to increase the likelihood of participants to complete the trial.

Defining NFCI and FCI

It is extremely important to note that NFCI and FCI, can occur both under compensable and

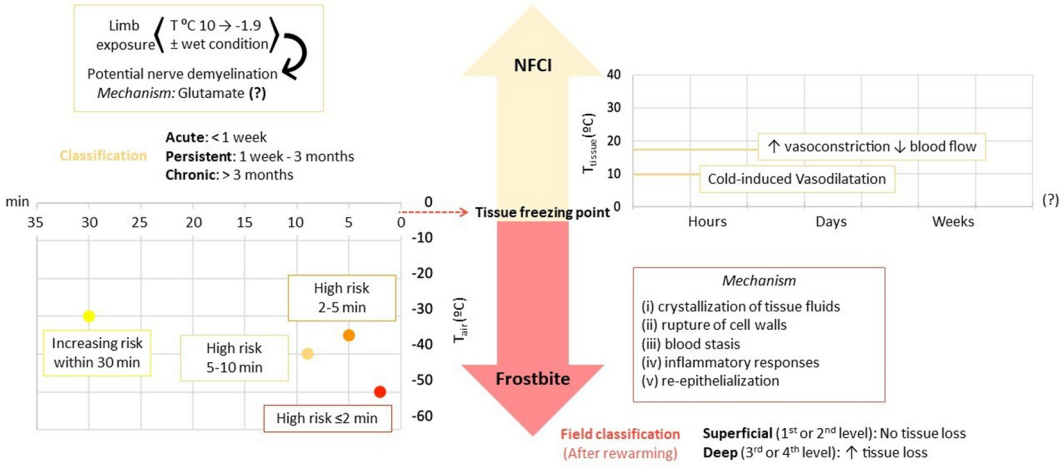

Figure 3. Conceptual representation conditions leading to risks of cold weather injuries including nonfreezing cold weather injuries (NFCI) and frostbite. The symbol (?) denotes a lack of scientific support. Wind speed of 5 km/h at 10 meters was considered. The website used for the wind chill chart was: https://www.candac.ca/.

uncompensable cold conditions or in other words, even when core temperature remains constant. The severity of these injuries is highly variable with the most vulnerable regions of the body being at the hands, feet, and face [28–31]. Of great concern also, a history of both NFCI and FCI can increase the risks for additional injury and compromise performance during subsequent cold exposure. Figure 3 provides a conceptual representation of conditions that may lead to the development of NFCI and FCI.

In general, NFCI are defined as chronic cold exposure responsible for causing persistent sensory symptoms, followed by a painful rewarming, and residual symptoms such as hypersensitivity to cold and sensory neuropathy after the rewarming process [32,33]. These injuries generally occur when extremities are exposed to cold temperatures for several hours or days. However, there is a lack of evidence related to the required duration of a sustained cold exposure in the development of NFCI symptoms. The slow decrease in temperature (i.e. tissue cooling from 25°C to 10°C) seems to be responsible for the pathophysiological changes caused by a NFCI [34]. Overall, NFCI have been linked mainly with the reduction of peripheral blood flow due to cold-induced vasoconstriction, affecting limb perfusion [34,35]. In addition, NFCI have also been observed in individuals feeling cold while remaining static [36], when individuals are dehydrated in the cold [37] or possibly when wearing restrictive footwear

In contrast to NFCI, FCI are caused by damage to the human body tissue when skin surface temperatures reach below the freezing point at approximately −0.55°C [38]. Notably, the wind chill index uses-approximately −4.8°C as temperature for 5% risk of developing frost bite at the cheek [39]. Clinically, the levels of frostbite can vary from superficial to deep [40]. Although all tissues may be affected, variations related to site, pressure, insulation, or susceptibility to wetting have an impact on the prevalence of FCI in some areas (i.e. face, fingers and hands, the tip of nose and ears) [41,42]. Recent results have shown that reductions in temperature with altitude also increases the likelihood of frostbite [43]. Hypoxia in the cold may result in hemoconcentration, small vessels blockage, hypercoagulability [44–46].

At the whole-body level, risks for NFCI and FCI are linked closely to the capacity of individuals to maintain T_{skin} by minimizing H_{loss} and increasing H_{prod}. By redistributing warm blood from the periphery to the core, H_{loss} is minimized at the cost of increasing the risks for developing both NFCI and FCI from reduced blood flow to the hands and feet. However, to counteract the increased vasoconstriction-related risks for NFCI and FCI, peripheral resistance increases from cold-induced hypertension to allow for enhanced circulatory function [47]. Rising blood pressure and a surge of circulating catecholamines, particularly noradrenalin, during cold exposure is indicative of a strong sympathetic nervous system response [48]. Although seemingly counterintuitive for the anticipated action of circulating noradrenalin, heart rate decreases in the cold through parasympathetic activation aimed at regulating metabolic demand while maintaining adequate cardiac output [49]. Together, the balance of sympathetic and parasympathetic influence on the cardiovascular system during cold exposure maximizes efficiency of blood supply supporting H_{prod} while reducing exposure of warm blood to cold skin. The severity of any potential NFCI and FCI during compensable and non-compensable cold depends on the duration of exposure and whether temperatures decrease below skin freezing temperatures (below ~ −0.55°C). While most of these injuries can be prevented by adequate cold protection, it remains that individual physiological, metabolic, and morphological characteristics that affect both H_{loss} and H_{prod} may inherently attenuate the risks for developing NFCI and FCI by better protecting T_{core} and T_{skin}. It was hypothesized that finger cold-induced vasodilation (CIVD) could be related to risks of CWI. However, no relation was found between CIVD and risks of CWI [50]. In addition, over the last 80 y, cold research has convincingly demonstrated that cold response is highly variable between humans which leads to higher vulnerability in specific population and specific individuals within a population.

Cold defense mechanisms

Interindividual variations in acute cold responses. Since humans have evolved primarily in warm

regions of the Earth near the equator, expansion to cold weather areas of the world would have been impossible without learning how to work as a collective (e.g. team work, shared tasks, and community) and without crucial advancements in technology (e.g. insulated shelters, warm clothing, and the mastery of fire) [51]. However, under conditions where these cold countermeasures are unavailable or inappropriate, individuals must rely on a number of physiological and metabolic responses as well as their *morphological adaptations* in an attempt to reduce H_{loss} (*insulative adaptations*) and increase H_{prod} (*metabolic adaptations*) [3]. Both insulative and metabolic adaptations to cold are highly diverse between populations and within individuals of a given population partly due to large differences in morphology and body composition. They depend on genetic traits acquired through natural selection over thousands of generations prior to the development of advanced cold protection technologies. However, even within a given genetic makeup, individuals are still able to modify and possibly improve their tolerance to cold through *acclimation* (achieved in a laboratory setting) or *acclimatization* (achieved in a natural setting). When taken in combination, the numerous potential variants in cold adaptation, acclimation, and acclimatization in a given population and between populations provide support for the wide array in cold responses found in humans [13,52,53]. Unfortunately, methods for assessing cold responses are quite diverse and consequently, comparisons between various cold studies are extremely difficult. In this context, much research is still needed to fully understand the factors that determine cold responses within and between populations. With this said, it remains that physical principles of heat transfer are the sole driving force for H_{loss} in the cold based on individual morphological and insulative adaptations.

Individual differences in body morphology are the main determinant for cooling rates, heat storage, and ultimately survival time. In biophysical terms, for a specific body shape and composition and work rate, H_{loss} will be determined from rates of conduction, convection, radiation, evaporation [54]. In addition, body morphology and composition also play a large role in the determination of H_{prod} which, if optimal, has the potential to reduce the risk of NFCI and FCI. According to popular belief, body fat percentage has often been deemed the primary determinant for cold protection and cold tolerance. Clearly, subcutaneous adipose tissue is the most insulative tissue in the human body, however unlike the denser and substantially more insulative layer of blubber seen in Arctic marine mammals, there is little evidence that white adipose tissue conserves heat adequately to be considered a primary factor in reducing H_{loss} in cold ambient conditions [55]. Instead, body fat provides a high-volume with minimal addition to total body surface area which affect body morphology and appears to effectively reduce heat transfer [56]. When examining differences between men and women in cold water immersions, there are profound variations in H_{prod} and H_{loss} despite being controlled for body fatness [57]. It was observed that, among other unknown contributing factors, morphological differences in fat distribution between males and females affecting surface-to-volume ratios contributed more to total H_{loss}, and therefore H_{prod} requirements, than the absolute amount or relative percentage of body fatness [56,57]. Using these sex comparisons, it can be inferred that body morphologies that consist of smaller surface-to-volume ratios are considered ideal to attenuate heat dissipation during cold exposure. In addition, ovarian hormones estradiol and progesterone influence physiological thermoregulation in women but research findings indicate that these hormones can modulate the cutaneous vasoconstrictor response, and alter fuel selection and NST. However, when anthropometrics differences are considered, there seems to be a minimal thermoregulatory advantage in terms of overall ability to tolerate cold [58]. It is generally accepted that individuals with large mass or volume, low surface body area, and high body fat percentage preserved the most heat in cold water, reducing the need for heat production mechanisms [56]. As a result, the most vulnerable populations were identified as small individuals with high surface-area-to-volume ratios [56,57]. These determinations were established during cold water immersion but do not necessarily translate directly in cold air. By definition, H_{prod} mechanisms during non-compensable cold exposure are working at

maximal rates, but unable to compensate for the substantial H_{loss} to the environment thereby resulting in a decrease in T_{core}. In such situations, maximizing factors that promote heat conservation through the reduction of H_{loss}, low surface area, translate to increased time to hypothermia [56]. In contrast, compensable cold exposures require submaximal H_{prod} intensities to counter H_{loss} [59], indicating that the factors contributing to H_{prod} play a stronger role in defining vulnerable populations. Therefore, cold tolerance in humans are likely associated with an optimal body morphology and body composition during compensable cold exposure. Differences in body composition between individuals in previous literature have been mainly examined under non-compensable conditions using cold water immersion [51,56,60,61]. However, most human cold weather exposure occurs in cold air and is generally compensable; provided clothing and equipment is balanced to the activity level.

Finally, it is important to note that not only does muscle mass modulate thermogenenic capacity and overall H_{prod} but it also provides important insulative properties [62,63]. While individual differences in body morphology and body composition are well known to influence cooling rates and survival time, it remains that research consistently shows that cold water immersion (especially <18°C) inevitably and rapidly leads to hypothermia. In contrast, during cold air exposure, cooling rates are greatly reduced and thus, hypothermia should only occur accidentally, following unforeseen events or following a series of inadequate decisions. In the long-term, cold air exposure can be tolerated for several hours to several days depending on the equipment available and the severity of the conditions. However, conditions that are initially compensable can become non-compensable as H_{prod} mechanisms fatigue [8,9]. Under such conditions, preventing hypothermia will require the individual to make adequate decisions to prevent further H_{loss} and/or increase H_{prod} in an attempt to reduce the risk of hypothermia. In this context, it is crucial for individuals to monitor regularly their level of cold stress and use proper countermeasures or behaviors to maintain cold responses within manageable range and prevent hypothermia.

Cold adaptation variants. Humankind is comprised of numerous genetic variations that determine an individual's phenotype including physiological responsiveness to environmental temperature changes (i.e. vasoconstriction, vasodilation), skin characteristics (i.e. sweat gland density, skin thickness, coloration) and anthropometrics (i.e. body shape, height, weight, body composition, segmental length). Within a given population, specific thermoregulatory phenotypes evolved according to environmental pressures and required to regulate body temperature in a specific region of the Earth. As an extreme example of cold adaptations, circumpolar residents have adapted and thrived for thousands of years in the coldest regions of the world [64]. They also have acquired key knowledge and survival skills to deal with extreme cold conditions [65]. In the 1950s and 1960s, cold adaptations of humans living in various regions of the world attracted the attention of a number of scientists [66]. In general, cold-adapted populations such as the Inuit/Eskimos [65–69], northern First Nations/American Indians [66,70–72] and Saami [66,68] respond physiologically and metabolically in a similar way to acute cold as populations living closer to the equator. However, some key differences have been reported which may improve cold tolerance and survival in the cold [66]. Generally, Arctic populations have higher basal metabolic rate, higher hand and feet temperatures, and increased blood flow to the forearms and hands. Higher than predicted weight-corrected basal metabolic rates (~20%) were also found in the Yakut an indigenous population living in the cold regions of the Sakha Republic of Russia [73,74].

It remains that comparing results between these cold studies and between races (i.e. Arctic populations *vs* Caucasians) is extremely difficult because of methodological and analysis biases as well as important morphological and body composition differences between Arctic dwellers and Caucasians [65]. For example, some proposed physiological and metabolic differences between Arctic dwellers and Caucasians are reduced or disappear when corrections are made for differences in morphology and body composition [65,75]. Also, when the resting metabolic rate of Inuit living in more southern areas is measured, results are similar to values found in Caucasians

living in the same area. This supports strongly that cold acclimatization plays a greater role in modulating cold responses independently of racial differences. Instead, cold tolerance and survival success in these various groups were achieved through a variety of biological mechanisms and likely compensated largely by climate-adapted behaviors. Again, these results highly support the premise that body morphology (i.e. anthropometrics), body mass, and body composition (i.e. muscle and fat mass) are likely the most important determinants of individual cold tolerance between and within populations.

In humans as in other animals, it is important to note that total body mass and body surface area are the most important determinants of neutral air temperature and rate of heat loss. In humans, Verbraecken et al. (2006) reported that in 1868 patients total body surface area varies 2.8-fold from 1.28 to 3.56 m^2 whereas total body weight varies 4.5-fold from 44 to 196 kg. Figure 4 illustrates differences in neutral air temperature nude individuals included within the range in total body weight reported above and exposed to cold air (see Appendix A for calculations) [76]. Average body mass of different regions of the world have been added to this figure to indicate the average risk of a given population during cold exposure. Results indicate that body mass is highly related to the risk of hypothermia between individuals and between world populations. Interestingly, Arctic populations have a relatively low body weight on average indicating that behavioral cold adaptations were key to ensure survival. Clearly, in all human populations, behavioral thermoregulation including wearing protective clothing, building shelter, and setting up a heat source is essential to prevent risks of hypothermia as well as NFCI and FCI.

