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TOPICAL REVIEW

Potential health benefits of cold-water immersion: the central role of PGC-1α

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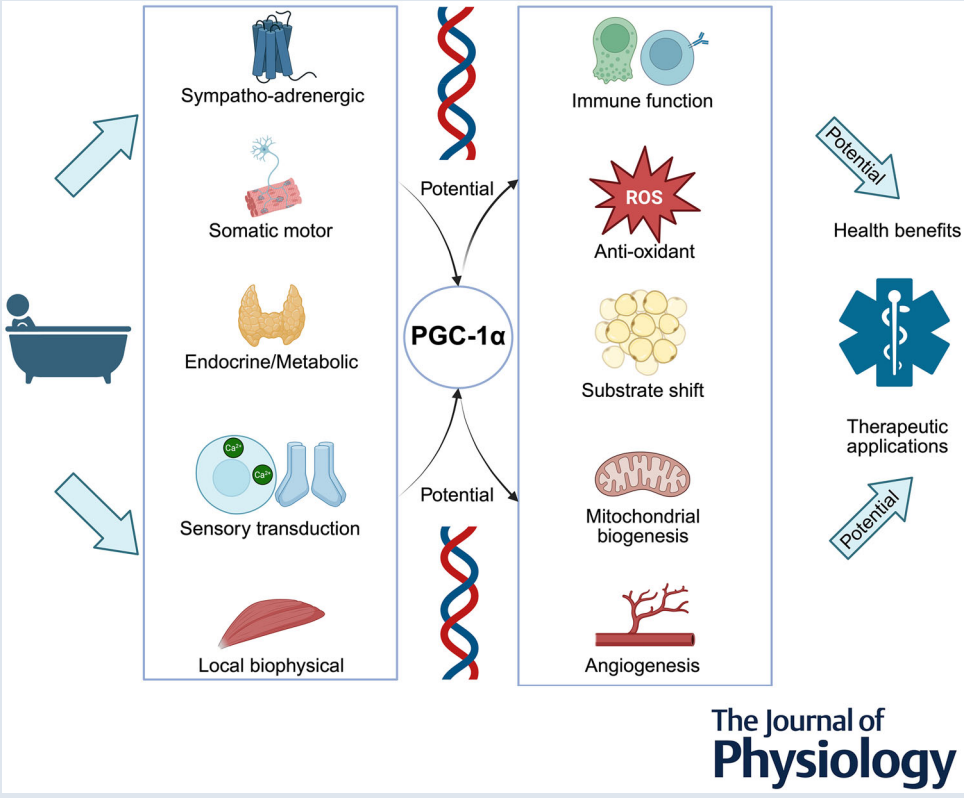

Abstract figure legend Cold-water immersion (CWI) elicits autonomic, somato-motoric (shivering thermogenesis), endocrine and metabolic, sensory transduction, and local biophysical effects that may converge on the transcriptional co-activator PGC-1α (centre). From this hub, canonical programmes like mitochondrial biogenesis/respiration, angiogenesis, antioxidant/immune modulation and metabolic shifts are engaged and may contribute to potential health benefits (right).

Abstract Cold-water immersion (CWI) elicits a coordinated thermoregulatory and stress-response programme that may converge on molecular pathways linked to peroxisome proliferator-activated receptor-γ co-activator-1α (PGC-1α), a master regulator of mitochondrial

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biogenesis and a coordinator of angiogenesis, antioxidant defence and metabolism. Through activation of peripheral cold receptors (e.g. TRPM8), CWI triggers sympathetic noradrenaline release and hypothalamic–pituitary–thyroid axis stimulation (TSH→D2→T3), driving β-adrenergic/cAMP–PKA–p38MAPK–CREB signalling that could robustly upregulate PGC-1α and uncoupling protein-1 in brown adipose tissue and skeletal muscle. Concurrent shivering-induced Ca^{2+} fluxes engage calcium/calmodulin-stimulated protein kinase II and calcineurin, enhancing PGC-1α expression in an AMP-activated protein kinase (AMPK)-independent manner. Elevated PGC-1α coactivates nuclear respiratory factors (NRF1/NRF2) and mitochondrial transcription factor A to expand mitochondrial content and oxidative capacity, while upregulating key antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase). Together with oestrogen-related receptor α, PGC-1α can co-activate vascular endothelial growth factor, a pathway compatible with angiogenesis and improved perfusion; however, in humans the link to CWI remains indirect and is largely limited to acute molecular responses. Downstream metabolic adaptations, including increased fatty acid oxidation (via carnitine palmitoyltransferase 1, peroxisome proliferator-activated receptors α/γ and AMPK) and fibroblast growth factor 21 secretion, enhance insulin sensitivity and energy expenditure. Most of the evidence currently rests on molecular signalling data, heterogeneous study designs, or acute gene expression responses. Direct evidence for increased mitochondrial content, improved mitochondrial function, or long-term health benefits in humans is scarce. Therefore, this article introduces a hypothetical dose–response relationship, linking immersion time to proposed health benefits and death, and provides practical recommendations for safe CWI protocols.

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Introduction

The use of cold-water immersion (CWI) has a long-standing history as a therapeutic, health-promoting and sport-recovery intervention. As early as the year 3500 B.C., cold exposures were used for therapeutic purposes in Egypt (Wang et al., 2006). Around 400 B.C., Hippocrates employed cold to treat medical conditions like pneumonia, hepatitis and herpes (Tsoucalas et al., 2015). He also attributed the potential for improved preservation of energy and power and also for relaxation to cold exposure (Allan et al., 2022). These historical observations demonstrate a long-standing interest in the use of cold therapies to promote human health. The immersion in cold water can be defined as immersion in water at a temperature <15°C, whereas ice bathing is related to water temperatures <5°C (Bleakley et al., 2012; Knechtle et al., 2020). Although there is no consensus on the minimum proportion of body surface that must be immersed to qualify as CWI, most experimental protocols and recreational practitioners use head-out immersion to approximately the level of the sternum. Extensive research has investigated the physiological challenges associated with cold-water survival. For example, Tipton demonstrated that sudden stimulation of the peripheral cutaneous cold receptors initiate hazardous physiological responses, collectively known as the 'cold-shock' response (Tipton, 1989).

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The benefits of cold-water immersion for post-exercise recovery remained scientifically largely unexplored until the 1960s, when Clarke's research brought attention to this topic (Clarke, 1963). Since then, the interest in 'cold' research has constantly increased (Allan et al., 2022) and the physiological reactions to cold stress have been successively uncovered in numerous studies (Castellani & Young, 2016; Medicine, 1996; Tipton, 1989). The use of CWI as an athletic recovery intervention has become widely adopted in the athletic field, primarily due to the water's superior thermal conductivity compared with air (Bleakley et al., 2014). The beneficial effects of cold in this area can be assigned to its change in the vasomotor tone (i.e. vasoconstrictive effects), its effect of reducing cellular metabolism and increased analgesia (White & Wells, 2013). On the other side, CWI during recovery from resistance-type exercise was associated with a reduced capacity of skeletal muscle to incorporate dietary amino acids into *de novo* myofibrillar protein (Fuchs et al., 2020). Furthermore, CWI reduced myofibrillar protein synthesis rates over the course of prolonged resistance-training programmes (Fuchs et al., 2020). Independent of effects on exercise-induced adaptations, the subsequent section examines the evidence regarding potential generalized health benefits of CWI.

Numerous health benefits of cold water have been suggested. Especially in the popular sciences, CWI has been postulated to have antioxidative effects, enhance the immune system's capacity, contribute to weight loss and boost mood (News, 2023; Yankouskaya et al., 2023). Although the popular sciences and anecdotal reports on this topic, spread for example on social media, make cold therapies appear to be a magical cure, most of these claims remain highly controversial from a scientific perspective (Esperland et al., 2022).

Nevertheless, the regular exposure to cold water or ice water has become a popular contemporary trend. Scientific studies on regular cold-water exposure have primarily investigated the effects on metabolism (Checinska-Maciejewska et al., 2017; Gibas-Dorna et al., 2016), the cardiovascular system (Kralova Lesna et al., 2015; Manolis et al., 2019), the immune system (Brazaitis et al., 2014; Janský et al., 1996) and well-being (van Tulleken et al., 2018). Isolating the independent effects of cold-water exposure *per se* is challenging because the water temperature, immersion depth and duration vary widely across studies. The hydrostatic pressure and convection alter preload, afterload and individual factors, modifying the cold-shock response in addition to co-factors like physical activity level or health status.

Peroxisome proliferator-activated receptor gamma co-activator-1 alpha (PGC-1α) functions as a transcriptional co-activator and is now widely recognized as a key regulator of mitochondrial biogenesis in skeletal muscle (Puigserver & Spiegelman, 2003). Its role as a so-called 'master regulator' is supported by rodent studies showing that elevated levels of PGC-1α enhance insulin sensitivity (Handschin & Spiegelman, 2006; Lira et al., 2010), protect against age-related muscle loss (Ji & Kang, 2015) and improve physical endurance (Baar et al., 2002; Lin et al., 2002). Due to the importance of these adaptations for both health and athletic performance, the mechanisms controlling PGC-1α expression in human skeletal muscle have become a major focus of current research. Notably, acute bouts of exercise have been shown to upregulate PGC-1α expression (Bartlett et al., 2012, 2013; Perry et al., 2010), with the extent of this response being influenced by exercise intensity (Egan et al., 2010) and mediated by upstream signalling pathways. In line with its initial identification as a gene responsive to cold (Puigserver et al., 1998), increasing evidence from both animal models (Kim et al., 2005; Oliveira et al., 2004; Stancic et al., 2013) and human studies (Ihsan et al., 2014; Ihsan et al., 2015; Slivka et al., 2012, 2013) has shown that both short-term and sustained cold exposure, whether through low ambient temperatures or CWI, can elevate PGC-1α expression. Collectively, these findings suggest that cold exposure may potentiate the molecular response typically triggered by exercise, potentially amplifying the cellular adaptations associated with endurance training.