Over the last decades, attempts were made to document the prevalence of CWI in individuals of various races living or required to operate in cold

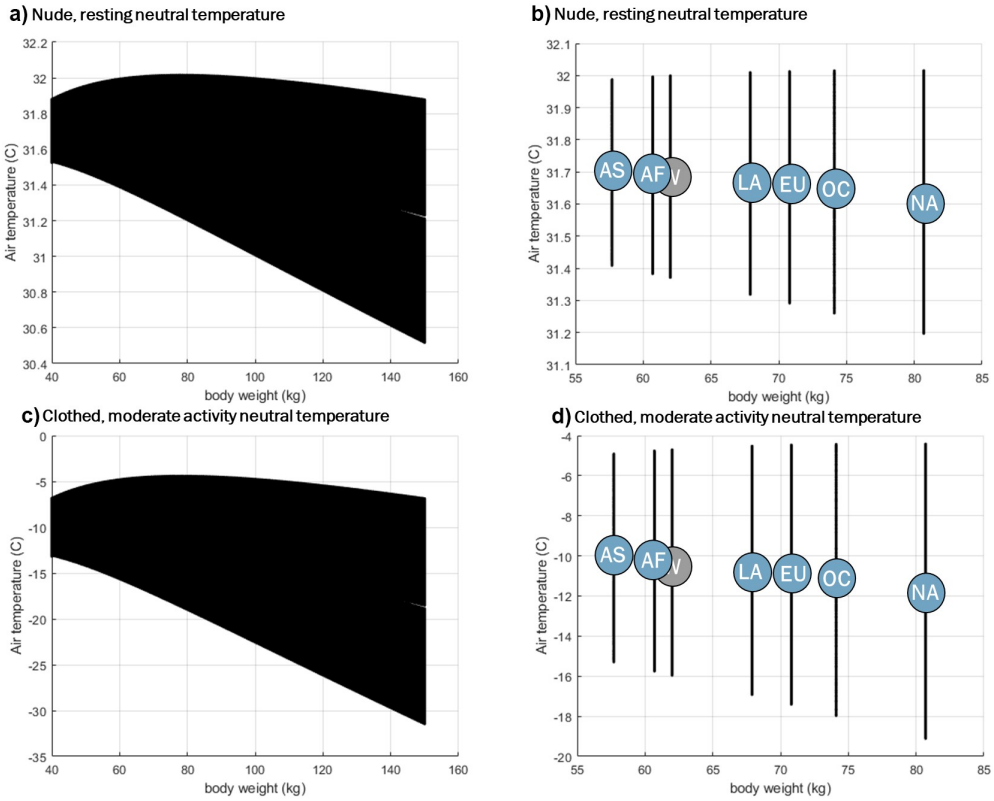

Figure 4. Panel A) nude resting neutral temperature for full range of population spanning small body surface area (1. 4 m^2) and very large body surface area (3 m^2). Panel B) nude resting neutral temperature for specific population average body weights: AS: Asia, AF: Africa, W: World, LA: Latin America, EU: Europe, OC: Oceania, NA: North America.. Panel C: Clothed (2. 5clo), moderate activity (4 MET) neutral temperature for full range of population spanning small body surface area (1. 4 m2) and very large body surface area (3 m2).; Panel D) Clothed (2. 5clo) moderate activity (4 MET) neutral temperature for specific population average body weights. For all panels resting metabolic rate is calculated according to Roza & Shizgal for 35 year old persons; male and female metabolic rates are combined.

weather conditions. DeGroot et al. (2003) concluded in a U.S. military report spanning 10 y, African American males and females had 4-fold and 2.2-fold the incidence of CWI compared to Caucasian American, respectively [77]. Candler et al. (1997) also found African Americans had higher rates of CWI in Alaska [78]. In contrast, several other military reports found CWI to be higher in Caucasian Americans than African Americans [79,80]. The higher incidence of CWI males compared to females also contradicts the expected higher risk for CWI in women [77]. Lastly, Tek & Mackey (1993) found no effect of race on risk for CWI [81]. When comparing physiological and thermoregulatory responses to cold exposure, African American men showed to have lower T_{skin}, T_{core}, and H_{prod} in compensable conditions [82]. Another study found African descendant males had greater vasoconstriction responses than Asian descendant or Caucasian males, placing African descendants at the greatest risk for CWI [83]. It should be noted that there were no indications of regions of African or Asian descent in any of the reported studies. Considering there is greater genetic variation between race subgroups of Africa than any other race [84], this may contribute to the mixed results found throughout the literature on CWI as it pertains to race. Although some studies have indicated that the incidence of NFCI differs between races [36,77], this evidence is contrary to that reported in another study [81] and has several limitations (e.g. sample size, control population). Considering these factors, the role played by race in the prevention of NFCI remains unclear. While this work provides some insights on racial cold vulnerability, it remains epidemiological and highly anecdotal in nature and additional work is required to clearly establish racial differences in cold responses.

Acute cold response variants. Some models on the origins of cold thermoregulation posits that deep body temperature is perpetually controlled *via* a negative feedback loop, whereby T_{core} serves as both the control variable and the predominant feedback signal and T_{skin} provides a rapidly-responding auxiliary feedback signal [85,86]. Others suggest that thermoregulatory responses are under feedforward control driven by changes in T_{skin}, thereby activating cold-defense effectors before any detectable change in T_{core} can occur [87,88]. Regardless of the preferred model used to illustrate this thermoregulatory control, it has become evident that each cold-defense effector response (i.e. vasoconstriction, brown adipose tissue, and shivering) is independently controlled, with each effector being driven by different combinations of T_{core} and T_{skin} inputs.

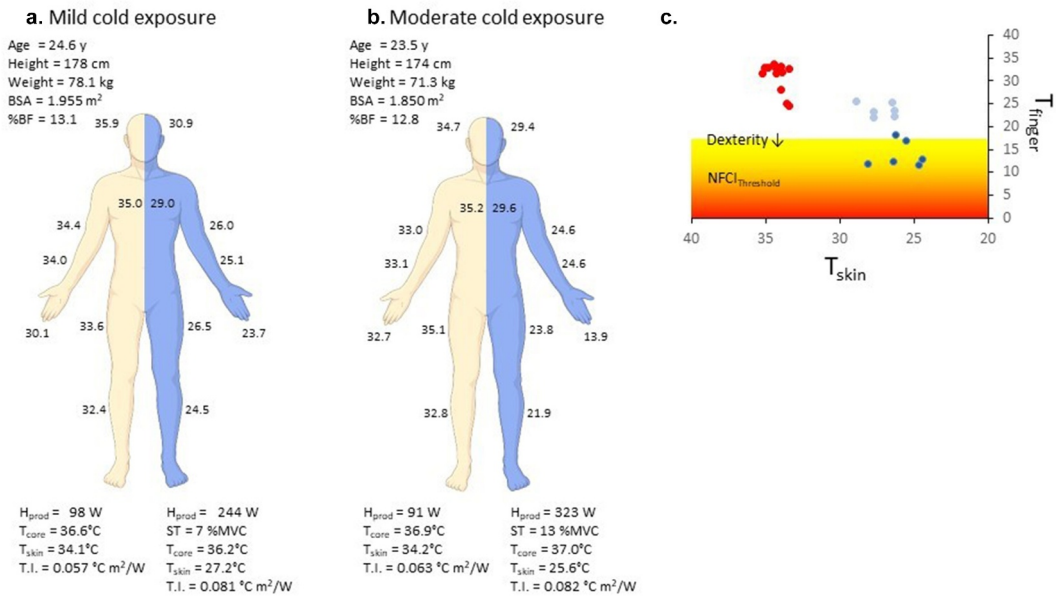

Figure 5. Average changes in regional skin temperature at baseline and between 75–90 min of A. mild cold exposure and B. moderate cold exposure. – including metabolic response. Data modified from Haman et al (2002) and Haman et al (2004, 2005).

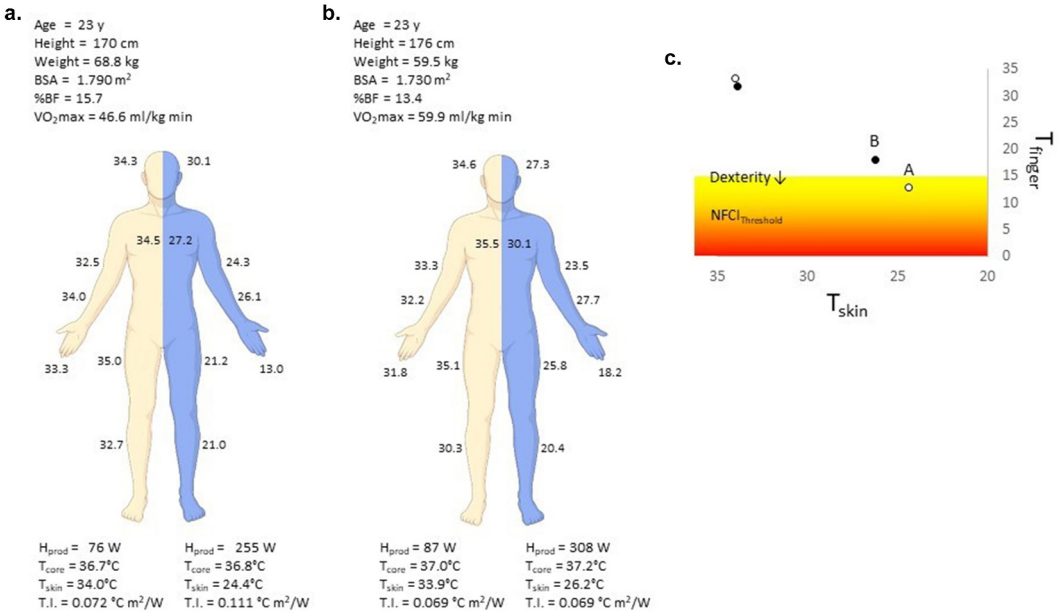

Figure 6. Average changes in regional skin temperature at baseline and between 75–90 min in two non-cold acclimatized men of similar morphology. A) insulative responder with lower extremity skin temperature and B – metabolic responder with higher extremity skin temperature. Data modified from Haman et al (2002) and Haman et al (2004, 2005).

In essence, all humans on Earth respond acutely to cold using the same insulative and metabolic processes which contribute to a various degree based on individual adaptations (morphological, insulative, and metabolic) and/or acclimatization (insulative and metabolic). To counterbalance increases in H_{loss}, humans rely on the activation of insulative responses (i.e. peripheral vasoconstriction) to reduce H_{loss} and the activation of pathways to increase $H_{prod.}$ Figure 5 shows an example changes in regional skin temperature and metabolic response during mild and moderate cold exposure, and Figure 6 shows an example of changes in regional skin temperature for an insulatory responder (lower skin temperature, lower metabolic response) *vs.* a metabolic responder (higher skin temperature, higher metabolic response). Note that the insulative responder is at greater risk for dexterity issues or CWI than the metabolic responder.

Cold exposure activates temperature-sensitive receptors (thermoTRP) located in the dermis and epidermis [89]. The information received is integrated by various parts of the brain including the thalamus, cerebral cortex, and preoptic area of the hypothalamus which stimulates cold-defense mechanisms. As such, changes in T_{skin} come as the first line of defense in the cold in an attempt to prevent a decrease in T_{core}. Even 2°C decrease in whole-body T_{skin} is sufficient to initiate peripheral cutaneous vasoconstriction (CVC) as well increase in H_{prod} in young adult males [90]. Each cold defense response [i.e. vasomotor tone, brown adipose tissue (BAT) thermogenesis, and shivering thermogenesis (ST)] appears to be independently controlled, with each mechanism driven by different combinations of peripheral and central thermosensory input, reflected by T_{skin} and T_{core}, respectively. It is possible that both the apparent differences in thresholds and the interaction between these H_{prod} responses can be explained by their slight differences in activation mechanisms and neural circuits, rather than temperature thresholds [91–94]. Despite progress made in characterizing the central neural network that leads to the recruitment of ST, the spinal circuitry itself, and therefore variations of interindividual responses, is relatively unknown [88,95]. The prevailing view of the neural pathway ST-activation speculates that the essential step to initiate this response through skin cooling resides centrally [88]. Thus, identifying variations of neural input in ST intensity and patterns may provide insight to individual risks of CWI.

The distribution of cold- *vs*. warm-sensitive thermoreceptors or neurons may also shed some light on interindividual variability in the response to a cold stimulus. For example, warm-sensitive receptors are present in at least 60% of spinal nerves innervating the gastrointestinal tract, small intestine, and bladder, compared to 30% or less in spinal nerves innervating the skin or skeletal muscles [96]. The feedback provided from internal thermoreceptors such as these may explain why, for the same T_{core}, whole-body thermogenesis is slightly lower in overweight or obese compared to lean individuals exposed to the same mild cold stimulus [97–101]. This is further supported by the lower cooling temperature required to elicit a relatively similar thermogenic response between lean and obese men [102,103]. Together, these studies suggest that centrally located thermoreceptors or temperature-sensitive neurons may be modulating heat production, relative to lean individuals, to set the basal thermoregulatory tone for individuals who are overweight or obese.

In addition to the neural control of thermal effectors (vasoconstriction, BAT, ST), skin blood flow is also governed by local regulation [104,105]. Independent of neural control mechanisms, skin blood flow closely follows Arrhenius law (or Q10-effect) such that for each 10°C change in local skin temperature there is a 50% change in local skin blood flow [106]. Therefore, skin vasoconstriction may be maintained even after neural vasoconstrictor tone returns to basal levels [107].

In humans, H_{prod} is increased primarily through asynchronous muscle contractions or ST and to a lesser extent, by non-shivering thermogenesis (NST) (i.e. BAT and futile cycles). Both ST and NST are initiated when T_{skin} decreases below normal values (~33°C). Maximal H_{prod} in the cold seems relatively conserved between individuals reaching ~5 times basal values [108]; a value 4–5 times lower than maximal H_{prod} during exercise. The exact reason for this upper limit during cold exposure remains unknown. Most importantly, in the context of this review, maximal H_{prod} capacity is highly variable between individuals and dependents mainly on differences in the total mass of heat generating tissues; primarily skeletal muscle mass and to a much lesser extent BAT mass. Of all potential heat generating tissues, skeletal muscle is by far the greatest contributor of heat. In an average lean individual weighing 72 kg, skeletal muscles represent ~40% of total body mass or ~30 kg [109,110].

Even though ST in skeletal muscles provides most of the heat, it also presents itself with an important downfall. Both ST and voluntary movement use the same efferent neural pathways and consequently, ST interferes with voluntary movements resulting in a reduction in motor control and performance [111]. Identifying strategies to reduce ST and increase NST, while maintaining overall H_{prod} would be crucial to increase cold tolerance and maintain physical performance. Despite a general pattern emerging, muscle recruitment patterns are highly variable, even among morphologically similar men and women [13,52,112–115]. While some individuals rely almost entirely on upper body muscles, others depend more on upper leg muscles [12,114]. Also, within muscles, some individuals rely more on burst shivering (short, high intensity, type II muscle fibers) and others on continuous shivering (long, low intensity, type I muscle fibers) [116]. Exact reasons for these large interindividual variations in ST, even amongst morphologically similar individuals, are unknown but may be related partly to variations in fiber composition [117]. Human skeletal muscles are made of the different types of fibers and the presence of these various fiber types varies greatly between skeletal muscles and individuals [118]. In a given individual, ST and burst rate are extremely consistent even when carbohydrate (CHO) availability is modified in men [12] or when measurements are made at the luteal and follicular phases of the menstrual cycle in women [113]. The rhythmic nature, ST intensity, and ST pattern have all been suggested to be determined locally in the spinal cord, potentially through a proprioceptive sensory feedback loop [119–121]. At the whole body level, variations in relative contributions of high intensity bursts to total ST and the recruitment of various muscle groups do not seem to affect H_{prod} during mild to moderate intensity cold exposure [114,116]. However, they have important consequences on metabolic fuel selection [12] as well as possibly on shivering endurance, cognitive capacity, and survival in the cold [52]. In this context, any increases in the contribution of NST to total

H_{prod} would reduce this effect and this can be achieved through cold acclimation/acclimatization.

Over the last decades, many attempts have been made to identify differences in cold response between men and women. However, there is currently no consensus in sex-associated differences in the prevention of CWI [36,41,122,123]. At the whole body level, thermoregulatory responses in women and men differ little when morphological and body composition differences are considered [124–126]. Consequently, most of the difference between women and men would be related to average differences in body surface-area-to-volume ratio and lean-to-fat tissue ratio between sexes. While women tend to have a higher body surface area and higher percent body fat than men, it remains that cold responses would differ little between women and men where these parameters are similar. Metabolically, women respond similarly whether in follicular or luteal phase but oxidize more lipids then men [113]. With this said, some differences in peripheral cold responses have been noted between sexes [127] which links to a higher presence of Raynaud's phenomenon in women then in men [128]. During local hand cooling and recovery, women also showed a lower finger temperature and blood flow then men [127]. Similar findings were confirmed by a number of other researchers [121,129,130]. Interestingly, no such difference in skin temperature was found between Inuit women and men [131]. Whether these differences in peripheral blood perfusion and temperature in the cold between women and men may be linked to increased risk of CWI remains to be established.

While sex differences in cold response seem unclear at best, research suggests that individuals over the age of 60 y are less cold tolerant partly because of reduced peripheral vasoconstriction and heat conservation when compared to younger people [125]. In addition, it is unclear whether sarcopenia could result in a reduction in heat production with the decrease in muscle mass. Exact reasons for these differences remain unclear but it has been documented that older adults are at higher risk for mortality and morbidity in the cold [20,132–134]. However, it is important to note that most cold-related deaths in older adults, are attributed to cold-induced hypertension, and therefore increased cardiac strain, leading to myocardial infarction and stroke [20,132]. Even during mild cold exposure (20°C, seminude) young adults showed faster recovery of systolic blood pressure which coincided with increased H_{prod} in young adults, whereas their older counterparts even showed a decrease in H_{prod} [90]. Recently, it has been established that reduced neural input in older adults is attributed to impairments in peripheral vasculature altering their ability to vasoconstrict [135]. Consequently, T_{skin} is higher during the initial few hours of cold exposure allowing greater heat exchange. Wagner and Horvath (1985) found an increased T_{skin} in older adults during the first 2 hours of cold exposure translated to a decline in T_{core} (−0.3°C) in 10°C ambient air, a temperature considered to be compensable in younger adults [136]. Following 2 to 3 h of cold exposure, however, the initial blunting of vasoconstriction is negligible and T_{skin} of older adults are comparable to younger adults [137–139]. Furthermore, age-related blunted vasoconstriction is predominantly observed on ventral forearm skin sites but not necessarily at the hands [140]. Despite comparable T_{skin} in long-term cold exposure, the reduced cold tolerance from the inability to adequately vasoconstrict or respond metabolically in otherwise compensable environments places older adults at higher risk of CWI.

It is important to note that cold response may be influenced by a number of factors including fatigue, nutrition, or negative energy balance and hydration. In response to hypothermic casualties during a 9 week training of U.S. Army Rangers, Young et al. (1998) determined that chronic sleep, exertional fatigue, and negative energy balance significantly affects thermal tolerance and susceptibility to hypothermia [141]. Another U.S. military operations study found declines in thermoregulation maintenance under conditions of sleep deprivation, negative energy balance, and exertional fatigue during short duration (3.5 days) cold exposure [142]. When isolating sleep deprivation and cold exposure, however, some studies have found no thermoregulatory impacts during acute sleep deprivation (53 h) conditions [143,144]. In addition to isolating sleep deprivation during cold exposure, Oliver *et al.* (2015) repeated the same stressors found in Young *et al.* (1998), but with

shorter duration of the stressors [141,144]. It can be surmised that the effect on thermoregulatory systems found in these studies are dependent on duration of the stressors.

In a study examining a 9 week military training, chronic negative energy balance reduced mental capacity and ability to thermoregulate [141]. When applied in short bouts of negative energy balance of a few days, the risks of hypothermia are considered minimal [144]. Positive energy balance of 150% overfeeding has no metabolic or BAT effect either in acute cold exposure or during cold acclimation [145,146]. Several studies show that shivering in prolonged immersion of 18°C water produce 80% of total heat from CHO oxidation when glycogen reserves are artificially elevated, and the same percentage, but from lipid oxidation, when glycogen reserves are depleted [10,147,148]. However, such drastic changes in fuel selection do not affect cold tolerance because H_{prod} appears to be independent of glycogen availability (see Figure 7).

Conversely to CHO availability, dehydration seems to modify cold response, particularly in cold water immersions, which results in a strong diuretic response. A combination of redistribution of the blood to the core and cold-induced hypertension stimulate baroreceptors in the heart, promoting increased urine output through the Henry-Gauer reflex [149]. In cold water immersions, hydrostatic pressures magnify this reflex effect which can account for 1–3% body mass lost through urine output [150,151]. While in a hypohydrated state, submaximal exercise in cold environments required greater oxygen uptake, reducing mechanical efficiency and time to exhaustion [152]. The effect of reduced exercise performance in the cold while hypohydrated, however, is reversed once euhydration is restored [152]. Hypohydration in cold ambient air conditions can also affect thermoregulation. O'Brien et al. (1998) examined men during 2-hour exposures at 7°C cold ambient air exposure while euhydrated, isotonic hypohydrated using ingested furosemide, and hypertonic hypohydrated of 4% decrease in body mass from induced sweating [153]. Although heat balance remained intact during all conditions, preserving the compensable element of the environment, vasoconstrictive tone under both hypohydrated hydration statuses were affected. The combination of hypohydration and hypovolemia in the hypertonic hypohydrated condition had the greatest effect on impairing skin temperature regulation during cold exposure. These impairments in vasoconstrictive tone and skin temperature while in a hypohydrated state, however, plateaued after 90 min of exposure. In response to mitigate the hypohydrated effect

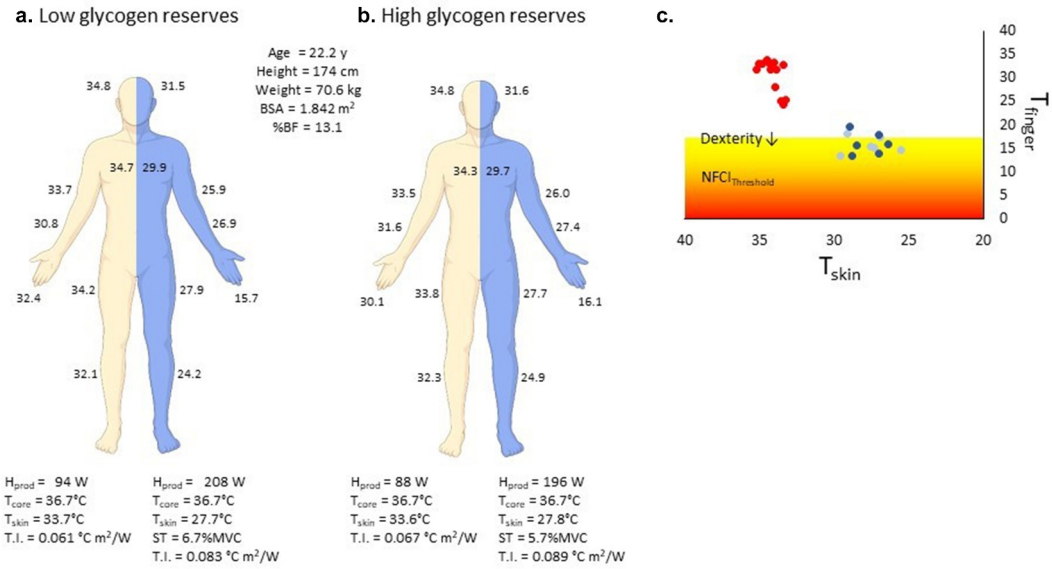

Figure 7. Average changes in regional skin temperature at baseline and between 105–120 min of mild cold exposure in non-cold acclimatized men with A. low glycogen reserves and, B. high glycogen reserves during moderate cold exposure. Data modified from Haman et al (2004).

during cold exposure, a follow-up study by O'Brien (2005) examined cold exposure with a hyperhydrated status and found little impact on the thermoregulatory system [154]. Additionally, in these cold conditions, hyperhydration from glycerol ingestion lowered urine output more than hyperhydration through only water. The benefits of minimizing fluid loss with glycerol hyperhydration may be amplified in long duration cold exposure. Therefore, hyperhydration using glycerol may be the best strategy to reduce thermoregulatory stress in cold exposure with greatest potential to minimize the effect of hydration on exercise in the cold.

Although the effect of hydration status on frostbite injury is unknown, appropriate hydration and protection against hypovolemia may be important for frostbite recovery [40]. It is important to highlight that oral fluids should be avoided in cases where the patient is not alert, vomiting, or not capable of swallowing. In these cases, intravenous (IV) normal saline should be prescribed for the maintenance of blood volume. Ideally, this fluid should be warmed (37–42°C) before infusion. The infusion must occur rapidly and in small boluses (e.g. 250 mL) given the risk of fluid cooling or freezing [40].

Finally, it was generally assumed that the contribution of NST to total heat production in humans was negligible due to the lack of BAT and to the lack of NST capacity in skeletal muscle. However, recent research seems to suggest otherwise. Over the last decade, it was shown that not only is BAT present in adult humans but it is also metabolically active [101,155,156]. The greatest variability found in BAT between individuals is dependent on body size. In healthy adult humans, BAT is present in small amounts compared to what is observed in rodents; only ~30-350 g [157]. In overweight and obese individuals, however, several studies have found that these individuals have reduced, and in some cases negligible, quantities of BAT [158,159]. It is difficult to ascertain in the current literature the magnitude of contribution of BAT to cold thermogenesis. Some compensable cold exposure studies have indicated a positive correlation between H_{prod} and BAT [160,161], while other studies have indicated skeletal muscle activity dictates H_{prod} [97,162]. Large variations in the amount of BAT present between individuals may account for many of the inconsistencies found in the literature between H_{prod} and skeletal muscle or BAT.

Skeletal muscle is the most abundant tissue in the human body. In addition to contribution of H_{prod} through ST, skeletal muscle houses calcium channel pumps and mitochondria used in NST. Among the skeletal muscle framework, different types of fibers allow for a range of endurance (type I, oxidative) to power (Type IIa and IIb, glycolytic) outputs. Regardless of fiber type, all muscle fibers contain the sarcoplasmic reticulum (SR) where calcium flows to incite muscular contraction. Different isoforms of the SR found in either fast-twitch and slow-twitch fibers have shown to have varying contributions to NST [163]. Fast-twitch fibers are enriched with the SR isoform, SERCA 1, which has the highest H_{prod} [164]. Meanwhile, slow-twitch fibers contain the SERCA 1 isoform mixed with a secondary SR isoform SERCA 2 which produces heat at slower rates. In essence, a small change in skeletal muscle mass and composition of fiber typing equate to large variations in the NST contribution to whole body H_{prod}.

Cold acclimation/acclimatization variants. Repeated cold exposures allow the body to acclimate or acclimatize in various ways depending on the duration and intensity of the cold exposure. In 1961, Davis showed that 31 days of cold air exposure (~12°C, 8 h/day) resulted in an ~80% reduction in ST and ~15% reduction in whole-body H_{prod} in healthy men previously acclimatized to summer conditions of ~20-30°C [165]. More than five decades later, Blondin *et al.* (2017) showed that 4 weeks of daily compensable cold exposure in unacclimated men using a liquid conditioned suit (2 h/day for 5 weeks) was sufficient to elicit a ~ 20% decrease in ST response for the same given H_{prod} [117]. Similarly, using cold water immersion acclimation at 14°C for 7 consecutive days, Gordon et al. (2019) demonstrated a 40% reduction of ST for the same given H_{prod} [166]. Among these changes in ST, H_{loss} mechanisms also vary greatly after acclimation. Several studies have established a decrease in T_{skin} post-cold water immersion acclimation, indicating greater preservation of T_{core} [167–169]. Following cold air acclimation, however, T_{skin} has been found to increase

Table 1. Parameters related to insulative, metabolic, and core temperature responses during acute cold response in non-cold adapted/acclimatized/acclimated individuals.

Experiment summary	Insulative responses	Metabolic responses	Cold tolerance
		RACIAL DIFFERENCES	
		Experimental	
Rennie & Adams, 1957[196]	Insulative: N/A	Hprod: Increased acutely; Less in African Americans than Caucasians	Cold tolerance: N/A
Race: African American, Caucasian	Tskin: Decreased acutely in both groups; No difference between Caucasian and African Americans in the first half of cold exposure but lower in African Americans in the second half; cyclic rewarming observed in Caucasians	Shivering: Proportional to change in heat production	Tcore: Decreases acutely; No difference between groups
Type: Air	Blood flow: Cold-induced vasodilation is more common in Caucasians than African Americans; No difference in finger cooling		Thermal comfort and sensation: N/A
Temperature: −12°C Duration: 90 min Clothing: Standard, bare hands			Sleep: N/A
Adams & Covino, 1958[197]	Insulative: N/A	Hprod: Higher in Inuit during control period and throughout test; Increased acutely in all groups, with increase starting later in African American group (55 min for Caucasian and Inuit in comparison to 85 min in African American)	Cold tolerance: Greater in Inuit
Race: Caucasian, African American, Inuit	Tskin: No difference between Caucasian and African Americans; Higher in Inuit	Shivering: Later onset and lower in African Americans	Tcore: Unchanged acutely; Higher in Inuit but no difference between African Americans and Caucasians
Type: Air Temperature: 17°C Duration: 120 min Clothing: Light	Blood flow: N/A		Thermal comfort and sensation: N/A Sleep: N/A
Baker, 1959[198]	Insulative: Less heat loss in Caucasians for same amount of adipose tissue; Greater surface area for African Americans	Hprod: N/A	Cold tolerance: N/A
Race: African American, Caucasian	Tskin: Decreases acutely in both groups; Lower in African Americans	Shivering: N/A	Tcore: Lower in African Americans; Decreases acutely in both groups; Greatest difference during rewarming period
Type: Air Temperature: 10°C Duration: 120 min Clothing: Light	Blood flow: N/A		Thermal comfort and sensation: N/A Sleep: N/A
Iampietro et al., 1959[199]	Insulative: N/A	Hprod: Increased acutely in both groups, with later onset in African American group; Greater rewarming shown by Caucasian subjects	Cold tolerance: N/A

(*Continued*)

Table 1. (Continued).

Experiment summary	Insulative responses	Metabolic responses	Cold tolerance
Race: African American, Caucasian	Tskin: No differences between groups, except 100 mins into experiment (lower in African Americans); Fingers and toes cooled at same rate and to same extent in both groups; Fewer rewarming cycles in African American group; Higher finger temperatures in Caucasians	Shivering: N/A	Tcore: Decreased acutely in both groups, No difference between groups
Type: Air and water (finger immersion)	Blood flow: Returned later in African American group		Thermal comfort and sensation: N/A
Temperature: 10°C (air) and 0°C (water) Duration: 120 min (air) and 45 min (water) Clothing: Nude (except cotton shorts)			Sleep: N/A
Andersen et al., 1963[67]	Insulative: N/A	Hprod: Increased acutely in both groups; greater metabolic rate increase in Caucasians (62%) in comparison to Inuit (27%); Same amount of work on the bicycle provided the Inuit more heat per mass	Cold tolerance: N/A
Race: Inuit, Caucasian	Tskin: Decreased, but did not go as low in Inuit'; Rewarming started earlier in Inuit	Shivering: Less in Inuit	Tcore: Unchanged for both groups while resting; Increased for both groups with exercise
Type: Air	Blood flow: Decreased during cold exposure; Quicker vasodilation onset due to rewarming in Inuit's		Thermal comfort and sensation: N/A
Temperature: 5°C Duration: 30 min resting and 30–45 min bicycle pedaling Clothing: Nude			Sleep: N/A
	Epidemiological		
DeGroot et al., 2003[200]	● Highest incidence rates observed in Alaska natives/Inuit males; however, the number of cases was low (n = 20)		
Race: African American, Asian/Pacific Islander, Alaska Native/Inuit, Caucasian, Hispanic	● Analysis was limited to Caucasians and African Americans due to unreliable confidence intervals		
Method: The U.S. Army Research Institute of Environmental Medicine Total Army Injury and Health Outcomes Database (TAIHOD) was searched for hospitalizations with ICD-9-CM diagnosis codes for frostbite, hypothermia, immersion foot, chilblains, and other.	● African Americans were hospitalized for cold-weather injuries at 2.2 times the rate of Caucasians		
	● African American men were injured approximately 4 times as often, and African American women were injured 2.2 times as often as their Caucasian counterparts.		
Burgess & Macfarlane, 2009[201]	● African Americans had more severe injuries (30 times the relative incidence of peripheral cold injury) than Caucasians		
Race: African American, Caucasian, Pacific Islander, Gurkhas	● Pacific Islanders had a relative incidence of peripheral cold injury 2.6 times that of Caucasians		

(*Continued*)

Table 1. (Continued).