While heat exposure has been linked to the activation of PGC-1α (Liu & Brooks, 2012; Yamaguchi et al., 2010), it is notable that PGC-1α was originally identified in research focused on how cold exposure influences the expression of uncoupling proteins (UCP) (Puigserver et al., 1998). In that initial study, mice exposed to cold temperatures (4°C) for 3–12 h showed a marked increase in PGC-1α mRNA levels within brown adipose tissue (BAT), accompanied by elevated expression of mitochondrial oxidative phosphorylation (OXPHOS) components such as cytochrome-c-oxidase (COX) 2, COX4 and ATP synthase (Puigserver et al., 1998). Similar findings have been observed in hibernating animals, where cold exposure leads to a broad induction of PGC-1α across multiple tissues, including skeletal muscle (Eddy & Storey, 2003). This effect is thought to be mediated by adrenergic signalling pathways, particularly through cAMP responsive element-binding protein (CREB) activation at the PGC-1α promoter (see Fig. 3), as comparable increases in PGC-1α transcription were also seen in brown fat and muscle cell cultures treated with the β-adrenergic agonist isoproterenol (Puigserver et al., 1998). Although these *in vitro* findings highlight a central role for β-adrenergic – CREB dependent transcriptional control of PGC-1α, the precise intracellular intermediates and their physiological relevance following CWI remain to be delineated.

Therefore, this review seeks to summarize the key molecular pathways by which CWI stimulates PGC-1α

expression and to explore the associated potential health benefits.

Additionally, we provide practical recommendations for safe cold-water exposure, highlight the main risks that can arise if critical safety guidelines are not followed and emphasize the requirements for future studies on mechanistic aspects of CWI.

Thermal sensation and acute responses. Any environmental condition that raises heat loss and triggers heat-preservation mechanisms can be categorized as cold stress (Haman et al., 2022). Although the term 'cold water' has no precise definition, it is usually defined as water at <15°C since most observable harmful reactions to cold water seem to peak while submerged between 10 and 15°C (Tipton et al., 1991). Since the thermal conductivity of water is 25 times higher than, for example, air (Toner & McArdle, 2011), even in moderately cold water, heat dissipation occurs rapidly due to conduction and convection (blood circulation), which deliver heat from deeper tissues to the skin (Castellani & Young, 2016). This disparity in thermal conductivity results in different thermoneutral zone temperatures for water immersion compared with air cooling. The thermoneutral zone is generally reported to be between 31 and 33°C for water, with noticeable shivering often occurring below this temperature range, whereas the thermoneutral zone in the air is between 22 and 24°C (Cannon & Keatinge, 1960; Craig & Dvorak, 1966). The critical water temperature reflects the water temperature between 28°C and 34°C, in which a nude individual can tolerate a 3 h prolonged water immersion without experiencing shivering thermogenesis (Rennie et al., 1962). Humans mainly use behavioural thermoregulatory strategies to survive in cold environments, such as migration, constructing or seeking shelter, wearing clothing and utilizing fire-making skills (Blondin & Haman, 2018).

The physiological effects of cold stress vary greatly depending on the exposure medium (air *vs*. water), level of cold (differences in temperature and humidity) and exposure duration (minutes *vs*. days).

To preserve homeostasis, the body initiates a variety of cold-protective processes (Fig. 1). Initially, a cold signal is transduced through the transient receptor potential melastatin 8 (TRPM8) receptors from the skin to the brain. These receptors are temperature-sensitive, calcium-permeable, cation ion channels that also respond to specific chemical stimuli such as menthol (Johnson et al., 2009). Although these receptors are possibly one of the best studied innocuous cool sensors (<27°C), the transient receptor potential canonical 5 (TRPC5) exhibits cold sensitivity *in vitro* and can be activated by cooling in the temperature range of 37–25°C (Zimmermann et al., 2011). Besides transient receptor potential (TRP) channels, the transmembrane guanylyl cyclase G (GC-G) may directly respond to cooling and mediate the cool sensation in the mouse Grueneberg ganglion that is located at the rostral tip of the nose (Chao et al., 2015). Mammalian transient receptor potential ankyrin 1 (TRPA1) has a cold temperature activation threshold of about 17°C *in vitro* and was first cloned as a noxious cold sensor (Story et al., 2003). However, as TRPA1 knockout mice escape noxious cold temperatures largely normally, there is disagreement on the physiological involvement of TRPA1 in noxious cold feeling (Kwan et al., 2006). Previous research mostly used candidate gene approaches to find temperature sensors, successfully identifying many heat-sensitive TRP channels. However, this method has been less effective for detecting cold sensors, especially those outside the known thermosensor families like TRP channels (Xiao & Xu, 2021). A recent unbiased genetic screen in *C. elegans* identified glutamate receptor 3 (GLR-3), a kainate-type glutamate receptor, as a cold sensor (Gong et al., 2019). GLR-3 is expressed in the intestine, the right amphid sensory neuron E (ASER) and ring interneurons A (RIA), and is essential for cold sensitivity (≤18°C) and ASER-mediated cold-avoidance behaviour (Gong et al., 2019). Ectopic expression of GLR-3 or its mouse homolog glutamate receptor ionotropic kainate 2 (GluK2) imparts cold sensitivity to normally insensitive cells, and homologs from zebrafish, mouse and human also function as cold sensors in heterologous systems (Gong et al., 2019), indicating evolutionary conservation. Notably, mammalian kainate receptors, including GluK2, have both ionotropic and metabotropic functions (Rodríguez-Moreno & Lerma, 1998).

When the skin is exposed to cold, it triggers a receptor-mediated neural pathway extending from the dorsal horn of the spinal cord to the lateral brachial nucleus and then to the preoptic area of the hypothalamus (Fig. 2). Efferent signals are then transmitted from the brain through the intermediolateral cell column of the spinal cord to sympathetic nerves, which control the skin's blood vessels (Castellani & Young, 2016).

Reflex cutaneous vasoconstriction represents the body's immediate autonomic response to reduce convective heat loss and preserve core temperature during cold exposure (Alba et al., 2019). In addition to heat-preservation mechanisms, thermogenesis is another important mechanism to counteract cold exposure. Shivering, consisting of involuntary muscle contractions, generates heat as most of the metabolic energy is converted into thermal energy (Castellani & Young, 2016). Non-shivering thermogenesis, resulting predominantly from BAT and skeletal muscle proton leak, have been demonstrated to be significant contributors to this kind of

heat production (Blondin et al., 2017; Ouellet et al., 2012). However, in adults exposed to cold, shivering thermogenesis remains the dominant source of heat production (Gordon et al., 2019). Noradrenaline is the main neurotransmitter together with neuropeptide-Y, contributing to the reflex cold-induced vasoconstriction in the skin's blood vessels (Charkoudian, 2010; Stephens et al., 2001). Local cooling of the blood vessels in the skin also results in vasoconstriction. During the first minutes of the local cooling response, noradrenaline via the α2-adrenergic receptor predominantly mediates vasoconstriction (when no reflex cooling occurs from other areas) (Johnson, 2007). However, the decrease in cutaneous blood flow as cooling proceeds is caused by non-adrenergic and non-neuronal mechanisms (Thompson-Torgerson et al., 2008). This vasoconstrictive response begins when the skin temperature falls below 35°C and reaches its maximum when skin temperature falls to 31°C or lower.

PGC-1α and cold exposure

PGC-1α-related molecular pathways in response to cold-water immersion. Some results suggest that the positive effects that can arise from cold might be mediated by the modulation of specific molecular factors, like PGC-1α (Ihsan, Watson, & Abbiss, 2014). PGC-1α is a transcription co-activator that interacts with many different transcription factors involved in glucose/fatty acid metabolism, mitochondrial biogenesis, adaptive thermogenesis, fibre type switching in skeletal muscle and cardiac development, among other biological processes (Liang & Ward, 2006). It is strongly expressed in tissues with high oxidative activity, such as BAT, the heart, brain and skeletal muscle (Liang & Ward, 2006; Puigserver et al., 1998). PGC-1α is upregulated in response to increased energy demands such as cold, exercise, and fasting (Ventura-Clapier et al., 2008). Instead of binding specific sequences of DNA (Puigserver & Spiegelman, 2003), PGC-1α coactivates several nuclear