Experiment summary	Insulative responses	Metabolic responses	Cold tolerance
Method: Patients who attended the Institute of Naval Medicine Cold Injuries Clinic underwent investigative procedures for a minimum of 3 months, where they took timed infra-red photographs during the rewarming process. Patients are graded on a 9-point scale, with the following descriptors: Normal, Within Normal Limits, Lower Limit of Normal, Mild, Mild/Moderate, Moderate, Moderate/Severe, Severe or Very Severe. Ethnicity data was obtained from the Defense Analytical Services (DASA) in Upavan.	● No difference between Caucasians and Gurkhas		
	SEX DIFFERENCES		
	Experimental		
McArdle et al., 1984[60]	Insulative: Women with low fat did not maintain Tcore upon cold exposure as effectively as men of similar percent fat	Hprod: Increased acutely in all groups; greater increase in lean subjects; no difference between sexes	Cold tolerance: N/A
Type: Water	Tskin: Decreased acutely in both groups; No difference between sexes	Shivering: Higher in colder water temperatures; higher in men for ΔTcore greater than − 1.0°C compared with women.	Tcore: Decreased acutely in all groups; Greater decrease in women at 20°C and 24°C
Gender: Men and women Hormonal status: N/A Temperature: 20, 24 and 28°C Duration: 60 min Clothing: Light (bathing attire)	Blood flow: N/A		Thermal comfort and sensation: N/A Sleep: N/A
Cooke et al., 1990[129]	Insulative: N/A	Hprod: N/A	Cold tolerance: N/A
Type: Air	Tskin: N/A	Shivering: N/A	Tcore: Increased acutely in both groups during total body warming, no difference between groups
Gender: Men and women	Blood flow: Greater in men at basal levels; increased during total body warming, greater increase in women; decreased in both groups during cold exposure, greater decrease in men; reduced response to cooling in women; no correlation between female hand blood flow and levels of serum estrogen or progesterone.		Thermal comfort and sensation: N/A
Hormonal status: N/A Temperature: 23°C for cold exposure, 45°C for total body warming Duration: 20 min for cold exposure, 40 min for total body warming Clothing: Light for cold exposure, heavy for total body warming			Sleep: N/A

(*Continued*)

Table 1. (Continued).

Experiment summary	Insulative responses	Metabolic responses	Cold tolerance
White, Ross and Mekjavic 1992[193]	Insulative: No difference in adipose tissue masses between groups, although males are heavier; adiposity is proportional to Tcore, but no difference between sexes; surface area: mass ratio is inversely proportional to Tcore	Hprod: Increased acutely in both groups	Cold tolerance: N/A
Type: Water Gender: Men and women Hormonal status: N/A Temperature: 30.6°C Duration: 50 min Clothing: Light (bathing attire)	Tskin: N/A Blood flow: N/A	Shivering: Absent for most	Tcore: Decreased acutely in both groups Thermal comfort and sensation: N/A Sleep: N/A
Bartelink, 1993[127]	Insulative: Subcutaneous adipose tissue was greater in postmenopausal women and lowest in males in comparison with all female groups; greater hand volume in males	Hprod: Higher in postmenopausal women compared with other women	Cold tolerance: N/A
Type: Water (hand immersion) Gender: Men and women Hormonal status: premenopausal, premenopausal taking oral contraceptives and postmenopausal Temperature: 15°C Duration: 5 min Clothing: Light, gloves	Tskin: Higher in males compared with women using oral contraceptives and premenopausal women; pre-cooling skin temperature was lower than postmenopausal women and men; lower minimum finger skin temperature during cooling in premenopausal women using oral contraceptives; mean finger skin temperature was highest in males during recovery	Shivering: N/A	Tcore: N/A Thermal comfort and sensation: N/A Sleep: N/A
Gonzalez, 1998[202]	Insulative: Greater clothing insulation decreased required heat production to maintain deep body temperature	Hprod: Increased acutely during cold exposure; Attenuated during midluteal phase	Cold tolerance: Greater cold tolerance during midluteal phase
Type: Air Gender: Women Hormonal status: premenopausal, not taking oral contraceptives. Temperature: 20° to −5°C at − 0.32°C/min	Tskin: Lower in *ensemble A* than *ensemble B* Blood flow: Acute peripheral vasoconstriction occurred during all thermal transient runs.	Shivering: Attenuated during luteal phase in both ensembles; no difference in threshold between phases or ensembles.	Tcore: Higher in luteal phase than follicular phase in *ensemble A* experiments, increases acutely, followed by decrease; higher at 50, 70 and 80 min in follicular phase in *ensemble A*; Higher in follicular phase at 70 and 80 min in *ensemble B* than during the luteal phase, and decreased with cold exposure; Higher with elevated reproductive hormone levels Thermal comfort and sensation: Lower sensitivity during luteal phase Sleep: N/A

(*Continued*)

Table 1. (Continued).

Experiment summary	Insulative responses	Metabolic responses	Cold tolerance
Duration: 80–120 min Clothing: *Ensemble A*: Standard (1.33 clo); *Ensemble B*: Heavy (2.58 clo). Both ensembles included work gloves (0.86 clo) and army boots and socks (1.8 clo).			
Charkoudian & Johnson, 1999[203]	Insulative: N/A	Hprod: N/A	Cold tolerance: N/A
Type: Liquid-conditioned suit	Tskin: Decreased acutely in both groups during cold exposure	Shivering: N/A	Tcore: Higher on high-hormone compared with low-hormone days
Gender: Women	Blood flow: Decreased acutely in both groups during cold exposure; Proportional to Tskin; vasoconstriction occurred at a higher Tcore during the high hormone phase		Thermal comfort and sensation: No difference between high-hormone and low-hormone.
Hormonal status: premenopausal taking oral contraceptives			Sleep: N/A
Temperature: 36°C and decreased by 0.2°C/min until shivering			
Duration: 12–15 min			
Clothing: N/A			
Pellerin & Candas, 2002[204]	Insulative: N/A	Hprod: Unchanged acutely	Cold tolerance: Less in women
Type: Air		Shivering: N/A	Tcore: N/A
Gender: Male and Female	Tskin: Decreased acutely during cold exposure		Thermal comfort and sensation: Thermal comfort is dominant for women; Cold is unpleasant in both groups
Hormonal status:			Sleep: N/A
Temperature: 14°C or 19°C, subjects could modify experimental conditions by changing either temperature of noise every 10 mins of the first hour	Blood Flow: N/A		
Duration: 120 min			
Clothing: Standard (0.6 clo)			
Stephens et al., 2002[205]	Insulative: N/A	Hprod: N/A	Cold tolerance: N/A
Type: Liquid conditioned suit	Tskin: Decreased acutely in both high-hormone and low-hormone phases; no difference between groups	Shivering: N/A	Tcore: N/A
Gender: Women	Blood flow: No difference in cutaneous vascular conductance across phases; Persistent vasoconstrictor response in high-hormone phase; Vasoconstrictor response absent during low-reproductive hormone phase		Thermal comfort and sensation: N/A
Hormonal status: premenopausal taking oral contraceptives			Sleep: N/A
Temperature: 34°C, lowered to 31°C			
Duration: 15 min			
Clothing: N/A			
Thompson & Kenney, 2004[206]	Insulative: N/A	Hprod: N/A	Cold tolerance: N/A

(*Continued*)

Table 1. (Continued).

Experiment summary	Insulative responses	Metabolic responses	Cold tolerance
Type: Liquid conditioned suit Gender: Men and women Hormonal status: premenopausal and taking oral contraceptives (follicular phase), postmenopausal Temperature: 34°C, lowered to 30.5°C Duration: 45 min Clothing: N/A	Tskin: Decreased acutely in both sexes Blood flow: No difference between sexes	Shivering: N/A	Tcore: N/A Thermal comfort and sensation: N/A Sleep: N/A
Schellen et al., 2012[207] Type: Air Gender: Men and women Hormonal status: premenopausal and taking oral contraceptives (luteal phase), premenopausal and not taking oral contraceptives (luteal phase) Temperature: 24.5°C Duration: 240 min Clothing: Standard (0.6 clo)	Insulative: N/A Tskin: Decreased acutely during cold exposure for both males and females; lower in females; higher during radiant cooling than convective cooling in males; lower during radiant cooling than convective cooling in females. Blood flow: Less in women	Hprod: Unchanged acutely Shivering: N/A	Cold tolerance: Less in females Tcore: Higher in females compared to males in both radiant and convective cooling Thermal comfort and sensation: Less comfort in females, even after rewarming Sleep: N/A
	Epidemiological		
DeGroot et al., 2003[200] Gender: Men and women Method: The U.S. Army Research Institute of Environmental Medicine Total Army Injury and Health Outcomes Database (TAIHOD) was searched for hospitalizations with ICD-9-CM diagnosis codes for frostbite, hypothermia, immersion foot, chilblains, and other.	Similar incidence of cold-weather injuries between men and women		
	RAYNAUD'S SYNDROME		
	Experimental		
Halperin, Cohen and Coffman, 1983[208] Type: Air Gender: Men and women Temperature: 25°C or 20°C	Insulative: N/A Tskin: N/A	Hprod: Increased acutely in all patients with Raynaud's disease and in normal subjects in thermoneutral and cold exposure conditions during mental stress; greater in normal subjects during cold exposure Shivering: N/A	Cold tolerance: N/A Tcore: N/A Thermal comfort and sensation: N/A Sleep: N/A

(*Continued*)

Table 1. (Continued).

Experiment summary	Insulative responses	Metabolic responses	Cold tolerance
Duration: 10 min	Blood flow: Decreased acutely in normal patients in thermoneutral conditions during mental stress; Increased acutely in patients with Raynaud's disease in thermoneutral conditions during mental stress; Decreased acutely in normal patients during cold exposure		
Clothing: Not specified			
	MORPHOLOGY		
	Experimental		
Hart et al., 1962[65]	Insulative: No difference in lean body mass similar between groups despite Inuit's smaller weight	Hprod: Higher basal metabolism in Inuit's; Unchanged acutely throughout the night in Inuit's; Increased acutely in Caucasians during periods of shivering	Cold tolerance: N/A
Type: Air	Tskin: Declined acutely during cold nights; Cooled in the following order: pectoral and forehead, arm and thigh, foot; Feet cooled to a greater extent in white men on cold nights; Decreased less in Inuit's than in Caucasians	Shivering: During cold nights, bursts were recorded in both groups; No differences observed in terms of intensity	Tcore: Decreased acutely during the cold nights in both groups
Temperature: 4–6°C	Blood flow: Greater in Inuit's	Heat production: Increased to the same levels as that of the white subjects on cold nights, but increased less compared with warm nights than the white subjects	Thermal comfort and sensation: N/A
Duration: 480 min			Sleep: Interrupted by shivering and cold in both groups
Clothing: Light			
Buskirk et al., 1963[209]	Insulative: Proportional to total body fat content; Per cent body fat is proportional to heat debt; Subjects with more than 30% body fat showed about twice the insulation over the chest, upper arm, and lateral thigh in comparison to subjects with less than 30% fat	Hprod: Increased acutely in both lean and obese subjects; Greater increase in lean subjects in comparison to obese subjects; inversely proportional to thermal insulation	Cold tolerance: N/A
Type: Air			
Temperature: 26.6°C and 10°C	Tskin: Decreased acutely in both lean and obese individuals; Lower in obese subjects	Shivering: Increased acutely; Greater increase in lean subjects; proportional to metabolic rate	Tcore: Better maintained in obese subjects; Core to surface gradient was larger in obese as compared to lean subjects
Duration: 120–240 min			
Clothing: Light	Blood Flow: N/A		Thermal comfort and sensation: Less comfort in both lean and obese subjects during cold exposure; no difference between groups Sleep: N/A
Ducharme, VanHelder and Radomski,[210] *1991*	Insulative: In resting individuals, unperfused muscle tissue provides a significant contribution to the body's total insulation	Hprod: Variable between treatments	Cold tolerance: N/A
Type: Water (forearm or hand immersion)			Tcore: Increased acutely for all water temperatures

(*Continued*)

Table 1. (Continued).

Experiment summary	Insulative responses	Metabolic responses	Cold tolerance
Temperature: 15, 20, 30, 33 or 36°C	Tskin: Temperature profile inside forearm became steeper as the water temperature decreased; Decreased acutely with cold exposure	Shivering: No shivering observed	
Duration: 180 min			Thermal comfort and sensation: N/A
Clothing: Light	Blood Flow: Decreased acutely due to vasoconstriction at all temperatures		
			Sleep: N/A
White, Ross and Mekjavic 1992[193]	Insulative: No difference between adipose tissue masses of men and women, but greater muscle tissue mass in men	Hprod: N/A	Cold tolerance: N/A
Type: Water		Shivering: Absent in most	Tcore: Decreased acutely during cold exposure; Large variation between subjects; not affected by adiposity and muscularity when the variance and gender were held constant
Temperature: 30.6°C	Tskin: N/A		Thermal comfort and sensation: N/A
Duration: 50 min	Blood flow: N/A		Sleep: N/A
Clothing: Light (bathing attire)			
Wyckelsma et al., 2021[211]	Insulative: N/A	Hprod: XX individuals consumed less energy and thus less susceptible to developing muscle fatigue; heat production increased at the end of the exposure, no difference between groups; Improved via increased muscle tone in XX individuals; More frequent bursting activity in RR individuals	Cold tolerance: Improved in alpha-actinin-3 deficient individuals
Type: Water		Shivering: Less pronounced in XX individuals	Tcore: Decreased acutely in individuals lacking alpha-actinin-3 (XX) and functioning alpha-actinin-3 (RR) individuals during cold exposure; Higher in individuals lacking alpha-actinin-3 (XX) during cold exposure
Temperature: 14°C	Tskin: Decreased acutely in both lacking alpha-actinin-3 individuals (XX) and functioning alpha-actinin-3 individuals (RR); No difference between groups in rate of decline		Thermal comfort and sensation: N/A
Duration: 120 min			Sleep: N/A
Clothing: Light	Blood flow: N/A		
	SLEEP/FATIGUE		
	Experimental		
Elsner, Andersen and Hermansen, 1960[70]	Insulative:	Hprod: No difference between seasons; basal metabolic rates higher in Inuit's than Caucasians.	Cold tolerance: N/A
Type: Air	Tskin: Decreased acutely during the night	Shivering: N/A	Tcore: Decreased acutely overnight
Temperature: 0–3°C	Blood flow:		Thermal comfort and sensation: N/A
Duration: 480 min			Sleep: N/A
Clothing: Light			
Sleep manipulations: N/A			

(*Continued*)

Table 1. (Continued).