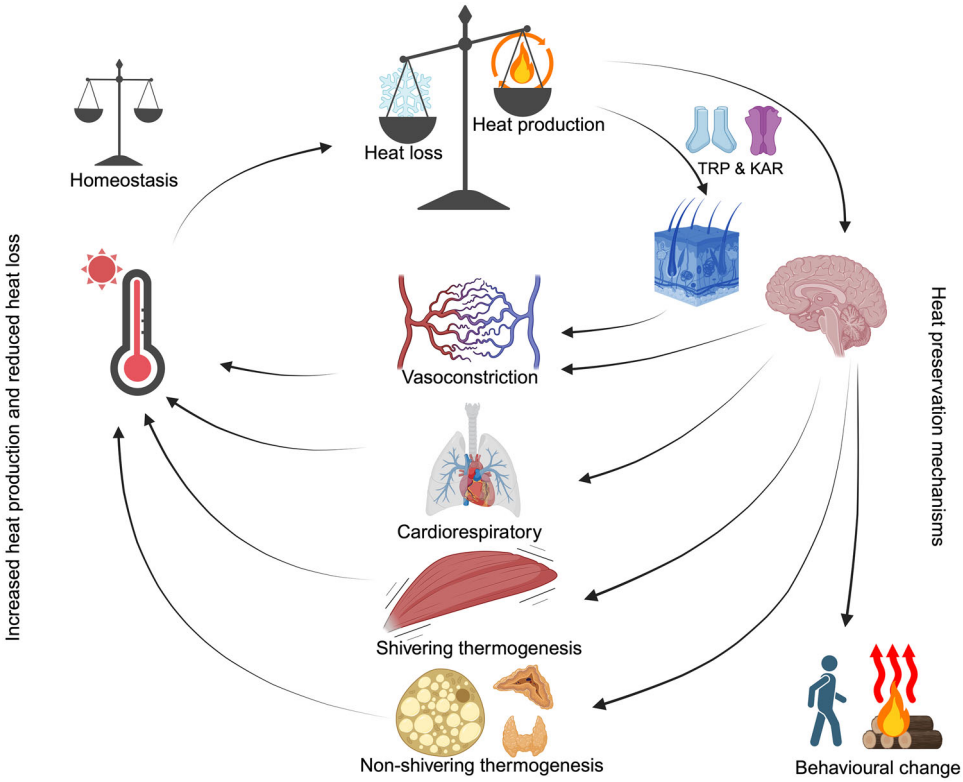

Figure 1. Schematic representation of thermoregulatory mechanisms in response to cold exposure
The cold signal is mediated to the central nervous system through peripheral cold receptors like transient receptor potential channels (TRP) and Kainate-type glutamate receptors (KAR) in the skin; Aδ/C-fibre input to dorsal horn → lateral parabrachial nucleus → preoptic area and brainstem integrators. Increasing heat loss triggers heat-preservation mechanisms to balance the heat production and heat loss. β-adrenergic activation leads to immediate cardiorespiratory responses such as hyperventilation and tachycardia. Behavioural changes, such as seeking shelter in warmer environments, vasoconstriction of peripheral blood vessels (via α_2-adrenoreceptors), shivering thermogenesis (via somatic motor drive to skeletal muscle) and non-shivering thermogenesis through brown adipose tissue (via sympathetic β-adrenergic activation) and gland activation (adrenal catecholamines; i.e. adrenaline/noradrenaline), and hypothalamic–pituitary–adrenal axis activity, lead to increased heat production until homeostasis is reached.

receptors, including peroxisome proliferator-activated receptors (PPARs) (Liang & Ward, 2006), which (PPAR-α and PPAR-β/δ) have been shown to promote fatty acid oxidation in tissues like the heart (Gilde et al., 2003). PGC-1α also interacts with and co-activates oestrogen-related receptors (ERRs), key transcriptional factors for the regulation of cellular energy metabolism. Most glycolysis-related genes have been found to be regulated by ERRα and ERRγ, particularly in response to various environmental challenges or biological stresses (Audet-walsh & Giguére, 2015; Cai et al., 2013). In muscle tissue, ERRα coordinates mitochondrial biogenesis, muscle regeneration/differentiation and, along with ERRγ, modulates OXPHOS and angiogenesis (Huss et al., 2015).

ERRα signalling plays an important role in lipogenesis in white adipose tissue (WAT) and thermogenesis in BAT (Huss et al., 2015). PGC-1α contributes to the regulation of mitochondrial biogenesis and respiration by strongly inducing the expression of the transcription factors, NRFs, NRF1 and NRF2 (Ventura-Clapier et al., 2008). NRF1 and NRF2 control the expression of numerous mitochondrial genes (e.g. NADH dehydrogenase subunit 8, and succinate dehydrogenase subunit B) (Kelly & Scarpulla, 2004).

On the mitochondrial level, UCPs are of particular interest for cold responses and thermoregulation. UCPs increase proton conductance across the inner mitochondrial membrane, dissipating the proton-motive force and uncoupling electron transport from ATP synthesis; the proton movement induced by uncoupling generates heat (Puigserver et al., 1998; Wei et al., 2009). UCPs 1–3 protect against radical oxygen species (ROS) production, thereby reducing oxidative damage; for example, in the heart (Cadenas, 2018). Mammals express

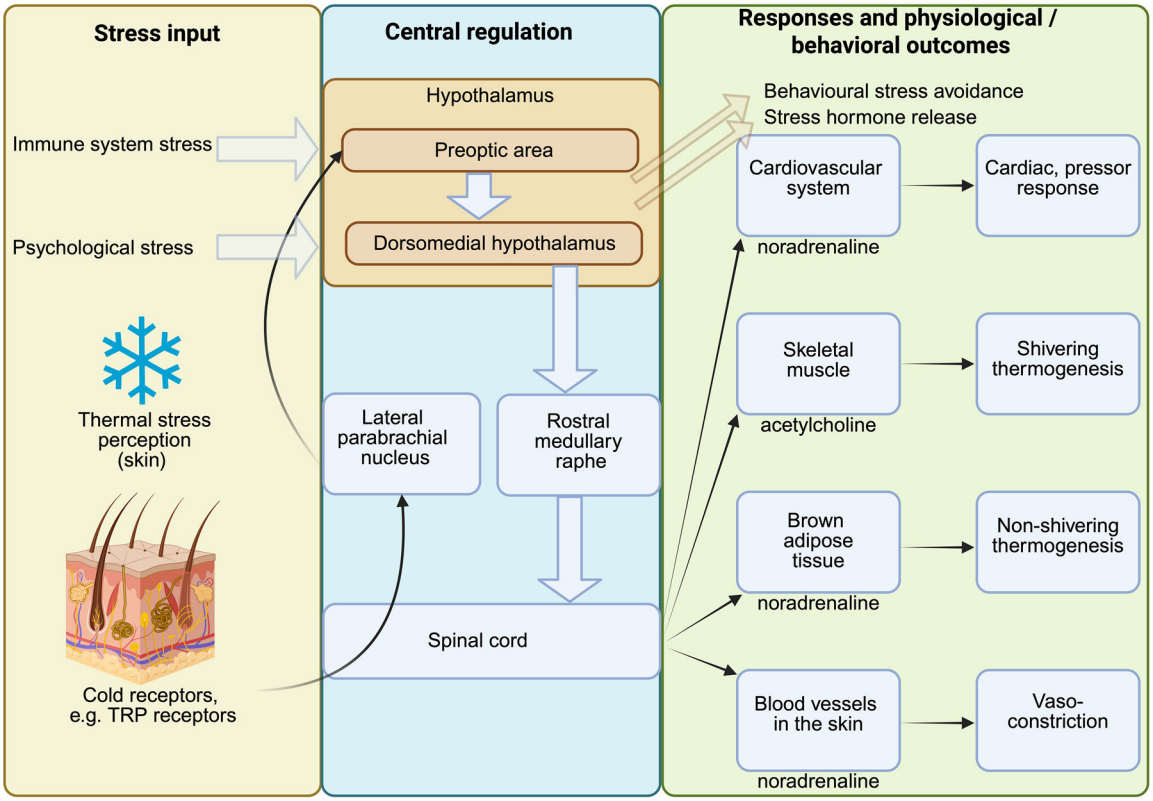

Figure 2. Signals and pathways by which cutaneous cold sensing drives hypothalamic-brainstem networks to coordinate cardiovascular, thermogenic and vasomotor responses
Peripheral cold receptors in the skin (TRPM8/TRPA1-expressing Aδ/C fibres) transduce cooling and relay glutamatergic input via dorsal horn (lamina I) projection neurons to the lateral parabrachial nucleus. The signals ascend to the preoptic area integrators, whose predominantly GABAergic output disinhibits the dorsomedial hypothalamus, thereby activating rostral raphe pallidus premotor neurons. These premotor centres drive (1) sympathetic noradrenergic outflow to cutaneous vasoconstrictors (α_1-adrenergic) increasing total peripheral resistance and mean arterial pressure, (2) sympathetic β-adrenergic signalling to brown adipose tissue to increase thermogenesis, and (3) reticulospinal pathways to spinal α-motor neurons, with acetylcholine at the neuromuscular junction mediating shivering thermogenesis. Cardiac chronotropy is shaped by sympathetic noradrenaline (tachycardia), while adrenal catecholamines amplify systemic responses. Collectively, these pathways integrate afferent cold signals with autonomic, endocrine and motor effectors to conserve heat and restore internal homeostasis.

at least five types of UCP, and UCPs 1–3 are best studied. UCP-1 is specific to brown adipocytes (Ricquier, 2017), while UCP-2 is widely expressed (Donadelli et al., 2014) and UCP-3 can be predominantly found in skeletal muscle and BAT (Ledesma et al., 2002). PGC-1α and other co-regulators are essential for the coordinated control of UCP-1 gene transcription (Villarroya et al., 2017). Transcription factors like PPARs, sterol regulatory element-binding proteins and PGC-1α directly control UCP-2 transcription (Liu et al., 2014; Tian et al., 2018). Moreover, the PGC-1α/PPAR-β axis is a crucial pathway that activates UCP-3 in skeletal muscle cells by PGC-1α transactivation of a distal PPAR response element at the UCP-3 promoter (Lima et al., 2019). In addition to UCP-mediated proton conductance, other inner mitochondrial membrane mechanisms can contribute to uncoupling and thermogenesis. The adenine nucleotide translocase (ANT; also referred to as the ADP/ATP carrier, AAC) is abundant in the inner membrane and has been shown to mediate a substantial fraction of basal proton conductance in multiple tissues, acting as a regulated route for H^+ re-entry that is distinct from ATP synthase (Bertholet et al., 2019; Brand et al., 2005). ANT-dependent H^+ flux can be promoted by long-chain fatty acids and by chemical uncouplers, and recent structural/electrophysiological work indicates that AAC/ANT itself is capable of H^+ transport under physiological modulatory conditions, where long-chain fatty acids promote and ADP/ATP restrain flux (Bertholet et al., 2019). Free fatty acids are also central modulators of mitochondrial leak: they act both as activators/co-factors of UCP-1 in BAT and, via protonophore-like cycling or protein-assisted transport models, as direct promoters of UCP-independent proton leak (Fedorenko et al., 2012). Mechanistic models (fatty acid cycling, fatty acid-assisted H^+ transport and protein-mediated shuttling) remain debated, but collectively they imply that free fatty acids and ANT can contribute to thermogenic proton conductance independent of UCP-1 (Bertholet et al., 2019; Wojtczak & Wieckowski, 1999). Collectively, these findings outline plausible pathways by which cold exposure could influence metabolic, vascular and anti-oxidant programmes; however, durable health benefits attributable to CWI alone remain to be demonstrated in humans.