Experiment summary	Insulative responses	Metabolic responses	Cold tolerance
Andersen et al., 1963[67]	Insulative: N/A	Hprod: Increased acutely in both groups; greater metabolic rate increase in Caucasians (62%) in comparison to Inuit (27%); Same amount of work on the bicycle provided the Inuit more heat per mass; no difference between groups at high levels of work	Cold tolerance: N/A
Race: Inuit, Caucasian	Tskin: Decreased acutely during cold exposure in both Caucasians and Inuit's; Greater decrease in Caucasians; rewarming of the skin progressed earlier in Inuit's during exercise	Shivering: Visible shivering and restlessness during entire period of no-load exercise; Shivering started after a few minutes of sitting	Tcore: Unchanged acutely while resting; decreased while pedaling with no workload; increased acutely when external work was performed; lower in Inuit's during cold exposure and no difference between cold and warm in Caucasians
Type: Air	Blood flow: Decreased acutely in both Caucasians and Inuit's		Thermal comfort and sensation: N/A
Temperature: 5°C Duration: 30 min resting, 35–45 min pedaling Clothing: Nude Sleep manipulations: N/A			Sleep: N/A
Young et al., 1998[141]	Insulative: Increase in both lean and fat mass during longer recovery period	Hprod: Increased for all trials; Higher in short recovery trial than both the trial immediately after exercise and the trial after long recovery, between which no difference was found	Cold tolerance: Chronic exertional fatigue cold tolerance
Type: Air Temperature: 10°C	Tskin: Decreased acutely in all trials; Higher immediately after exercise trial	Shivering: N/A	Tcore: Decreased acutely in all trials; No difference between trials; Increased acutely during the short recovery trial; Decline after 60 mins of cold exposure in both trials immediately after exercise and short recovery but not long recovery; Increased after 30 min in short recovery trials and persisted until minute 60, after which values returned to preexposure
Duration: 240 min Clothing: Light	Blood flow: N/A		Thermal comfort and sensation: Felt colder over the first 3 hours of the experiment, with no changes after; Subjects felt colder immediately after completing the last exercise of the training than during short or long recovery periods.
Sleep manipulations: Subjects were sleep deprived with 90 min of sleep in the preceding 24 hrs			Sleep: Most rated their feelings of fatigue as exhausted or extremely exhausted after sleep deprivation

(*Continued*)

Table 1. (Continued).

Experiment summary	Insulative responses	Metabolic responses	Cold tolerance
Tikuisis, Eyolfson and Giesbrecht, 2002[9]	Insulative: N/A	Hprod: Increased acutely until 60 min; Unchanged acutely during last 90 mins of immersion; inversely proportional to shivering fatigue; No difference between men and women	Cold tolerance: Variable
Type: Water	Tskin: Decreased acutely during cold exposure	Shivering: Variable in intensity and duration; Intensity inversely proportional to fatigue; 61% and 69% shivering capacity in men and women, respectively	Tcore: Decreased acutely during cold exposure
Temperature: 20°C lowered to 8°C	Blood flow: N/A		Thermal comfort and sensation: Cold sensation increased over time; Diminishing cold sensitivity led to diminished normalized shivering intensity
Duration: 480 min maximum			Sleep/Fatigue: Increased acutely with time
Clothing: Light (bathing attire)			
Sleep manipulations: N/A			
Raymann, Swaab and Van Someren, 2004[212]	Insulative: N/A	Hprod: N/A	Cold tolerance: N/A
Type: Liquid conditioned suit	Tskin: Decreased acutely; proximal skin temperature was affected by proximal and distal skin temperature	Shivering: N/A	Tcore: Decreased acutely during cold exposure; higher during warm exposure
Temperature: 33°C	Blood flow: Decreased acutely due to vasoconstriction		Thermal comfort and sensation: Thermal comfort was greater in cool conditions compared to warm conditions; thermal sensation was neutral during cold exposure
Duration: 9 blocks of 90 min over 2 days			Sleep: Unchanged by core and distal skin temperature manipulations; Decreased acutely with proximal skin warming
Clothing: N/A			
Manipulations: Lights were turned off from midnight until 0600; Subjects were awakened at 6			
Raymann et al., 2008[213]	Insulative:	Hprod: N/A	Cold tolerance: N/A
Type: Liquid conditioned suit	Tskin: Proximal skin warming enhanced deeper stages SWS and S2 of sleep at the cost of S1 and Wake in young adults and even more so in elderly without sleep complaints. Distal skin warming enhanced REM sleep and suppressed S1 (alpha range) and induced some increase in the beta range	Shivering: N/A	Tcore: Unchanged
Temperature: 31.7–34.6°C	Blood flow: N/A		Thermal comfort and sensation: Higher sensitivity in older participants
Duration: 330 min			Sleep: Skin warming improved age-related sleep problems; Deeper sleep and suppressed wakefulness due to proximal warming in young and older subjects without sleep complaints In young and older subjects without sleep complaints; Distal skin warming enhanced REM sleep and suppressed light sleep; In elderly insomniacs: proximal warming enhanced SWS and REM sleep; distal warming enhanced S1 and suppressed REM sleep

(*Continued*)

Table 1. (Continued).

Experiment summary	Insulative responses	Metabolic responses	Cold tolerance
Clothing: N/A Sleep manipulations: Sleep time allowed was limited to 5.5 h (from 00:30–6:00)			
Romeijn et al., 2012[214] Type: Air	Insulative: N/A Tskin: Dissociation between hand-arm and foot-leg gradients due to sleep deprivation in contrast to normal sleep; Sleep deprivation did not affect upper body Tskin gradients, but did lower hand-arm Tskin gradient and increased foot-leg Tskin gradients; Sleep deprivation induced heat loss activation from the heat in presence of activation of heat preservation from the hands	Hprod: N/A Shivering: N/A	Cold tolerance: N/A Tcore: No difference between normal sleep and sleep deprivation
Temperature: Not specified	Blood flow: Less in sleep deprived individuals due to greater vasoconstriction of the hand; higher in toes		Thermal comfort and sensation: N/A
Duration: 90 min Clothing: Bathing attire Sleep manipulations: modified constant protocol over 2 days: on one occasion, participants were allowed a normal night of sleep at home, and on the other occasion, participants had to remain awake all night			Sleep: N/A
	AGE *Experimental*		
Spurr, Hutt and Horvath, 1955[215] Type: Water (hand immersion)	Insulative: N/A Tskin: Decreased acutely in all age groups; Less variations in older subjects; Cooling and rewarming rates were more rapid in the youngest group of subjects; No difference between young adults and ages individuals; No differences in entire rewarming curves between any of the groups	Hprod: N/A Shivering: N/A	Cold tolerance: N/A Tcore: N/A
Temperature: 10°C	Blood flow: Hunting reaction occurs later in the elderly and is less pronounced; no difference between young adults and aged.		Thermal comfort and sensation: Possibility of greater sensibility and vascular reactivity in younger subjects
Duration: 10, 20 and 30 min for aged, children and young adults, respectively Clothing: Not specified			Sleep/Fatigue: N/A
Wagner & Horvath, 1985[216, 217]	Insulative: N/A	Hprod: Constant at 20°C; Increased in all subjects during 15°C and 10°C exposures, with greater increases occurring at 10°C; When metabolic rate at 28°C was used as a base, increase for 15°C and 10°C were greater in older subjects, especially older women; Slower increase in young women compared to older men	Cold tolerance: Unchanged acutely

(*Continued*)

Table 1. (Continued).

Experiment summary	Insulative responses	Metabolic responses	Cold tolerance
Type: Air	Tskin: Increased acutely during first 45 min in men and 90 min in young women; unchanged acutely in older women at thermoneutral environment; Higher in younger men than women at 28°C and 20°C and higher in younger men than all other groups at 15°C and 10°C; Higher in older men than older women at 10°C	Shivering: Higher in older women, and lowest in younger men	Tcore: No difference between groups at 28°C, but tended to be lower in older men; constant in older women in cold environments; constant in younger women at 20°C; slower decreasing rate in older men than younger men at 20°C; Decline of younger women was less than that of younger and older men during 15°C exposure; No difference in decreasing rate in young and older men at 15°C; No difference in rate of decrease in 10°C for younger women, young men and older men
Temperature: 28, 20, 15 and 10°C	Blood flow: N/A	Heat production: – –	Thermal comfort and sensation: Thermal sensation decreased acutely with age
Duration: 120 min			Sleep/Fatigue: N/A
Clothing: Light			
Thompson & Kenney, 2004[206]	Insulative: N/A	Hprod: N/A	Cold tolerance: N/A
Type: Liquid conditioned suit	Tskin: Decreased acutely	Shivering: N/A	Tcore: N/A
Temperature: 34°C, lowered to 30.5°C	Blood flow: Attenuated vasoconstriction in older subjects		Thermal comfort and sensation: N/A
Duration: 45 min			Sleep: N/A
Clothing: N/A			
Raymann et al., 2008[213]	Insulative: N/A	Hprod: N/A	Cold tolerance: N/A
Type: Liquid conditioned suit	Tskin: Increased acutely in both younger and older participants	Shivering: N/A	Tcore: Unchanged acutely
Temperature: 31.7–34.6°C	Blood flow: N/A		Thermal comfort and sensation: Higher sensitivity in older participants
Duration: 330 min			Sleep: Skin warming improved age-related sleep problems; In elderly insomniacs, proximal warming enhanced SWS and REM sleep, distal warming enhanced S1 and suppressed REM sleep; Proximal skin warming enhanced deeper stages SWS and S2 of sleep at the cost of S1 and Wake in young adults and even more so in elderly without sleep complaints; Distal skin warming enhanced REM sleep and suppressed S1 (alpha range) and induced some increase in the beta range
Clothing: N/A			
Sleep manipulations: Sleep time allowed was limited to 5.5 h (from 00:30–6:00)			
	DEHYDRATION		
	Experimental		
O'Brien, Young and Sawka, 1998[153]	Insulative: Higher in isotonic hypohydration than in hypertonic hypohydration, but not euhydration	Hprod: Increased acutely during cold exposure; No differences between trials; heart rate was higher during isotonic hypohydration preexposure than euhydration, but not hypertonic hypohydration	Cold tolerance: N/A

(*Continued*)

Table 1. (Continued).

Experiment summary	Insulative responses	Metabolic responses	Cold tolerance
Type: Air	Tskin: No difference between averages in isotonic hypohydration, hypertonic hypohydration and euhydration; Decreased acutely during euhydration during cold exposure; Plateau after 90 min during hypertonic hypohydration	Shivering: N/A	Tcore: Increased acutely for all trials; Plateau for hypertonic hypohydration after 60 min, while it decreased continuously in euhydration and isotonic hypohydration subjects
Temperature: 7°C	Blood flow: Attenuated vasoconstrictor response to cold with hypohydration; decreased acutely in all groups		Thermal comfort and sensation: N/A
Duration: 120 min Clothing: Light			Sleep: N/A
O'Brien et al., 2005[154]	Insulative: N/A	Hprod: Increased acutely in both groups using water and glycerol; No difference between trials	Cold tolerance: N/A
Type: Air	Tskin: Decreased acutely during cold exposure	Shivering: Unchanged acutely	Tcore: Increased acutely during cold exposure
Temperature: 15°C	Blood flow: Greater fluid retention with glycerol treatment than with water alone during cold exposure; decreased acutely by end of cold exposure in both water and glycerol trials		Thermal comfort and sensation: N/A
Duration: 240 min Clothing: Light			Sleep: N/A
		Epidemiological	
Kuht, Woods and Hollis, 2018[36] Methods: Patients with suspected NFCI sent to a military UK NFCI clinic were characterized. Demographics, medical history and situational risk factors leading to their injuries were analyzed, and comparison was made between those subsequently diagnosed with NFCI and those receiving alternate diagnoses.	Dehydration has been found to reduce skin temperatures during cold exposures in the laboratory, but has not yet been proven as causative in NFCI		

after acclimation [170,171]. This increase may be key to provide protection for CWI by maintaining a higher average T_{skin} and the increased peripheral circulation may also be beneficial for increasing manual dexterity. Also, under compensable conditions, greater T_{skin} are considered ideal after acclimation for optimizing thermal comfort and maximizing cognitive function without increasing metabolic stress from ST [64,171,172].

Table 1 summarizes findings from cold exposure studies on the effects of key parameters that may alter insulative and metabolic responses as well as cold tolerance within individuals and between populations.

Mitigating CWI

Mitigating risks of CWI requires a good understanding and proper education on the different types of cold conditions that may result in the development of CWI [36]. Establishing safe practices in the cold requires individuals to combine information including temperature, humidity, wind speed, duration of exposure, and type of activity performed [173]. As imminent risk of developing CWI, the onset of ST is a sign of cold stress indicating imminent hypothermia if the source of H_{loss} is not addressed [112,174]. This pre-hypothermic response provides warning signals for individuals to take appropriate actions by increasing thermal protection or finding shelter. A considerable concern of cold protective clothing is balancing under-protective H_{loss} from insufficient insulation and over-protective H_{loss} from evaporation of perspiration during physical activity [175]. As such, different climatic conditions require varying degrees of emphasis on insulation to appropriate necessities for perspiration from physical activity and windchill. Regardless of climate severity, general guidelines dictate materials should minimize moisture from perspiration and maximize protection against windchill, particularly for the head, ears, nose, cheeks, feet, and hands [175,176]. In addition, the identification of the main signs and symptoms of NFCI includes peripheral cooling and/or pain and numbness in the extremities which warrant avoidance of future exposure. In addition, early treatment is essential to mitigate future complications. Medical personnel must receive specific training to recognize and treat cold injuries [31].

To prevent NFCI, individuals must remain particularly vigilant and avoid prolonged periods of exposure in wet and cold conditions (e.g. 12 h–4 days of cold exposure) [177]. There are recommendations to regularly change to dry socks (i.e. 2–3 times per day) in cold-wet environments and air-dry feet at least 8 h out every 24 h. In case of 48 h of foot immersion, it is suggested for individuals to dry their feet for 24 h after exposure. However, these specific recommendations are based on research of warm water and tropical immersion foot [178,179]. There remains a lack of clear evidence regarding the best practices to prevent NFCI during cold exposure. Clearly, however, the use of adequate clothing to protect the body against cooling is essential for the prevention of NFCI [31]. Extra attention should be given to hands and feet. Constrictive footwear and clothing that may result in decreased blood flow need to be avoided [31,180]. Also, it is important to remain physically active during exposure to cold temperature and employ strategies to maintain core temperature [31,177,180]. It has been shown that exercising for 15–20 min is sufficient to increase foot and toe temperature [181]. There is inconsistent evidence about the association between the previous and current NFCI and its role in NFCI prevention [36,41]. Quantitative data from a recent representative case series showed that body mass index is not associated with NFCI. However, the percentage of body fat was not analyzed. Other characteristics, such as previous medical or family history are not predictors of NFCI [36].