The role of PGC-1α in cold-induced molecular pathways. Thermoregulatory control operates through three main pathways: the sensory afferent axis, the thermoregulatory control centre and the efferent pathways. According to contemporary thermoregulatory models, a negative feedback mechanism continuously regulates core body temperature. Deep (core) temperature serves as the main feedback signal and control variable in this system. The feedback arises from temperature-sensitive neurons in the brain or TRP channels located in the brain, spinal cord and visceral organs. Additionally, skin temperature acts as a fast-responding secondary feedback signal, mediated by TRP channels in the skin, offering either negative or positive control (Romanovsky, 2014; Werner, 2010). On the other hand, some theories suggest that feedforward mechanisms control thermoregulatory responses, in which variations in skin temperature set off cold-defence reactions (Morrison, 2016; Nakamura, 2024). An example of such a feedforward mechanism in thermoregulation is when a sudden drop in skin temperature triggers shivering and vasoconstriction before core body temperature begins to decline. It has been suggested that each cold-defence effector response (i.e. vasomotor tone, BAT, and shivering thermogenesis) is thought to be regulated independently. Each effector is influenced by unique combinations of core temperature and skin temperature inputs (Haman & Blondin, 2017). Cold exposure triggers a complex physiological stress response that involves both thermoregulatory and neuro-endocrine systems (Fig. 3). In addition to activating peripheral thermogenic mechanisms, cold acts as a potent stimulus for the release of β-endorphins, endogenous opioids synthesized in the pituitary gland as part of the hypothalamic–pituitary–adrenal axis activation. This release is thought to be initiated via sympathetic–adrenergic pathways and corticotropin-releasing hormone signalling, contributing to analgesia and improved mood during cold exposure (Esperland et al., 2022; Shevchuk, 2007).

β-adrenergic signalling pathways. Cold stimulation leads to the release of noradrenaline from the sympathetic nervous system which initiates adrenergic signalling via β-adrenergic receptors (Liu et al., 2019). β-adrenergic receptors are mostly coupled to Gs protein and activate adenylyl cyclase, which synthesizes cyclic adenosine monophosphate (cAMP) (Pidoux & Taskén, 2010). It has been postulated that cAMP promotes the production of interferon regulatory factor 4 (IRF4) in BAT (Kong et al., 2014). This cytokine in turn mediates UCP-1 expression through interaction with PGC-1α (Kong et al., 2014, 2018). cAMP activates cAMP-dependent protein kinase A (PKA) and downstream targets, such as p38 mitogen-activated protein kinases (MAPK) and CREB (Cao et al., 2004; Liu et al., 2017; Shi & Collins, 2017). p38 MAPK phosphorylates nuclear factor activating transcription factor 2 (ATF 2), which enhances the transcription of PGC-1α (Cao et al., 2004). The zinc-finger protein Zfp516 is induced by cold stimulation through the CREB/ATF2 pathway, mediated by PKA (Dempersmier et al., 2015). Finally, the activated p38 MAPK activates myocyte enhancer factor 2 (MEF2) (Abu Shelbayeh et al., 2023) and can directly phosphorylate

PGC-1α, thereby enhancing its transcription-regulating activity (Cao et al., 2004).

Thyroid hormone crosstalk. In addition to the intracellular signalling cascades triggered by β-adrenergic stimulation, systemic endocrine responses play a crucial role in cold adaptation. Among these, thyroid hormones have long been recognized as central regulators of thermogenesis. The hypothalamic–pituitary–thyroid axis tightly regulates circulating thyroid hormone levels through a negative feedback mechanism (Fliers et al., 2014; Joseph-Bravo et al., 2015). The thyroid gland primarily produces thyroxine (T4), with smaller amounts of the biologically active hormone 3,3′,5-triiodothyronine (T3). Notably, in many tissues, the enzyme type 2 deiodinase (D2) converts T4 into T3 (van der Spek et al., 2017). Cold exposure strongly stimulates the hypothalamic–pituitary–thyroid axis, increasing thyrotropin-releasing hormone synthesis, thyroid-stimulating hormone release and circulating thyroid hormone levels. Together, these changes promote thermogenesis and facilitate cold adaptation (Zhang et al., 2018) with elevated levels of T3 and T4 in the blood during cold adaptation (Eastman et al., 1974). Moreover, generation of T3 in target tissue not only raises the basal metabolic rate but also synergizes with β-adrenergic signalling to drive UCP-1 expression. Specifically, T3 acts via the receptor subtype T3Rβ1 to potentiate adrenergic induction of UCP-1 and D2 (Martinez de Mena et al., 2010). Moreover, hypothyroidism significantly reduced UCP-3 levels (by around 70%), a fatty acid transporter and thermoregulator, in skeletal muscle, while hyper-

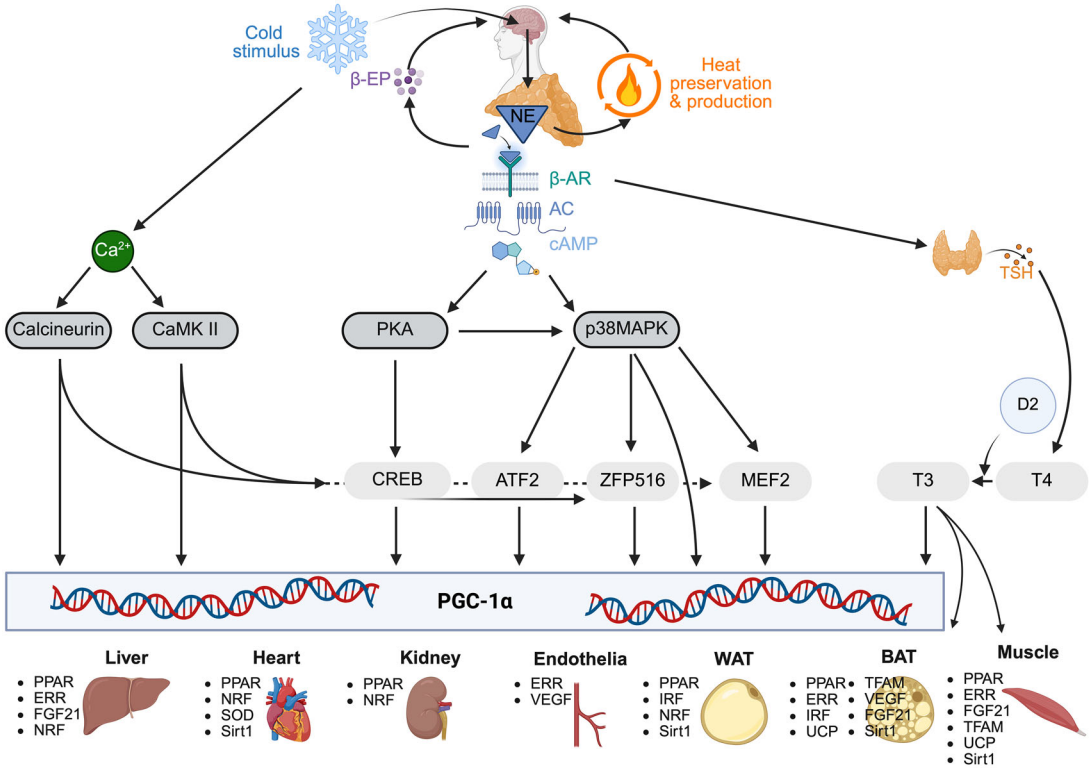

Figure 3. Putative cold-induced activation of thermogenic and metabolic pathways via PGC-1α
Cold stimuli triggers the release of noradrenaline (NE) and β-endorphines (β-EP), activating β-adrenergic receptors (AR) → adenyl cyclase (AC), and cyclic adenosine monophosphate (cAMP), protein kinase (PKA), p38 mitogen-activated protein kinases (p38 MAPK) and subsequent intracellular signalling cascades involving calcium (Ca^{2+}) → calcineurin and calcium/calmodulin-stimulated protein kinase II (CaMK II). These pathways stimulate transcription factors (cAMP responsive element-binding protein (CREB), activating transcription factor 2 (ATF2), myocyte enhancer factor 2 (MEF2), and the zinc-finger protein 516 (ZFP516)) which upregulates PGC-1α. Thyroid-stimulating hormone (TSH) via type 2 deiodinase (D2) increases local T3, upregulating PGC-1α expression with a direct influence on uncoupling protein (UCP) expression. Ultimately, the cold-stimulus promotes tissue-specific adaptations in several tissues like liver, heart kidney, endothelium, white adipose tissue (WAT), brown adipose tissue (BAT) and muscle tissue, enhancing energy metabolism and contributing to beneficial health effects. PPAR: peroxisome proliferator-activated receptor, ERR: oestrogen-related receptors, IRF: interferon regulatory factor 4, FGF21: fibroblast growth factor 21, TFAM: mitochondrial transcription factor A, VEGF: vascular endothelial growth factor, NRF: nuclear respiratory factors, SOD: superoxide dismutase, Sirt1: Sirutin 1, WAT, white adipose tissue, BAT, brown adipose tissue.

thyroidism induced a sixfold increase in UCP-3 levels in rats (Gong et al., 1997). Consistent with this, T3 injections increased UCP-3 expression fivefold in skeletal muscles and fourfold in WAT and BAT (Gong et al., 1997). Today T3 is known to stimulate UCP-1 and UCP-3 expression in various tissues, enhancing the adrenergic response. Thus, enhanced deiodination of T4 to T3 during cold exposure amplifies the adrenergic upregulation of UCPs, leading to heat production to facilitate rapid thermogenesis (Tsibulnikov et al., 2020).