While the damage caused by NFCI is harder to determine, FCI can cause lasting damage to affected tissues. In severe cases, amputation of gangrene is necessary to prevent the spread of rapidly dying tissue. Of the surviving tissue, there are often symptoms of neuropathy and damaged vasoconstriction responses that may lead to reduced ability to counteract cold environments [182–184]. When examining elite alpinists with previously injured tissue, including some amputations, cold water immersion of the previously injured hand felt significantly colder compared to the uninjured hand [185]. Although there were no differences in rewarming

rate between previously injured and healthy tissue, hands with previously injured tissue were consistently lower T_{skin} throughout rewarming [182,185]. To reduce the risk of further cold injuries, repeating local cooling to the extremities can improve tissue perfusion, assuming no injury to the tissue during local acclimation [186–188].

Of great importance also, thermal sensation and thermal comfort define the psychological response to cold exposure. This component is often overlooked when assessing changes in H_{loss} and H_{prod}. Thermal sensation provides information on how cold or hot the body feels under the given conditions and it is then processed as thermal comfort during the whole body temperature changes [189,190]. The mechanisms of thermal sensation and thermal comfort, however, are subjective and difficult to clearly define. Evidence from previous studies has indicated that a change in thermal sensation and thermal comfort are the precursors to thermoregulatory behavior responses in animals and humans [189,191]. Despite the close link typically seen between these two types of assessments, they are thought to be independent as thermal comfort is seen to rely on the feedback of whole-body temperature while thermal sensations can be elicited based on regional cooling [190]. To support such claims, Frank et al. (1999) found that the reduction of either T_{core} or T_{skin} by 1°C elicited similar thermal comfort responses despite the large increase in ST and vasoconstrictive responses [192]. Differences in mechanisms related to these different sensory responses could explain why differences in thermal sensation, thermal comfort, and whole-body cold responses exist between individuals of similar morphology and body composition.

Future directions

This review highlights the major challenges posed by cold weather survival and establishes that understanding individual differences in cold responses are key to provide appropriate CWI protection. Traditionally, research in this field has focused on providing overall, averaged responses to cold temperatures. While this approach provided important information on overall trends between groups or populations, it did little to improve our understanding of the CWI risks faced by a given individual located further from the average response. In view of the large variations in metabolic, insulation and morphological adaptations within humans, further research is needed to obtain information on the risks of CWI as they relate to the biophysical thermic characteristics of individuals and how clinical conditions influence the risk of CWI. This includes improving current knowledge on 1) the importance of the insulative and metabolic influences of body composition and [193], 2) on core warming capacity and heat storage for the improvement of peripheral temperatures [194]. Such findings would be essential to provide more tailored cold protection solutions and decision-making tools for military command. While seemingly simple at first glance, the major obstacle is associated with the incapacity to clinically assess accurately certain types of CWI.

Despite their ill-effects, few studies have clearly addressed the causality of NFCI and current knowledge is almost exclusively based on empirical clinical observations [195]. Unfortunately, the exact cold conditions that may lead to the development of NFCIs remain unclear at best [195]. Future work should not only focus on improving the identification and classification of early signs of NFCIs as well as on the improvement of current knowledge on the mechanisms involved in the development of these chronic CWI. Vale et al. highlights the need for more evidence-based algorithms to diagnosis and treat NFCI [33]. There is a lack of literature related to high quality research focused on vascular and neural aspects of NFCI [195]. Further work should evaluate characteristics of NFCI in a large sample and consider an appropriate control group matched for modifiable factors (e.g. type of activity during injury) and individual characteristics (i.e. anthropometric and demographic variables). Moreover, Eglin et al. also suggested the control for physical fitness and cold/wet condition due to the importance of comparing individuals exposed to same conditions but with different outcomes [195].

In contrast to NFCI, FCI have received far more attention due mainly to their severity and importance of tissue sparing treatments. With this said, far less is known on their long-term outcomes as they relate to: 1) pre- and post-thaw therapies/procedures focused on reducing frostbite injury, and 2) management of long-term consequences of frostbite to improve frostbite morbidity. Additionally, only exercise has shown moderate-quality evidence in preventing frostbite [40]. Further studies in preventing

frostbite should focus on consolidating evidence related to the maintenance of peripheral perfusion and cold protection. They should also take a more integrative approach to relate the importance of core warming or local warming in the prevention of FCI. Currently, there is low to very-low evidence level justifying the use of anti-inflammatory drugs, fluids, and low-molecular-weight dextran in frostbite treatment. In the context, the development of consistent evidence ideally using randomized controlled trials or exceptionally strong observational studies would be key.

Conclusions

This review shows that: 1) all humans are highly at risk of developing CWI without adequate knowledge and protective equipment and 2) that understanding the large interindividual variability in morphology, insulation, and metabolism is essential to reduce potential risks for CWI between and within populations. When exposed to environmental cold, the body struggles for a balance between H_{prod} and H_{loss}. Maintaining this balance allows conditions to be considered compensable, avoiding the detrimental effects of CWI. Some individual characteristics and statuses such as age, race, sleep deprivation, hypohydration, and previous cold injuries, may expose vulnerabilities in some individuals. To counteract these shortcomings, interventions of equipment, nutrition, hypohydration, and/or cold acclimation can mitigate the risks for CWI.

The main causes of NFCI are the sustained exposure to cooling temperatures between 25°C and 10°C and/or wet conditions. The feet are the most at risk; however, NFCI can affect any body part. Overall, NFCI diagnosis is based on comprehensive history, general examination, and injury classification. NFCI are classified in four different stages according to the exposure duration to cold temperatures, skin color, and other specific symptoms. In case of suspected NFCI, the patient should be first evacuated from the cold and/or wet environment if possible and subsequently receive immediate and additional management. Prevention is still the major way of avoiding long-term consequences such as cold sensitivity. Frostbite is mainly related to the exposure to temperatures close to tissue freezing point (−0.55°C). The diagnosis of frostbite starts with a clinical approach and is followed by the injury classification. Frostbite can be clinically differentiated into superficial (first and second levels.) and deep (third and fourth levels). Imaging exams to evaluate the level of tissue damage should be performed in deep cases of frostbite. Although there are different treatments available (e.g. iloprost and tPA), the first management is highly determinant of prognosis. Clearly, preventing and mitigating risks of CWI is key when exposed to cold conditions. Much work remains to clearly understand how individual morphological, physiological, and psychological differences can modulate cold responses and the risk of developing cold weather injuries.

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List of abbreviations

CWI	Cold Weather Injury
FCI	Freezing Cold Injury
NFCI	Nonfreezing Cold Injury
H_{loss}	rate of Heat Loss
H_{prod}	rate of Heat Production
Tcore	Core temperature
Tskin	Skin Temperature
CVC	Cutaneous Vasoconstriction
BAT	Brown Adipose Tissue
ST	Shivering Thermogenesis
CHO	Carbohydrates
SR	Sarcoplasmic Reticulum

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References

[1] Sullivan-Kwantes W, Goodman L. The new cold war. Temperature. 2017;4(4):341–344. doi:10.1080/23328940.2017.1381799.
[2] Yurkevicius BR, Alba BK, Seeley AD, et al. Human cold habituation: Physiology, timeline, and modifiers. Temperature. 2022 (in press). doi:10.1080/23328940.2021.1903145.
[3] Daanen HAM, Van WD. Human whole body cold adaptation. Temperature. 2016;3(1):104–118. doi:10.1080/23328940.2015.1135688.
[4] Imbeault M-A, Mantha OL, Haman F. Shivering modulation in humans: effects of rapid changes in environmental temperature. J Therm Biol. 2013;38(8):582–587.
[5] Gagge AP, Gonzalez RR. Mechanisms of heat exchange: biophysics and physiology. In: Fregly MJ, Blatteis CM, editors. Handbook of Physiology: environmental Physiology. Hoboken, NJ,USA: John Wiley & Sons, Inc; 1996:45–84.
[6] Castellani JW, Ikäheimo C.M, Montgomery H, Paal P, Tipton M.J, *et al.* ACSM expert consensus statement: injury prevention and exercise performance during

cold-weather exercise. Curr Sports Med Rep. 2021;20 (11):594–607. doi:10.1249/JSR.0000000000000907.
[7] Kingma BRM, Frijns AJH, Schellen L, et al. Beyond the classic thermoneutral zone: Including thermal comfort. Temperature. 2014;1(2):142–149. doi:10.4161/temp.29702.
[8] Tikuisis P. Predicting survival time for cold exposure. Int J Biometeorol. 1995;39(2):94–102.
[9] Tikuisis P, Eyolfson DA, Xu X, et al. Shivering endurance and fatigue during cold water immersion in humans. Eur J Appl Physiol. 2002;87(1):50–58.
[10] Young AJ, Sawka MN, Neufer PD, *et al.* Thermoregulation during cold water immersion is unimpaired by low muscle glycogen levels. J Appl Physiol. 1989;66(4):1809–1816.
[11] Martineau L, Jacobs I. Free fatty acid availability and temperature regulation in cold water. J Appl Physiol. 1989;67(6):2466–2472.
[12] Haman F, Legault SR, Weber JM. Fuel selection during intense shivering in humans: EMG pattern reflects carbohydrate oxidation. J Physiol. 2004;556(1):305–313.
[13] Blondin DP, Tingelstad HC, Mantha OL, et al. Maintaining thermogenesis in cold exposed humans: relying on multiple metabolic pathways. Compr Physiol. 2014;4:1383–1402.
[14] Petrone P, Asensio JA, Marini CP. Management of accidental hypothermia and cold injury. Curr Probl Surg. 2014;51(10):417–431.
[15] Lin YC, Hong SK. Physiology of water immersion. Undersea Biomed Res. 1984;11(2):109–111.
[16] Bowes HM, Eglin CM, Tipton MJ, et al. Swim performance and thermoregulatory effects of wearing clothing in a simulated cold-water survival situation. Eur J Appl Physiol. 2016;116(4):759–767.
[17] Haman F, Scott CG, Kenny GP. Fueling shivering thermogenesis during passive hypothermic recovery. J Appl Physiol. 2007;103(4):1346–1351.
[18] Allan JR. Survival after helicopter ditching: a technical guide for policy makers. Int. J Aviat Saf 1983;1:291–296.
[19] Golden F, Tipton MJ, Kinetics H. Essentials of Sea Survival. J. Hum. Kinet. 2002.
[20] Keatinge W. Medical problems of cold weather. The Oliver-sharpey lecture 1985. J R Coll Physicians L. 1986;20:283–287.
[21] Lee ECB, Lee K. Safety and survival at sea. London: Greenhill Books; 1989.
[22] Molnar GW. Survival of hypothermia by men immersed in the ocean. J Am Med Assoc. 1946;131 (13):1046–1050.
[23] Nunnely SA, Wissler WH. Prediction of immersion hypothermia in men wearing anti-exposure suitsand/or using liferafts. In AGARD-CP-286, A1-1-A1-8. 1980.
[24] Oakley EH, Pethybridge RJ. The Prediction of Survival during Cold Immersion: Results from the UKNational Immersion Incident Survey. INM report. No. 97011; 1997.
[25] Parsons K . Human Thermal Environments.The Effects ofHot, Moderate, and Cold Environments on Human Health, Comfort,and Performance, Third Edition (3rd ed.). 2003. CRC Press. doi:10.1201/b16750.
[26] Kulkarni K, Hildahl E, Dutta R, *et al.* Efficacy of head and torso rewarming Using a human model for severe hypothermia. Wilderness Env Med. 2019;30(1):35–43.
[27] Haman F, Mantha OL, Cheung SS, *et al.* Oxidative fuel selection and shivering thermogenesis during a 12- and 24-h cold-survival simulation. J Appl Physiol. 2016;120 (6):640–648.
[28] Imray C, Grieve A, Dhillon S. Cold damage to the extremities: frostbite and non-freezing cold injuries. Postgrad. Med J. 2009;85(1007):481–488.
[29] Reamy BV. Frostbite: review and current concepts. J Am Board Fam Pract. 1998;11(1):34–40.
[30] Ströhle M, Rauch S, Lastei P, *et al.* Frostbite injuries in the Austrian Alps: a retrospective 11-year national registry study. High Alt Med Biol. 2018;19(4):316–320.
[31] Thomas JR, Oakley EHN. Nonfreezing cold injury. Textb Mil Med Med Asp Harsh Environ 2002;1:467–490.
[32] Anand P, Privitera R, Yiangou Y, *et al.* Trench foot or non-freezing cold injury as a painful vaso-neuropathy: clinical and skin biopsy assessments. Front Neurol. 2017;8(514). https://doi.org/10.3389/fneur.2017.00514.
[33] Vale TA, Symmonds M, Polydefkis M, *et al.* Chronic non-freezing cold injury results in neuropathic pain due to a sensory neuropathy. Brain. 2017;140(10):2557–2569.
[34] Ungley CC, Channell GD, Richards RL. The immersion foot syndrome. BJS. 2003;1946:17–31.
[35] Blackwood W. Injury from exposure to low temperature: pathology. Br Med Bull. 1944;2(7):138–141.
[36] Kuht JA, Woods D, Hollis S. Case series of non-freezing cold injury: epidemiology and risk factors. BMJ Mil Heal. 2019;165:400–404.
[37] Glennie JS, Milner R. Non-freezing cold injury. J R Nav Med Serv. 2014;100(3):268–271
[38] Handford C, Thomas O, Imray CHE. Frostbite. Emerg Med Clin North Am. 2017;35(2):281–299.
[39] Osczevski R, Bluestein M. The new wind chill equivalent temperature chart. Bull Am Meteorol Soc. 2005;86 (10):1453–1458.
[40] McIntosh SE, Freer L, Grissom CK, *et al.* Wilderness medical society clinical practice guidelines for the prevention and treatment of frostbite: 2019 update. Wilderness Env Med. 2019;30(4):S19–s32.
[41] Heil K, Thomas R, Robertson G, *et al.* Freezing and non-freezing cold weather injuries: a systematic review. Br Med Bull. 2016;117(1):79–93.
[42] Cheung SS. Responses of the hands and feet to cold exposure. Temperature. 2015;2:105–120. doi:10.1080/23328940.2015.1008890.
[43] Carceller A, Javierre C, Ríos M, et al. Amputation risk factors in severely frostbitten patients. Int J Environ Res Public Health. 2019;16(8):1351.