Calcium-dependent and adrenergic independent pathways. PGC-1α activation is influenced by crosstalk with various other pathways. For example, the increased expression of PGC-1α induced by raising cytosolic Ca^{2+} levels is mediated by calcium/calmodulin-stimulated protein kinase II (CaMK II), the predominant CaMK isoform in skeletal muscle (Zhang et al., 2014). Moreover, Ca^{2+}-mediated PGC-1α expression is likely regulated in part through the phosphatase calcineurin, which activates transcriptional factors involved in mitochondrial biogenesis and muscle adaptation (Ihsan, Watson, & Abbiss, 2014). In the context of cold adaptation, a significant (around 50%) increase in basal muscle Ca^{2+} levels in mice exposed to prolonged cold, accompanied by no significant change in AMP-activated protein kinase (AMPK) phosphorylation was reported (Bruton et al., 2010). AMPK is a key energy sensor that can also activate PGC-1α under metabolic stress, such as exercise or nutrient deprivation. AMPK is activated under conditions of low cellular energy (high AMP/ATP ratio), e.g. when ATP consumption outpaces production during intense muscle contraction (exercise), hypoxia or ischaemic stress (Carling, 2004; Hardie, 2003; Mulligan et al., 2007). However, the lack of AMPK activation in the study above suggests that Ca^{2+}-dependent signalling may act independently of AMPK to stimulate PGC-1α during cold adaptation. This hypothesis is supported by findings that multiple signalling pathways activated during muscle contraction, such as those involving CaMK II (Zhang et al., 2014) and calcineurin (Ihsan, Watson, & Abbiss, 2014), can stimulate PGC-1α independently of adrenergic input. Both kinases influence transcriptional regulators like MEF2 and CREB, which promote PGC-1α expression (Booth et al., 2015; Fernandez-Marcos & Auwerx, 2011). Interestingly, this Ca^{2+}-driven regulatory mechanism resembles intracellular signalling events triggered by exercise, where repeated muscle contractions increase cytosolic Ca^{2+}, activating CaMK II and calcineurin pathways (Fernandez-Marcos & Auwerx, 2011; Zhang et al., 2014). While these mechanisms are not exclusive to cold exposure, they may be particularly relevant in shivering thermogenesis or cold-exercise interventions, where skeletal muscle activity plays a key role in thermogenic adaptation (Booth et al., 2015; Fernandez-Marcos & Auwerx, 2011; Ihsan, Watson, & Abbiss, 2014; Zhang et al., 2014).

Health benefits of cold exposure

Figure 4 depicts a deliberately speculative model of potential molecular cascades initiated by CWI that could converge on PGC-1α and downstream processes (mitochondrial biogenesis, substrate switching, angiogenesis, antioxidant and immune modulation). The directional arrows represent plausible mechanistic links identified in the literature, which are supported to varying degrees by: (1) acute molecular/hormonal responses measured in humans, (2) studies combining CWI with exercise interventions, and (3) preclinical or *in vitro* experiments. Because the evidence base is heterogenous and predominantly relies on acute exposures and animal models, these arrows do not imply causal relationships, and translational validity remains to be demonstrated.

Mitochondrial biogenesis. Mitochondrial biogenesis can be defined as the making of new components of the mitochondrial reticulum (Miller & Hamilton, 2012). Mitochondrial transcription is stimulated by PGC-1α, PGC-1β and PGC-1-related co-activator, with PGC-1α being considered the master regulator of mitochondrial biogenesis. On the other hand, PGC-1α is strictly controlled on two levels: by transcriptional factors and external stressors (which could potentially include cold exposure) on the transcriptional level, and secondly through post-translational modifications, such as acetylation, phosphorylation, methylation or ubiquitination on the post-translational level (Di et al., 2018; Fernandez-Marcos & Auwerx, 2011). Activation of PGC-1α stimulates the expression of NRF1 and NRF2 which in turn promote nuclear-encoded mitochondrial transcription factor A (TFAM) expression (Irrcher et al., 2008; Olesen et al., 2010). TFAM translocates to mitochondria, where it initiates mitochondrial-DNA transcription and replication (Onyango et al., 2021). Although CWI has been shown to acutely increase PGC-1α mRNA expression in skeletal muscle (Ihsan, Watson, et al., 2014; Ihsan et al., 2015; Slivka et al., 2012, 2013), there is currently no direct evidence that this translates into higher mitochondrial content or improved mitochondrial respiratory capacity in humans, since increased PGC-1α levels do not necessarily translate to mitochondrial biogenesis changes (Miller & Hamilton, 2012).

The SIRT1 gene, which encodes sirtuine 1 (Sirt1), an NAD^+-dependent histone deacetylase, is known as a 'longevity gene' and is crucial for mitochondrial protein deacetylation (Wang et al., 2018). Sirt1-mediated deacetylation of PGC-1α is thought to enhance its activity

and promote mitochondrial quality and biogenesis. Additionally, Sirt1 interacts with AMPK, further linking energy-sensing pathways to mitochondrial regulation (Xu et al., 2021).

Angiogenesis. Blood flow is crucial for maintaining the oxygen and nutrients required for energy production. ATP is the primary energy source used by cells and it is most efficiently produced by (oxygen-dependent) OXPHOS. OXPHOS occurs in mitochondria, the main producers of ATP, in which the oxidation of substrates (e.g. glucose) yields energy in the form of ATP (Bonora et al., 2012; Glancy et al., 2021; Herzig & Shaw, 2018).

The endothelium is responsible for modulating the vascular tone by producing vasoactive substances that either constrict or dilate vessels (Kadlec et al., 2016). Nitric oxide (NO) has a vasodilatory effect on the endothelial smooth muscle cells. Pathologies where NO bioavailability is reduced, for example if increased ROS levels react with NO or disrupt NO production, lead to impaired endothelial dilatation (Davignon & Ganz, 2004; Kubo et al., 1991). Mitochondrial dysfunction is a contributing factor to endothelial dysfunction, mainly through excessive production of ROS (Davidson & Duchen, 2007; Kluge et al., 2013).

NO and PGC-1α interact to regulate ROS levels, though their interplay is complex (Borniquel et al., 2006). In the short term, NO suppresses PGC-1α expression, reducing mitochondrial antioxidant defence activity. Conversely, prolonged exposure to NO enhances antioxidant defences by promoting PGC-1α expression. This temporal regulation of antioxidant pathways via PGC-1α may explain the dual roles of NO as both a pro-oxidant and an antioxidant (Patel et al., 2000).

The formation of new blood vessels, known as angiogenesis, is an important physiological process for wound healing, growth and reproduction (Swerlick, 1995). Disruption in angiogenesis regulation can contribute to the pathogenesis of various diseases ranging from cancer and arthritis, to ischaemia and neurodegeneration (Tahergorabi & Khazaei, 2012). The therapeutic use of angiogenesis has been investigated extensively, especially as a potential treatment for ischaemic disorders (Fallah et al., 2019; Tahergorabi & Khazaei, 2012). Growth factors, such as vascular endothelial growth factor (VEGF) are pro-angiogenic signals that induce the process of angiogenesis (Chen

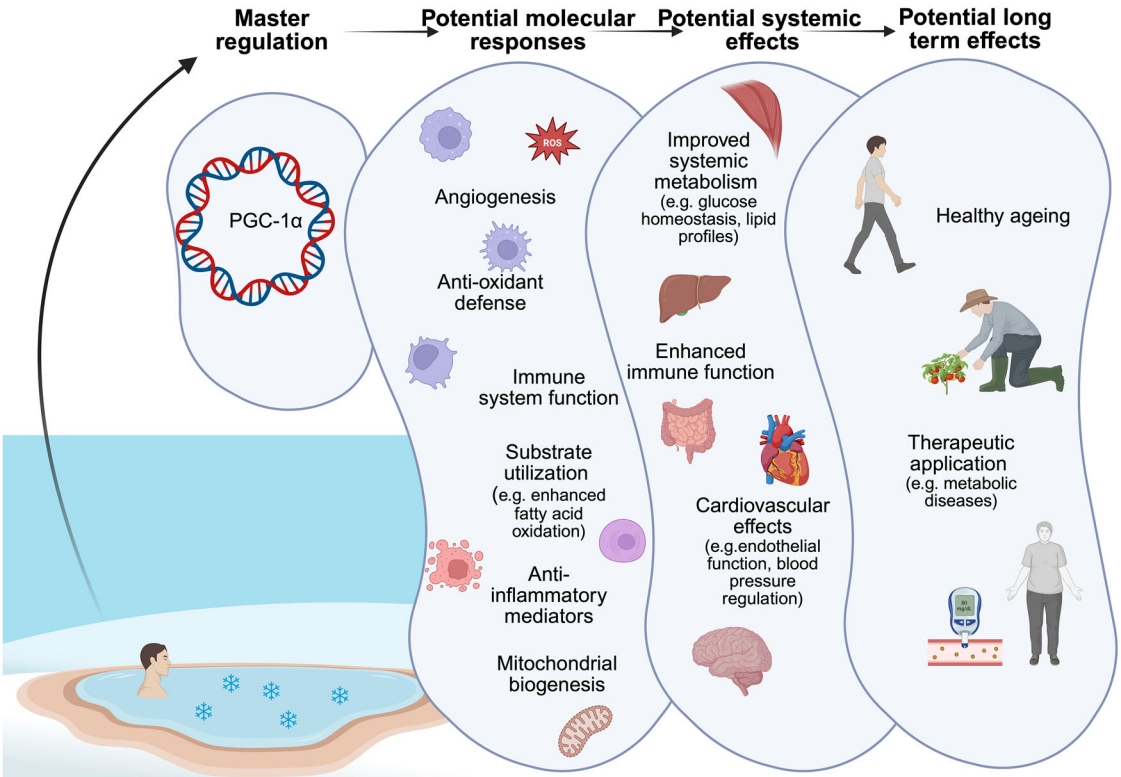

Figure 4. Hypothetical model: potential molecular pathways linking cold-water immersion-induced PGC-1α activity to downstream effects
Cold triggers adrenergic, Ca^{2+}-dependent and thyroid-related signalling which can activate PGC-1α, which may coordinate pathways related to mitochondrial biogenesis, substrate switching toward fatty acid oxidation, angiogenesis, anti-inflammatory mediators, antioxidant defenses and immune modulation.