[44] Hashmi MA, Rashid M, Haleem A, et al. Frostbite: epidemiology at high altitude in the Karakoram mountains. Ann R Coll Surg Engl. 1998;80(91):91–95.
[45] Zafren K. Frostbite: prevention and initial management. High Alt Med Biol. 2013;14(1):9–12.
[46] Zengren Y, Jiaying L, Fengzhi L, *et al*. Effect of acute hypoxia and hypoxic acclimation on hemorheological behavior in rats with frostbite. Clin Hemorheol Microcirc. 1999;20(3):189–195.
[47] Sun Z. Cardiovascular responses to cold exposure. Front Biosci (Elite Ed). 2010;E2(2):495–503.
[48] Wilkerson JE, Raven PB, Bolduan NW, et al. Adaptations in man's adrenal function in response to acute cold stress. J Appl Physiol. 1974;36 (2):183–189.
[49] Harinath K, Malhotra AS, Pal K, *et al*. Autonomic nervous system and adrenal response to cold in man at Antarctica. Wilderness Env Med. 2005;16 (2):81–91.
[50] Sullivan-Kwantes W, Moes K, Limmer R, et al. Finger cold-induced vasodilation test does not predict subsequent cold injuries: a lesson from the 2018 Canadian Forces Exercise. Temperature. 2019;6:142–149. doi:10.1080/23328940.2019.1574200.
[51] Burton AC, Edholm OG. *Man in a cold environment. London: Edward Arnold (Publishers) LTD*. 1955.
[52] Haman F. Shivering in the cold: from mechanisms of fuel selection to survival. J Appl Physiol. 2006;100 (5):1702–1708.
[53] van Ooijen AM, van Marken Lichtenbelt WDVM, van Steenhoven AA. Identification and importance of brown adipose tissue in adult humans. Br J Nutr. 2005;93(15):387–391.
[54] Parson KC. Human Thermal Environments. London: Taylor and Francis Ltd; 1993.
[55] Blix AS. Adaptations to polar life in mammals and birds. J Exp Biol. 2016;219(8):1093–1105.
[56] Gonzalez RR. Biophysics of heat transfer and clothing considerations. Human Performance Physiology and Environmental Medicine at Terrestrial Extremes. Indianapolis: Benchmark Press; 1988. p. 45–95.
[57] Pettit SE, Marchand I, Graham T. Gender differences in cardiovascular and catecholamine responses to cold-air exposure at rest. Can J Appl Physiol. 1999;24(2):131–147.
[58] Greenfield AM, Charkoudian N, Alba BK. Influences of ovarian hormones on physiological responses to cold in women. Temperature. 2022;9(1):23-45. doi: 10.1080/23328940.2021.1953688.
[59] Blondin DP, Haman F. Shivering and nonshivering thermogenesis in skeletal muscles. Handb Clin Neurol. 2018;156:153–173.
[60] McArdle WD, Magel JR, Gergley TJ, et al. Thermal adjustment to cold-water exposure in resting men and women. J Appl Physiol Respir Env Exerc Physiol. 1984;56:1565–1571.
[61] Toner WD, Michael M. Physiological adjustments of man to the cold. Human Performance Physiology and Environmental Medicine at Terrestrial Extremes. Indianapolis: Benchmark Press; 1988.
[62] Rennie, Covino B. G, Howell B. J, Song S. H., Kang B.S, Hong S. K, et al. Physical insulation of Korean diving women. J Appl Physiol. 1962;17(6):961–966. doi:10.1152/jappl.1962.17.6.961.
[63] Veicsteinas A, Ferretti G, Rennie DW. Superficial shell insulation in resting and exercising men in cold water. J Appl Physiol. 1982;52(6):1557–1564.
[64] Young AJ. Homeostatic responses to prolonged cold exposure: human cold acclimatization. In Melvin JF, Blatteis CM. (Eds).,Handbook of Physiology: Environmental Physiology, American Physiological Society, Bethesda, MD. Vol. 1783; 11996.
[65] Hart, Sabean, H.B., Hildes J.A., Depocas F., Hammel H. T., Andersen, K.L., Irving L, Foy G, *et al*. Thermal and metabolic responses of coastal Eskimos during a cold night. J Appl Physiol. 1962;17(6):953–960. https://doi.org/10.1152/jappl.1962.17.6.953
[66] Leppaluoto J, Hassi J. Human physiological adaptations to the arctic climate. Arctic. 1991;44(2):139–145.
[67] Andersen KL, Hart JS, Hammel HT, et al. Metabolic and thermal response of Eskimos during muscular exertion in the cold. J Appl Physiol. 1963;18(3):613–618.
[68] Andersen KL. Comparison of Scandinavian Lapps, Arctic fishermen, and Canadian Arctic Indians. Fed Proc. 1963;22:834–839.
[69] Hildes JA. Comparison of coastal Eskimos and Kalahari Bushmen. Fed Proc. 2004;22:843–845.
[70] Elsner RW, Andersen KL, Hermansen L. Thermal and metabolic responses of Arctic Indians to moderate cold exposure at the end of winter. J Appl Physiol. 1960;15 (4):659–661.
[71] Elsner RW, Andersen KL, Hermansen L. Thermal and metabolic responses of Arctic Indians to a standard moderate cold exposure at the end of winter. Tech Rep Arct Aeromed Lab US. 1961;108(3):1–11.
[72] Joy RJT. Responses of cold-acclimatized men to infused norepinephrine. J Appl Physiol. 1963;18(6):1209–1212.
[73] Snodgrass JJ, Leonard WR, Tarskaia LA, et al. Basal metabolic rate in the Yakut (Sakha) of Siberia. Am J Hum Biol. 2005;17(2):155–172.
[74] Leonard WR, Sorensen MV, Galloway VA, *et al*. Climatic influences on basal metabolic rates among circumpolar populations. Am J Hum Biol. 2002;14(5):609–620.
[75] Irving L., Andersen K.L., Bolstad A, Elsner R., Hildes J.A., Loyning Y., Nelms J.D., Peyton L.J., Whaley R.D., et al. Metabolism and temperature of Arctic Indian men during a cold night. J Appl Physiol. 1960;15(4):635–644. https://doi.org/10.1152/jappl.1960.15.4.635
[76] Verbraecken J, Van De Heyning P, De Backer W, et al. Body surface area in normal-weight, overweight, and obese adults. A comparison study. Metab. 2006;55 (4):515–524.
[77] DeGroot DW, Castellani JW, Williams JO, et al. Epidemiology of U. S. Army cold weather injuries, 1980-1999. Aviat Sp Env Med. 2003;74:564–570.

[78] Candler WH, Ivey H. Cold weather injuries among U. S. soldiers in Alaska: a five-year review. Mil Med. 1997;162(12):788–791.
[79] Daanen HA, van der Struijs NR. Resistance index of frostbite as a predictor of cold injury in arctic operations. Aviat Sp Env Med. 2005;76:1119–1122.
[80] Reynolds K, Williams J, Miller C, et al. Injuries and risk factors in an 18-day Marine winter mountain training exercise. Mil Med. 2000;165(12):905–910.
[81] Tek D, Mackey MS. Injury in a marine infantry Battalion. J Wilderness Med. 1993;4(4):353–357.
[82] Farnell, Pierce K.E., Collinsworth T.A., Murray L.K., Demes R.N., Juvancic-Heltzel J.A., Glickman E.L., et al. The Influence of ethnicity on Thermoregulation After Acute Cold Exposure. Wilderness & Environmental Medicine. 2008;19(4):238–244. https://doi.org/10.1580/07-WEME-OR-138.1
[83] Maley MJ, Eglin CM, House JR, et al. The effect of ethnicity on the vascular responses to cold exposure of the extremities. Eur J Appl Physiol. 2014;114(11):2369–2379.
[84] Gomez F, Hirbo J, Tishkoff SA. Genetic variation and adaptation in Africa: implications for human evolution and disease. Cold Spring Harb Perspect Biol. 2014;6(7):a008524–a008524.
[85] Romanovsky AA. Skin temperature: its role in thermoregulation. Acta Physiol. 2014;210(3):498–507.
[86] Werner J. System properties, feedback control and effector coordination of human temperature regulation. Eur J Appl Physiol. 2010;109(1):13–25.
[87] Morrison SF. Central control of body temperature. F1000Res. 2016;5:880.
[88] Nakamura K, Morrison SF. Central efferent pathways for cold-defensive and febrile shivering. J Physiol. 2011;589(14):3641–3658.
[89] Jänig W. Peripheral thermoreceptors in innocuous temperature detection. Handb Clin Neurol. 2018;156:47–56.
[90] Kingma BRM, Frijns AJH, Saris WHM, et al. Increased systolic blood pressure after mild cold and rewarming: relation to cold-induced thermogenesis and age. Acta Physiol. 2011;203(4):419–427.
[91] Bligh J. A theoretical consideration of the means whereby the mammalian core temperature is defended at a null zone. J Appl Physiol. 2006;100(4):1332–1337.
[92] Mekjavic IB, Eiken O. Contribution of thermal and nonthermal factors to the regulation of body temperature in humans. J Appl Physiol. 2006;100(6):2065–2072.
[93] Boulant JA. Neuronal basis of Hammel's model for set-point thermoregulation. J Appl Physiol. 2006;100(4):1347–1354.
[94] Cabanac M. Adjustable set point: to honor Harold T. Hammel. J Appl Physiol. 2006;100(4):1338–1346.
[95] Mekjavic IB, Morrison JB. A model of shivering thermogenesis based on the neurophysiology of thermoreception. IEEE Trans Biomed Eng. 1985;BME-32(6):407–417.
[96] Christianson JA, McIlwrath SL, Koerber HR, et al. Transient receptor potential vanilloid 1-immunopositive neurons in the mouse are more prevalent within colon afferents compared to skin and muscle afferents. Neuroscience. 2006;140(1):247–257.
[97] Blondin DP, Labbé S.M., Phoenix S., Guérin B., Turcotte E. E., Richard D., Carpentier A.C., Haman F., et al. Contributions of white and brown adipose tissues and skeletal muscles to acute cold-induced metabolic responses in healthy men. Physiol. J. 2015;593(3):701–714. https://doi.org/10.1113/jphysiol.2014.283598
[98] Claessens-van Ooijen AMJ, Westerterp KR, Wouters L, *et al.* Heat production and body temperature during cooling and rewarming in overweight and lean men. Obesity. 2006;14(11):1914–1920.
[99] Daniels J,F, Baker PT. Relationship between body fat and shivering in air at 15 C. J Appl Physiol. 1961;16(3):421–425.
[100] Nielsen B, Astrup A, Samuelsen P, et al. Effect of physical training on thermogenic responses to cold and ephedrine in obesity. Int J Obes Relat Metab Disord. 1993;17(7):383–390.
[101] van Marken Lichtenbelt WD, Vanhommerig JW, Smulders NM, *et al.* Cold-activated brown adipose tissue in healthy men. N Engl J Med. 2009;360(15):1500–1508.
[102] Hanssen MJ, van der Lans AAJJ, Brans B, *et al.* Short-term cold acclimation recruits brown adipose tissue in obese humans. Diabetes. 2016;65(5):1179–1189.
[103] van der Lans AAJJ, Hoeks J, Brans B, *et al.* Cold acclimation recruits human brown fat and increases nonshivering thermogenesis. J Clin Invest. 2013;123(8):3395–3403.
[104] Kellogg DL. In vivo mechanisms of cutaneous vasodilation and vasoconstriction in humans during thermoregulatory challenges. J Appl Physiol. 2006;100(5):1709–1718.
[105] Charkoudian N. Skin blood flow in adult human thermoregulation: how it works, when it does not, and why. Mayo Clin Proc. 2003;78(5):603–612.
[106] Fiala D, Lomas KJ, Stohrer M. Computer prediction of human thermoregulatory and temperature responses to a wide range of environmental conditions. Int J Biometeorol. 2001;45(3):143–159.
[107] Kingma BRM, Vosselman MJ, Frijns AJH, et al. Incorporating neurophysiological concepts in mathematical thermoregulation models. Int J Biometeorol. 2014;58(1):87–99.
[108] Eyolfson DA, Tikuisis P, Xu X, et al. Measurement and prediction of peak shivering intensity in humans. Eur J Appl Physiol. 2001;84(1–2):100–106.
[109] Rolfe DF, Brown GC. Cellular energy utilization and molecular origin of standard metabolic rate in mammals. Physiol Rev. 1997;77(3):731–758.
[110] Schmidt-Nielsen K. Scaling: why is animal size so important. New York: Cambridge University Press; 1984.
[111] Meigal A. Gross and fine neuromuscular performance at cold shivering. Int J Circumpolar Heal. 2002;61(2):163–172.

[112] Bell DG, Tikuisis P, Jacobs I. Relative intensity of muscular contraction during shivering. J Appl Physiol. 1992;72(6):2336–2342.
[113] Blondin DP, Maneshi A, Imbeault MA, et al. Effects of the menstrual cycle on muscle recruitment and oxidative fuel selection during cold exposure. J Appl Physiol. 2011;111(4):1014–1020.
[114] Haman F, Legault SR, Rakobowchuk M, et al. Effects of carbohydrate availability on sustained shivering II. Relating muscle recruitment to fuel selection. J Appl Physiol. 2004;96(1):41–49.
[115] Haman F, Blondin DP. Shivering thermogenesis in humans: origin, contribution and metabolic requirement. Temperature. 2017;4:217–226. doi:10.1080/23328940.2017.1328999
[116] Haman F, Péronnet F, Kenny GP, *et al*. Effects of carbohydrate availability on sustained shivering I. Oxidation of plasma glucose, muscle glycogen, and proteins. J Appl Physiol. 2004;96(1):32–40.
[117] Blondin DP, Daoud A, Taylor T, *et al*. Four-week cold acclimation in adult humans shifts uncoupling thermogenesis from skeletal muscles to brown adipose tissue. J Physiol. 2017;595(6):2099–2113.
[118] Simoneau JA, Bouchard C. Human variation in skeletal muscle fiber-type proportion and enzyme activities. Am J Physiol. 1989;257(E567–72):567–572.
[119] Perkins JF. The role of the proprioceptors in shivering. Am J Physiol. 1945;145(2):264–271.
[120] Schafer SS, Schafer S. The role of the primary afference in the generation of a cold shivering tremor. Exp Brain Res. 1973;17(4):381–393.
[121] Tanaka M. Experimental studies on human reaction to cold. Differences in the vascular hunting reaction to cold according to sex, season, and environmental temperature. Bull Tokyo Med Dent Univ. 1971;18(4):269–280.
[122] Doneva S, Binnie L, Non-freezing Cold Injury (NFCI) (2018).
[123] Taylor MS. Cold weather injuries during peacetime military training. Mil Med. 1992;157(11):602–604.
[124] Admiraal WM, Verberne HJ, Karamat FA, *et al*. Cold-induced activity of brown adipose tissue in young lean men of South-Asian and European origin. Diabetologia. 2013;56(10):2231–2237.
[125] Castellani JW, Young AJ. Human physiological responses to cold exposure: acute responses and acclimatization to prolonged exposure. Aut Neurosci. 2016;196:63–74.
[126] Anderson GS. Human morphology and temperature regulation. Int J Biometeorol. 1999;43(3):99–109.
[127] Bartelink ML, Wollersheim H, Leesmans E, et al. A standardized finger cooling test for Raynaud's phenomenon: diagnostic value and sex differences. Eur Hear J. 1993;14(5):614–622.
[128] Grisanti JM. Raynaud's phenomenon. Am Fam Physician. 1990;41(1):134–142.
[129] Cooke JP, Creager MA, Osmundson PJ, et al. Sex differences in control of cutaneous blood flow. Circulation. 1990;82(5):1607–1615.
[130] Daanen HA. Finger cold-induced vasodilation: a review. Eur J Appl Physiol. 2003;89(5):411–426.
[131] Miller LK, Irving L. Local reactions to air cooling in an Eskimo population. J Appl Physiol. 1962;17(3):449–455.
[132] Collins KJ. Effects of cold on old people. Br J Hosp Med. 1987;38(6):506–508. 510-512,514
[133] Taylor G. The problem of hypothermia in the elderly. Practitioner. 1964;193:761–767.
[134] Vaisrub S. Accidental hypothermia in the elderly. JAMA. 1978;239(18):1888.
[135] Alba BK, Castellani JW, Charkoudian N. Cold-induced cutaneous vasoconstriction in humans: function, dysfunction and the distinctly counterproductive. Exp Physiol. 2019;104(8):1202–1214.
[136] Wagner JA, Horvath SM. Cardiovascular reactions to cold exposures differ with age and gender. J Appl Physiol. 1985;58(1):187–192.
[137] Bernstein LM, Hick FK, Inouye T, et al. Body composition as related to heat regulation in women. J Appl Physiol. 1956;9:241–256.
[138] Collins KJ, Exton-Smith AN. Henderson award lecture. Thermal homeostasis in old age. J Am Geriatr Soc. 1983;31(9):519–524.
[139] Mathew L, Purkayastha SS, Singh R, et al. Influence of aging in the thermoregulatory efficiency of man. Int J Biometeorol. 1986;30(2):137–145.
[140] Kingma BRM, Frijns AJH, Saris WHM, et al. Cold-induced vasoconstriction at forearm and hand skin sites: the effect of age. Eur J Appl Physiol. 2010;109(5):915–921.
[141] Young AJ, Castellani JW, O'Brien C, *et al*. Exertional fatigue, sleep loss, and negative energy balance increase susceptibility to hypothermia. Eur J Appl Physiol. 1998;85(4):1210–1217.
[142] Castellani JW, Stulz DA, Degroot DW, *et al*. Eighty-four hours of sustained operations alter thermoregulation during cold exposure. Med Sci Sport Exercise. 2003;35(1):175–181.
[143] Caine-Bish NL, Potkanowicz ES, Otterstetter R, et al. Thermal and metabolic responses of sleep deprivation of humans during acute cold exposure. Aviat Sp Env Med. 2004;75:964–968.
[144] Oliver SJ, Harper Smith AD, Costa RJS, *et al*. Two nights of sleep deprivation with or without energy restriction does not impair the thermal response to cold. Eur J Appl Physiol. 2015;115(10):2059–2068.
[145] Peterson CM, Lecoultre V, Frost EA, *et al*. The thermogenic responses to overfeeding and cold are differentially regulated.Obesity. 2016;24(1):96–101.
[146] Schlogl M, Piaggi P, Thiyyagura P, *et al*. Overfeeding over 24 hours does not activate brown adipose tissue in humans. J Clin Endocrinol Metab. 2013;98(12):E1956–E1960.
[147] Martineau L, Jacobs I. Muscle glycogen availability and temperature regulation in humans. J Appl Physiol. 1989;66(1):72–78.
[148] Weller AS, Millard CE, Greenhaff PL, et al. The influence of cold stress and a 36- h fast on the