et al., 2025). Blood vessel formation itself is a complex physiological process (Karvinen et al., 2011) that upon stimulation is regulated by the coordination of a multitude of cellular processes by 'master regulators', such as hypoxia inducible factors (HIFs) (Burtscher et al., 2023). These transcription factors induce the expression of hundreds of genes necessary for adaptations to environmental stressors, such as hypoxia (Tirpe et al., 2019). HIFs have been identified to regulate the expression of various pro-angiogenic factors, including VEGF (Chen et al., 2009). The regulation of VEGF in response to hypoxia is thought to be mediated primarily through HIF-1α and HIF-2α (Ferrara et al., 2003). However, expression of VEGF can also be HIF-independent; for example, driven by ERRα coactivation (Rowe et al., 2010). PGC-1α can co-activate ERRα on conserved binding sites found in the promoter and in a cluster within the first intron of the VEGF gene (Arany et al., 2008). Thus, PGC-1α could potentially serve as a therapeutic agent for treating ischaemic diseases by elevating angiogenesis and improving blood flow in the affected tissues (Chinsomboon et al., 2009; Rowe et al., 2014). During four weeks of endurance training, regular post-exercise CWI application increased PGC-1α protein and several mitochondrial proteins (Ihsan et al., 2015). However, these data do not directly demonstrate angiogenesis or increased capillarity; they indicate upstream signalling compatible with such adaptations. Even though exercise is thought to be a powerful stimulus to induce PGC-1α expression, PGC-1α mRNA upregulation was not present in non-cold-immersed limbs, but in cold-immersed legs (Ihsan, W et al., 2014). This observation might suggest that the response could be mediated by cold-induced mechanisms, such as increased β-adrenergic activity (Hensel & Boman, 1960).

Consistent with the initial discovery as 'cold-inducible' factor, a growing body of literature from rodents (Oliveira et al., 2004; Stancic et al., 2013) and humans (Ihsan et al., 2015; Slivka et al., 2013) shows that acute and repeated exposure to cold environments might have the potential to upregulate PGC-1α expression. Evidence cited for increased capillary density with cold exposure derives from breath-hold divers *versus* active controls (Bae et al., 2003), a cross-sectional comparison with potential confounding by apnoea/hyperbaric stimuli and training status. Thus, it cannot serve as direct evidence that CWI *per se* increases capillary density, an effect thought to be mediated through the regulatory role of PGC-1α in promoting VEGF, the primary pro-angiogenic factor in skeletal muscle (Chinsomboon et al., 2009). Additionally, Joo and colleagues tested the hypothesis that both passive and post-exercise CWI increases PGC-1α and VEGF mRNA expression in human skeletal muscle (Joo et al., 2016). Passive CWI acutely increased PGC-1α and VEGF mRNA levels (Joo et al., 2016), but mRNA changes do not necessarily indicate increased VEGF protein, angiogenic signalling *in vivo*, or structural angiogenesis, in the context of notable post-transcriptional regulation. Although β-adrenergic activity may affect PGC-1α expression in human skeletal muscle, the precise mechanisms remain to be clarified; notably, Miura and colleagues interrogated β-adrenergic/exercise signalling rather than CWI specifically, so extrapolation to cold water *per se* is limited (Miura et al., 2007). In human skeletal muscle fibres, PGC-1α expression can be directly enhanced by increased intracellular cAMP, PKA activation/phosphorylation, and CREB binding to the PGC-1α promoter (Fernandez-Marcos & Auwerx, 2011; Puigserver & Spiegelman, 2003; Wu et al., 1999). Likewise, in both muscle and vascular endothelial cells, VEGF expression may be potentiated via β-adrenergic signalling through PGC-1α and ERRα (Chinsomboon et al., 2009). In summary, based on current data, there is no direct evidence that CWI increases angiogenesis or capillary density in either animal models or humans; available findings are largely limited to acute transcriptional responses (e.g. VEGF mRNA) and indirect/mechanistic inferences.

Fatty acid metabolism. To reduce and offset heat loss to the environment, humans, when exposed to cold, must increase cold-defence mechanisms that both produce and conserve heat. Accordingly, cold water increases the metabolic rate by 275 and 45 W in individuals with low and moderate body fat, respectively (Tikuisis et al., 1988). In healthy men living in typical summer conditions (ambient temperatures of 20–30°C with no deliberate cold exposure), 31 days of cold air exposure (∼12°C, 8 h per day) reduced skin temperature by ∼ 80% and whole-body heat generation by ∼ 15% (Davis, 1961). In another study, unacclimatized men that completed 4 weeks of daily compensable cold exposure (2 h per day at 10°C, 5 days per week) (Blondin et al., 2017) underwent a standardized acute cold challenge in the same liquid-conditioned suit (10°C). During that post-acclimation cold exposure, shivering thermogenesis was ∼ 20% lower than it had been in the identical cold challenge conducted before acclimation, despite matching whole-body heat production. Furthermore, the authors demonstrated that BAT volume and thermogenic capability rose by 45% and 182%, respectively, after cold acclimation and concurrently decreased skeletal muscle proton leak by combining isotopic and nuclear imaging techniques in these same subjects (Blondin et al., 2017). Moreover, cold exposure induces sympathetic nervous system activity and BAT metabolism in humans and can result in improved glucose metabolism without affecting pancreatic insulin secretion (Iwen et al., 2017). The metabolic and general health benefits arising from

metabolic adaptation and increased energy expenditure during cold applications are therefore important topics for future research.

In response to cold-induced stress, PGC-1α activates NRF1 and NRF2, which in turn drive the expression of nuclear-encoded mitochondrial genes such as TFAM, which is essential for mDNA replication and transcription (Ranasinghe et al., 2023), increasing oxidative capacity and favouring fatty acid-supported ATP production. These pathways are consistent with cold-evoked transcriptional programmes but do not by themselves demonstrate functional mitochondrial gains after CWI. Additionally, PGC-1α increases the expression of enzymes involved in fatty acid oxidation, such as carnitine palmitoyltransferase 1 (CPT1), which facilitates the entry of long-chain fatty acids into mitochondria for β-oxidation (Miura et al., 2014). The cold-related AMPK pathway increases glucose uptake and fatty acid oxidation in skeletal muscle cells to increase ATP production (Hayashi et al., 1998; Kurth-Kraczek et al., 1999). The arcuate, dorsomedial, paraventricular, and ventromedial nuclei, as well as the lateral hypothalamus and preoptic area, are some of the hypothalamic neurons that control thermogenesis and energy expenditure (Dimicco & Zaretsky, 2007; López & Tena-Sempere, 2017). When exposed to cold, the preoptic area of the hypothalamus becomes active and signals to neurons in the ventromedial nuclei, causing AMPK to become inactive and causing sympathetic outflow in the direction of BAT (Contreras et al., 2015; López & Tena-Sempere, 2017). There are two distinct ways whereby AMPK (in)activation and BAT are related: (1) through intracellular AMPK activation in brown adipocytes or (2) through downregulation of AMPK in the hypothalamus (van der Vaart et al., 2021). As mentioned above, AMPK activity mostly reflects the whole-body energy balance and raises energy levels through sympathetic nervous system outflow to metabolic organs like BAT, whereas AMPK activity in brown adipocytes is caused by a local energy deficiency (López, 2018; van Dam et al., 2015). When hypothalamic AMPK is inhibited, a signalling cascade is triggered, which leads to the excretion of noradrenaline near brown adipocytes (van der Vaart et al., 2021). Through noradrenaline binding to β2-adrenergic receptors in humans (or β3 in rodents) on the surface of brown adipocytes, intracellular cAMP rises via Gs-activated adenylyl cyclase, which activates PKA to phosphorylate lipases and trigger lipolysis; AMPK activation follows as an indirect response to the energetic changes, not by direct receptor binding or PKA phosphorylation (van Dam et al., 2015).

The PPARα pathway is also upregulated during cold exposure, regulating the expression of genes involved in fatty acid transport and oxidation. Upon cold-induced activation, PPARα increases the transcription of enzymes such as CPT1 and acetyl-CoA carboxylase, which enhance the breakdown of fatty acids for ATP production (Zhang et al., 2014). Cold exposure activated noradrenaline release and binding to β-adrenergic receptors stimulate the enzyme hormone-sensitive lipase to further promote lipolysis. This process generates free fatty acids that fuel the thermogenic process in BAT. Fibroblast growth factor 21 (FGF21), a hormone that regulates metabolism through various pathways to activate UCP-1, is involved in promoting the use of fat for energy by enhancing lipolysis and fatty acid oxidation (Chau et al., 2024). It also supports mitochondrial biogenesis in tissues like BAT and skeletal muscle, further facilitating thermogenesis. Mild cold exposure increases circulating FGF21 levels in humans, which is associated with enhanced lipolysis and cold-induced thermogenesis, suggesting that FGF21 could play a role in metabolic adaptations to cold environments (Lee et al., 2013). However, these results were observed during stays in cold climate chambers and not in cold water. Increased serum FGF21 levels were also detected after CWI, and were linked to increased BAT activation (Hanssen et al., 2015). Taken together, these pathways, AMPK activation, PPARα signalling, noradrenaline-induced lipolysis in BAT, UCP1-mediated thermogenesis, and FGF21 production work in concert to enhance fatty acid oxidation, thermogenesis and overall energy expenditure, supporting the body's adaptive response to cold exposure. Taken together, these mechanisms plausibly favour fatty acid oxidation and thermogenesis, but durable metabolic benefits from CWI alone remain to be established.

Redox regulation. Oxidative stress, inflammation, disease and ageing are strongly related. Oxidative stress can increase inflammation, and both are frequently higher in diseased and older individuals. CWI has been shown to positively impact the immune system by raising the metabolic rate and elevating catecholamine plasma concentrations (Huttunen et al., 2001; Leppäluoto et al., 2008). Regular CWI may also improve oxidative stress indicators and have some cardioprotective effects (Kralova Lesna et al., 2015), although this result was derived from a cross-sectional study between cold adapted swimmers and healthy controls. Any causal relationships remain to be demonstrated.

The immune system's response to common non-infectious stressors following CWI has been examined in a number of studies. In one study (Janský et al., 1996), plasma concentrations of interleukin (IL)-6, total T lymphocytes (CD3), T helper cells (CD4), T suppressor cells (CD8) and activated T and B lymphocytes increased after 6 weeks of consistent 1 h CWI at 14°C. α1-antitrypsin's plasma concentration decreased in the same investigation. While the evidence that

cold-water exposure modulates autonomic, vascular and metabolic responses is derived from interventional studies showing robust catecholamine surges and thermogenic activation during CWI, causal relationships of CWI and inflammation remain uncertain. However, observational cohorts of winter swimmers suggest associations with favourable lipid and inflammatory profiles (Sramek et al., 2000). IL-6 levels were considerably greater after a brief CWI period after an exercise session than during post-exercise rest at room temperature, according to a study examining the effects of this treatment (Pawłowska et al., 2021). IL-6 is the best investigated myokine, released in response to exercise stimuli and contributing to beneficial exercise adaptations (Severinsen & Pedersen, 2020). The cold -induced sympathetic activation and associated release of catecholamines such as noradrenaline stimulate β-adrenergic receptors on BAT and other tissues, triggering thermogenesis and via the upregulation of UCPs enhancing mitochondrial heat production. This in turn raises the production of ROS as byproducts of mitochondrial respiration. Although ROS are essential signalling molecules, excessive ROS production can lead to oxidative stress, which can damage cellular structures, including proteins, lipids and DNA. To counteract this, the body activates several protective mechanisms, with PGC-1α being a key player in regulating oxidative stress (Rius-Pérez et al., 2020).

Cold-induced PGC-1α activation and transcription relies on various signalling pathways, including AMPK and noradrenaline. Once activated, PGC-1α coordinates the expression of a wide range of genes involved in mitochondrial biogenesis and oxidative metabolism. This includes the upregulation of mitochondrial respiratory chain complexes, enhancing the capacity of mitochondria to generate ATP through OXPHOS. PGC-1α also plays a crucial role in protecting cells from oxidative stress by regulating the expression of antioxidant enzymes. One of the primary mechanisms by which PGC-1α mitigates oxidative damage is by increasing the transcription of genes involved in the cellular antioxidant response (Iacovelli et al., 2016). These include manganese superoxide dismutase (MnSOD) which in mitochondria converts superoxide radicals into hydrogen peroxide (Liu et al., 2022); catalase which decomposes hydrogen peroxide into water and oxygen (Heck et al., 2010), further reducing oxidative stress; and glutathione peroxidase which reduces hydrogen peroxide to water (Lubos et al., 2011), providing additional protection against oxidative damage. By upregulating these antioxidants, PGC-1α helps to balance the increased ROS production induced by enhanced mitochondrial activity during cold exposure, preventing cellular damage and maintaining cellular homeostasis. PGC-1α also acts as a co-activator for NRF1 and NRF2, two transcription factors that are crucial for mitochondrial function and the antioxidant response (Aquilano et al., 2013). Cold exposure enhances the activation of NRF1, which regulates the expression of mitochondrial respiratory chain genes, further enhancing mitochondrial oxidative capacity (Chung et al., 2017). PGC-1α's activation of NRF1 and NRF2 enhances mitochondrial biogenesis while simultaneously supporting the cellular antioxidant defence system, ensuring that the cold-induced increase in ROS does not overwhelm cellular defences.

Collectively, these mechanisms could increase systemic metabolism with potential cardioprotective effects, which might be used for therapeutic and healthy ageing purposes. Most of these outcomes are based on acute signalling or preclinical data and direct confirmation of functional improvements in humans following CWI is largely lacking.

Health risks of cold-water immersion

Cold water can provide beneficial health outcomes but also poses risks. Sudden stimulation of the peripheral cutaneous cold receptors can lead to the occurrence of a cold-shock response (Tipton, 1989), including a strong gasp response, uncontrollable hyperventilation, tachycardia and an increase in circulating stress hormones. Initiated by the dynamic response through sudden stimulation of the peripheral cold receptors, the physiological effects peak in the first 30 s of immersion and adapt over the first 2 min (Tipton & Bradford, 2014). This loss of the control of breathing alongside with aspiration of a small volume of water can result in drowning (Bierens et al., 2016; Tipton & Bradford, 2014). Water temperatures of around 10°C are already associated with similarly high risks of such hazardous responses like when being immersed in 5°C cold water (Tipton et al., 1991). Habituation to the cold-shock response can increase chances of survival, by reducing the strong physiological response and thereby the risk of water inhalation and drowning. Several studies demonstrated consistently the body's ability to reduce this stress response after the 4th or 5th exposure to cold water (Eglin & Tipton, 2005; Tipton et al., 1998, 2000). Some habituation to cold sensation and cold pain appears to occur already after the first or second trial (Smith et al., 2009). However, current evidence does not indicate that progressive increase in intensity (colder water), duration or frequency is required to retain cardiometabolic or mental benefits of CWI (Cain et al., 2025). Rather, regularity appears to be sufficient. On the other hand, given the rapid habituation of the ventilatory and cardiac components of the cold-shock response, a modest adjustment of stimulus parameters over time (e.g. slightly colder water, longer exposure, or greater body surface area) may be necessary to maintain a minimum physiological load. Importantly, current evidence does not

establish that this minimum effective dose must elicit a cold-shock response; whether provoking a cold-shock response is required for health-relevant adaptations remains unresolved. Progression can be considered if one seeks to preserve acute cold-shock magnitude but is not mandated by available data (Barwood et al., 2024). However, cold habitation also includes potential threats as it can produce so-called hypothermic habituation in which individuals lose their perceptual and physiological responses to cooling. The individual's shivering response is reduced and one feels paradoxically more comfortable as the body's core temperature continues to fall (Tipton, 2019).

If a person is able to control breathing following 2 min of cold exposure, the individual has to counteract the musculoskeletal impairment caused by neuromuscular cooling and interrupted nerve conduction (Castellani & Tipton, 2016). The arms are particularly susceptible to such impairments due to their surface area-to-mass ratio and the relatively superficial anatomical location of nerves and muscles (Bierens et al., 2016). Since the conduction velocity of the ulnar nerve falls by 15 m/s/10°C fall in local temperature, nerve block can occur at a temperature of 5–15°C for 1–15 min, leading to fatigue and a reduction in force production (Tipton & Golden, 2006). This is a particular problem when people immerse themselves occupationally in cold water, far away from the shore. As a consequence, drowning can be caused by physical incapacity and can occur before core temperature falls below 35°C (Bierens et al., 2016). However, even on exposure to severe cold stress (1°C water), an adult of average adiposity is unlikely to become hypothermic within 20 min (Stocks et al., 2004), although several factors like general health, body composition, morphology, sex, age, predisposing factors (e.g. pre-existing conditions) and exercising during exposure significantly modify the cold response (Esperland et al., 2022; Stocks et al., 2004). Tipton and colleagues established a model for the prediction of survival time in cold water (Tipton et al., 2022). The established 'maximum observed immersed search time' (MOIST) relationship is intended to (1) provide a means to incorporate knowledge of observed extreme survival possibilities, and (2) convey to search and rescue managers that in the absence of other information (e.g. that the victim may be aboard a raft or have gone ashore), the extent to which historic case information supports the assumption that the victim may still be alive. The functional expression for MOIST in hours is (Tipton et al., 2022):

$$MOIST = 5.75 \times exp\left(0.1 \times \text{sea surface temperature } [\text{in}^{\circ}\text{C}]\right)$$

This formula is based on the longest known survival cases in various water temperatures and includes a safety margin to accommodate human variability. It was designed not to be a prediction of typical survival time, but a 'not-to-exceed' estimate, essentially serving as a guide for the point beyond which it becomes unrealistic to expect someone to remain alive in the water. Lott and colleagues described the classic stages of hypothermia based on clinical signs that can lead to cardiac arrest. These can be found in Table 1 (Lott et al., 2021).

A large number of deaths may be attributable to arrhythmias initiated on immersion by the coincidental activation of the sympathetic and parasympathetic division of the autonomic nervous system by stimulation of cutaneous cold receptors around the body, called autonomic conflict (Shattock & Tipton, 2012). Perhaps one of the most powerful and reproducible ways of inducing the autonomic conflict described above is by rapid submersion in cold water (<15°C) with attempted breath-holding (Shattock & Tipton, 2012). Observed arrhythmias include predominantly supraventricular/junctional arrythmias, short bursts of ventricular tachycardia interposed between periods of bradycardia, supraventricular ectopics, and atrioventricular blocks (Datta & Tipton, 2006; Tipton et al., 1994). Shattock and colleagues have defined various predisposing factors for the occurrence of such fatal arrythmias during CWI. These are highlighted in Table 2 (Shattock & Tipton, 2012).