physiological responses to prolonged intermittent walking in man. Eur J Appl Physiol Occup Physiol. 1998;77(3):217–223.
[149] Reeves JW, Benjamin JJ, Mann CH. E. W. Comparison of physiological changes during long term immersion to neck level in water at 95°, 85°, and 75°F. (1966).
[150] Fregly MJ. Water and electrolyte exchange during exposure to cold. Pharmacol Ther. 1982;18 (2):199–231.
[151] Knight DR, Horvath SM. Urinary responses to cold temperature during water immersion. Am J Physiol. 1985;248(R560–6):560–566.
[152] Rintamaki H, Makinen T, Oksa J, et al. Water balance and physical performance in cold. Arct Med Res. 1995;54(Suppl 2):32–36.
[153] O'Brien C, Young AJ, Sawka MN. Hypohydration and thermoregulation in cold air. J Appl Physiol. 1998;84 (1):185–189.
[154] O'Brien C, Freund BJ, Young AJ, et al. Glycerol hyperhydration: physiological responses during cold-air exposure. J Appl Physiol. 2005;99(2):515–521.
[155] Cypess AM, Lehman S, Williams G, *et al*. Identification and importance of brown adipose tissue in adult humans. N Engl J Med. 2009;360(15):1509–1517.
[156] Virtanen KA, Lidell ME, Orava J, *et al*. Functional brown adipose tissue in healthy adults. N Engl J Med. 2009;360(15):1518–1525.
[157] Symonds ME, Aldiss P, Pope M, et al. Recent advances in our understanding of brown and beige adipose tissue: the good fat that keeps you healthy. F1000Res. 2018;7:1129.
[158] Orava J, Nuutila P, Noponen T, *et al*. Blunted metabolic responses to cold and insulin stimulation in brown adipose tissue of obese humans. Obes. 2013;21 (11):2279–2287.
[159] Vijgen GH, Bouvy ND, Teule GJJ, *et al*. Brown adipose tissue in morbidly obese subjects. PLoS One. 2011;6(2): e17247.
[160] Chen KY, Brychta RJ, Linderman JD, *et al*. Brown fat activation mediates cold-induced thermogenesis in adult humans in response to a mild decrease in ambient temperature. J Clin Endocrinol Metab. 2013;98(7): E1218–E1223.
[161] Ouellet V, Labbé SM, Blondin DP, *et al*. Brown adipose tissue oxidative metabolism contributes to energy expenditure during acute cold exposure in humans. J Clin Invest. 2012;122(2):545–552.
[162] Muzik, Mangner T.J., Leonard W.R., Kumar A., Janisse J., Granneman J. G., et al. 15 O PET measurement of blood flow and oxygen consumption in cold-activated human brown fat. J Nucl Med. 2013;54(4):523–531. https://doi.org/10.2967/jnumed.112.111336
[163] Lytton J, Westlin M, Burk SE, et al. Functional comparisons between isoforms of the sarcoplasmic or endoplasmic reticulum family of calcium pumps. J Biol Chem. 1992;267(20):14483–14489.
[164] Arruda AP, Nigro M, Oliveira GM, et al. Thermogenic activity of Ca2+-ATPase from skeletal muscle heavy sarcoplasmic reticulum: the role of ryanodine Ca2+ channel. Biochim Biophys Acta. 2007;1768 (6):1498–1505.
[165] Davis TR. Chamber cold acclimatization in man. J Appl Physiol. 1961;16(6):1011–1015.
[166] Gordon K, Blondin DP, Friesen BJ, *et al*. Seven days of cold acclimation substantially reduces shivering intensity and increases nonshivering thermogenesis in adult humans. J Appl Physiol. 2019;126(6):1598–1606.
[167] Budd GM, Brotherhood JR, Beasley FA, *et al*. Effects of acclimatization to cold baths on men's responses to whole-body cooling in air. Eur J Appl Physiol Occup Physiol. 1993;67(5):438–449.
[168] Jansky L, Janáková H., Ulicný B., Srámek P., Hosek V., Heller J., Parízková J., et al. Changes in thermal homeostasis in humans due to repeated cold water immersions. Pflugers Arch. 1996;432(3):368–372. https://doi.org/10.1007/s004240050146
[169] Stocks JM, Patterson MJ, Hyde DE, et al. Metabolic habituation following repeated resting cold-water immersion is not apparent during low-intensity cold-water exercise. J Physiol Anthr Appl Hum Sci. 2001;20:263–267.
[170] Leppaluoto J, Korhonen I, Hassi J. Habituation of thermal sensations, skin temperatures, and norepinephrine in men exposed to cold air. J Appl Physiol. 2001;90(4):1211–1218.
[171] Makinen TM, Palinkas L, Reeves D, *et al*. Effect of repeated exposures to cold on cognitive performance in humans. Physiol Behav. 2006;87(1):166–176.
[172] Hesslink J,R, D'Alesandro L, Armstrong MM 3rd. D. W. & Reed, H. L. Human cold air habituation is independent of thyroxine and thyrotropin. J Appl Physiol. 1992;72(6):2134–2139.
[173] Imray CHE. Non-freezing cold injury. In: BMJ Mil. Heal. 2019.
[174] Jacobs I. Nutritional Needs In Cold And High-Altitude Environments:Applications for Military Personnel in Field Operations. Institute ofMedicine (US) Committee on Military Nutrition Research. In Marriott BM, Carlson SJ.(Eds). Washington (DC): National Academies Press(US); 1996.
[175] Jussila K, Valkama A, Remes J, et al. The effect of cold protective clothing on comfort and perception of performance. Int J Occup Saf Erg. 2010;16(2):185–197.
[176] Lehmuskallio E, Lindholm H, Koskenvuo K, *et al*. Frostbite of the face and ears: epidemiological study of risk factors in Finnish conscripts. BMJ. 1995;311 (7021):1661–1663.
[177] Imray C, Richards P, Greeves J, et al. Nonfreezing cold-induced injuries. BMJ Mil Heal. 2011;157:79–84.
[178] Akers WA. Paddy foot: a warm water immersion foot syndrome variant. Part II. Field experiments, correlation. Mil Med. 1974;139(8):613–618.
[179] Allen A, Taplin D. Tropical immersion foot. Lancet. 1973;302(7839):1185–1189.

[180] NATO STO TG HFM-187. Management of Heat and Cold Stress Guidance to NATO Medical Personnel. *TR-HFM-187*. Vol. 323, 2013.
[181] Rissanen S, Rintamäki H. Effects of repeated exercise/rest sessions at–10 C on skin and rectal temperatures in men wearing chemical protective clothing. Eur J Appl Physiol Occup Physiol. 1998;78 (6):560–564.
[182] Gorjanc J, Morrison SA, Blagus R, et al. Cold susceptibility of digit stumps resulting from amputation after freezing cold injury in elite alpinists. High Alt Med Biol. 2018;19(2):185–192.
[183] Ingram BJ, Raymond TJ. Recognition and treatment of freezing and nonfreezing cold injuries. Curr Sport Med Rep. 2013;12(2):125–130.
[184] Carmeli E, Patish H, Coleman R. The aging hand. J Gerontol A Biol Sci Med Sci. 2003;58(2):146–152.
[185] Morrison SA, Gorjanc J, Eiken O, et al. Finger and toe temperature responses to cold after freezing cold injury in elite alpinists. Wilderness Env Med. 2015;26 (3):295–304.
[186] Brandstrom H, Grip H, Hallberg P, *et al.* Hand cold recovery responses before and after 15 months of military training in a cold climate. Aviat Sp Env Med. 2008;79(9):904–908.
[187] Leblanc J, Hildes JA, Heroux O. Tolerance of gaspe fishermen to cold water. J Appl Physiol. 1960;15 (6):1031–1034.
[188] Nelms JD, Soper DJ. Cold vasodilatation and cold acclimatization in the hands of British fish filleters. J Appl Physiol. 1962;17(3):444–448.
[189] Cabanac M, Serres P. Peripheral heat as a reward for heart rate response in the curarized rat. J Comp Physiol Psychol. 1976;90(5):435–441.
[190] Mower GD. Perceived intensity of peripheral thermal stimuli is independent of internal body temperature. J Comp Physiol Psychol. 1976;90(12):1152–1155.
[191] Flouris AD, Cheung SS. On the origins of cold-induced vasodilation. Eur J Appl Physiol. 2010;108 (6):1281–1282.
[192] Frank SM, Raja SN, Bulcao CF, et al. Relative contribution of core and cutaneous temperatures to thermal comfort and autonomic responses in humans. J Appl Physiol. 1999;86(5):1588–1593.
[193] White MD, Ross WD, Mekjavic IB. Relationship between physique and rectal temperature cooling rate. Undersea Biomed Res. 1992;19(2):121–130.
[194] Brajkovic D, Ducharme MB, Frim J. Relationship between body heat content and finger temperature during cold exposure. J Appl Physiol. 2001;90(6):2445–2452.
[195] Eglin CM, Montgomery H, Tipton MJ. Non-freezing cold injury: a multi-faceted syndrome. Brain. 2018;141:e9–e9.
[196] Rennie D, Adams T. Comparative thermoregulatory responses of Negroes and white persons to acute cold stress. J Appl Physiol. 1957;11(2):201–204.
[197] Adams T, Covino BG. Racial variations to a standardized cold stress. J Appl Physiol. 1958;12:9–12.
[198] American Negro-WhiTE Differences In The Thermal Insulative Aspects Of Body FAT PAUL T. BAKER Published by: Wayne State University Press Stable. (2021);31:316–324. https://www.jstor.org/stable/41448404.
[199] Iampietro PF, Goldman RF, Buskirk ER, et al. Response of negro and white males to cold. J Appl Physiol. 1959;14(5):798–800.
[200] DeGroot DW, Castellani JW, Williams JO, et al. Epidemiology of US Army cold weather injuries, 1980–1999. Aviat Space Environ Med. 2003;74(5):564–570.
[201] Burgess JE, Macfarlane F. Retrospective analysis of the ethnic origins of male British army soldiers with peripheral cold weather injury. J R Army Med Corps. 2009;155(1):11–15.
[202] Gonzalez RR, Blanchard LA. Thermoregulatory responses to cold transients: effects of menstrual cycle in resting women. J Appl Physiol. 1998;85(2):543–553.
[203] Charkoudian N, Johnson JM. Reflex control of cutaneous vasoconstrictor system is reset by exogenous female reproductive hormones. J Appl Physiol. 1999;87(1):381–385.
[204] Pellerin N, Candas V. Combined effects of temperature and noise on human discomfort. Physiol Behav. 2003;78(1):99–106.
[205] Stephens, Bennett L.A.T., Aoki K., Kosiba W. A., Charkoudian A., Johnson J.M., *et al.* Sympathetic nonnoradrenergic cutaneous vasoconstriction in women is associated with reproductive hormone status. Am J Physiol - Heart Circ Physiol. 2002;282 (1):264–272. https://doi.org/10.1152/ajpheart.2002.282.1.H264
[206] Thompson CS, Kenney WL. Altered neurotransmitter control of reflex vasoconstriction in aged human skin. J Physiol. 2004;558(2):697–704.
[207] Schellen L, Loomans MG, de Wit MH, et al. The influence of local effects on thermal sensation under non-uniform environmental conditions–gender differences in thermophysiology, thermal comfort and productivity during convective and radiant cooling. Physiol Behav. 2012;107(2):252–261.
[208] Halperin JL, Cohen RA, Coffman JD. Digital vasodilatation during mental stress in patients with raynaud's disease. Cardiovasc Res. 1983;17(11):671–677.
[209] Buskirk ER, Thompson RH, Whedon GD. Metabolic response to cold air in men and women in relation to total body fat content. J Appl Physiol. 1963;18(3):603–612.
[210] Ducharme MB, VanHelder WP, Radomski MW. Tissue temperature profile in the human forearm during thermal stress at thermal stability. J Appl Physiol. 1991;71 (5):1973–1978.
[211] Wyckelsma VL, Venckunas T, Houweling PJ, *et al.* Loss of α-actinin-3 during human evolution provides superior cold resilience and muscle heat generation. Am J Hum Genet. 2021;108(3):446–457.

[212] Raymann RJEM, Swaab DF, Van Someren EJW. Cutaneous warming promotes sleep onset. Am J Physiol - Regul Integr Comp Physiol. 2005;288 (6):1589–1597.

[213] Raymann RJ, Swaab DF, Van Someren EJ. Skin deep: enhanced sleep depth by cutaneous temperature manipulation. Brain. 2008;131(2):500–513.

[214] Romeijn N, Raymann RJEM, Møst E, *et al*. Sleep, vigilance, and thermosensitivity. Pflugers Arch. 2012;463(1):169–176.

[215] Spurr GB, Hutt BK, Horvath SM. The effects of age on finger temperature responses to local cooling. Am Heart J. 1955;50(4):551–555.

[216] Wagner JA, Horvath SM. Influences of age and gender on human thermoregulatory responses to cold exposures. J Appl Physiol. 1985;58(1):180–186.

[217] Imray CH, Richards P, Greeves J, Castellani JW. Nonfreezing cold-induced injuries. J R Army Med Corps. 2011 Mar;157(1):79–84. doi: 10.1136/jramc-157-01-14. PMID: 21465916.