Practical implications

'Hormesis' is a key evolutionary and physiological concept that includes biological plasticity responses and well-preserved stress defence mechanisms. It is defined as a biphasic (or triphasic, see below) phenomenon, with low-dose stimulation providing health-promoting effects and high-dose inhibition producing negative effects (Mattson, 2008). Cold water elicits a range of physiological responses, with both acute and adaptive mechanisms that primarily support thermoregulation but have crucial implications for metabolism, cardiovascular health and oxidative stress/inflammation management. The physiological responses can be categorized as hormesis-like responses, since regular cold-water exposures may induce protective plastic adaptations, while too long exposure to severe cold water entails substantial health risks, including death. Molecular mechanisms frequently implicated in cold adaptation, include mitochondrial biogenesis, angiogenesis, shifts in cellular metabolism, modulation of oxidative stress and inflammatory signalling pathways, with PGC-1α often being positioned as a central regulator. These mechanisms, however, mostly lack validation in humans, an important challenge for future research. While they may provide a mechanistic rationale for possible improvements in thermogenic capacity,

Table 1. Categories of hypothermia from Lott and colleagues

	Clinical findings	Estimated core temperature (°C)
Hypothermia I (mild)	Conscious, shivering*	35 to 32°C
Hypothermia II (moderate)	Impaired consciousness*, may or may not be shivering	<32 to 28°C
Hypothermia III (severe)	Unconscious*, vital signs present	<28°C
Hypothermia IV (severe)	Apparent death, vital signs absent	Classically <24°C**

*Shivering or consciousness may be impaired by comorbid conditions such as trauma, central nervous system conditions, toxins or drugs, such as sedative-hypnotic drugs or opioids, independent of core temperature.
**Cardiac arrest can occur at earlier or later stages of hypothermia. Some patients may have vital signs with core temperatures <24°C.

Table 2. Predisposing conditions associated with autonomic conflict during cold-water immersion

- Channelopathies (Long QT syndrome)
- Atherosclerosis
- QT interval does not match the prevailing heart rate
- Acquired (drug-induced) long QT syndrome
- Myocardial hypertrophy
- Ischaemic heart disease

metabolic efficiency, and antioxidant defence following controlled CWI, direct causal confirmation of these adaptations in humans, especially following repeated or regular CWI remains limited.

Neuroprotective pathways may be activated by mild environmental stressors (Burtscher et al., 2022), such as cold, leading to reductions in neuroinflammation and neurodegenerative processes, potentially through neurohormesis (Arumugam et al., 2006; Calabrese et al., 2018; Sahebnasagh et al., 2022). In a study involving mice, the RNA-binding motif protein 3 (known as a 'cold-shock protein') was overexpressed in the hippocampus (Peretti et al., 2015). This resulted in sustained synaptic protection for both prion disease-infected mice and those with Alzheimer's disease mutations when subjected to a cooling protocol. While the translational potential of, especially genetically modified, rodent models of human neurological diseases has limitations, these results indicate that CWI could be neuroprotective and thus might reduce the risk of developing neurodegenerative diseases (Esperland et al., 2022).

In response to cold exposure, the body engages thermoregulatory processes including vasoconstriction, shivering and non-shivering thermogenesis, primarily via BAT (van der Lans et al., 2013). Cold stress activates a transcriptional network centred on the co-activator PGC-1α, and involving downstream factors such as NRF1, NRF2 and ERRα which together drive upregulation of UCPs and mitochondrial biogenesis in human skeletal muscle (Joo et al., 2016; Zak et al., 2017). Repeated cold exposures also promote angiogenic signalling via upregulation of VEGF mRNA in human skeletal muscle following passive CWI (Joo et al., 2016), thereby improving vascular adaptation and oxygen delivery. From a metabolic perspective, acute and repeated cold-water immersion activates AMPK in human skeletal muscle, observed by increased AMPK phosphorylation following post-exercise cold-water baths (10 min at 10°C) in healthy adults (Allan et al., 2017). Although direct measurements of PPAR activation after CWI are scarce, passive CWI alone upregulates PGC-1α mRNA, the primary co-activator of PPARα/γ, implying downstream PPAR signalling and enhanced fatty-acid oxidation in human muscle (Joo et al., 2016). The antioxidative benefits of cold adaptation have likewise been demonstrated in human CWI protocols: winter swimmers exhibit elevated activities of catalase, glutathione peroxidase and SOD after repeated immersions (Park et al., 2021; Wesołowski et al., 2023). These upregulated enzymatic defences may mitigate ROS-induced damage, curb inflammation and may underlie the neuroprotective and cardiovascular resilience noted in habitual cold-water practitioners (Esperland et al., 2022; Ivanova & Blondin, 2021; Knechtle et al., 2020). One promising phenomenon that might partially explain the positive effects of cold water on health-related factors is cross-adaptation. This type of adaptation has been demonstrated, for example, in a study in which habituating the sympathetic nervous response to CWI also enhanced the body's reaction to moderate exercise in hypoxic conditions (Lunt et al., 2010). Despite these promising physiological benefits, several knowledge gaps remain. A critical limitation of the field is that the vast majority of studies have examined acute responses to a single or a few bouts of CWI, often focusing on transient changes in signalling molecules such as PGC-1α, AMPK or VEGF. Chronic studies that isolate the long-term effects of CWI alone, without concurrent exercise, are

virtually absent. This gap makes it difficult to determine whether acute molecular responses translate into persistent adaptations or health benefits. Future research should prioritize longitudinal interventions to establish whether repeated CWI yields durable improvements in mitochondrial content, vascular function, or systemic metabolism. The dose–response relationship between water temperature, immersion duration, and health outcomes requires further investigation to optimize CWI protocols. However, interesting findings suggest that during short-term stress, multiple physiological systems are activated to enable survival. Dhabhar and colleagues hypothesized that just as the short-term stress response (e.g. psychological stress in the face of danger) prepares the cardiovascular, musculoskeletal and neuroendocrine system for fight-or-flight, under certain conditions, stress responses may be required to prepare the body (e.g. immune system) for challenges (e.g. wounding or infection) that may be imposed by a potentially noxious stimulus (Dhabhar & McEwen, 1997; Dhabhar et al., 1995). Cold-water stress might be such a stressor, activating protective mechanisms that may not only reduce future cold-water risk but possibly have other beneficial effects as well (e.g. cross-adaptation for other extreme environments). On the other side, chronic or long-lasting (e.g. psychological or environmental) stress can be harmful, leading to deleterious effects (e.g. on the immune system) (Dhabhar, 2014). Therefore, we hypothesize that extensive and long-lasting cold-water baths, where a lot of heat energy is lost, and stress is produced, might not stimulate the desired health benefit, especially if combined with, for example, other environmental stressors, psychological stress or an already compromised immune system. It is important to note that there are significant individual differences in stress perception, processing, appraisal and coping strategies (Dhabhar & McEwen, 2007; Gunnar & Quevedo, 2007). To reap health benefits, it seems plausible that adequate regeneration periods are required after CWI. The extent and efficiency with which an organism returns to its resting zone and can regenerate after stress depends on resilience, which is defined as the capacity of psychophysiological systems to recover from challenging conditions. Psychological and physiological resilience factors determine the overall effects of stress on an individual (Dhabhar, 2009; Dhabhar & McEwen, 2007). Circadian cortisol rhythm evaluations might be of special interest in this context as the dysregulation of this rhythm is one marker that appears to coincide with the deleterious effects of chronic stress (Dhabhar & McEwen, 1997; Sephton & Spiegel, 2003). Indeed, Eimonte and colleagues showed that even a single cold bath in resting conditions with 14°C for 10 min led to increased cortisol levels compared with the control group up to 12 h post-immersion (Eimonte et al., 2021). On the other side, repeated activity in cold water also demonstrated abnormal daily cortisol variations in winter swimmers, leading to potential immunosuppression (Loria et al., 2014). Although the optimal cold-water dose for health benefits remains unknown and certainly depends on individual resilience factors, it is likely that shorter immersion times at appropriate times during the day (e.g. due to the sympathetic effects not closely before sleeping) may lead to more beneficial effects than longer exposures (Tipton et al., 2017). Based on the above-mentioned findings, a summary of the hypothetical triphasic dose–response curve of cold-water immersions on systemic health outcomes is presented in Fig. 5 with considerations for safe cold-water immersion given in Table 3.

In summary, cold exposure might trigger distinct transcriptional programmes in several organs like BAT and WAT, skeletal muscle, the cardiovascular system and the intestines. Cold-induced factors (such as PGC-1α, ERRs and IRF4) may synergistically enhance mitochondrial biogenesis and upregulate UCP1 expression, promoting non-shivering thermogenesis. PPARα/γ and FGF21 (mainly a hepatokine, but in stress situations also expressed in other tissues) facilitate fatty acid mobilization and improve glucose uptake. Concurrently, TFAM and VEGF could contribute to mitochondrial proliferation and angiogenesis, respectively, to meet the increased energetic demands associated with physiological temperature-regulation responses. Enhanced mitochondrial respiration elevates ROS production, which is counteracted by antioxidant systems regulated by nuclear factor erythroid 2-related factor 2 and SOD activity. These coordinated cellular and systemic adaptations contribute to increased energy expenditure and may improve metabolic health outcomes following repeated CWI.

Although CWI shows promise as a non-pharmacological approach for metabolic and cardiovascular health, the current evidence is largely preliminary. Future research should clarify the long-term health outcomes in humans, delineate mechanistic pathways including dose–response relationships, assess the translational relevance of findings from animal and combined-intervention studies and, in particular, establish standardized and optimized CWI protocols to test whether such exposures can reproducibly elicit health-promoting physiological adaptations. We recommend randomized, adequately powered trials that evaluate CWI alone (not combined with exercise) over sufficiently long interventions ($\geq$6–12 weeks for mitochondrial or performance endpoints), use pre-specified primary outcomes tied to organelle function (e.g. high-resolution mitochondrial respirometry, citrate synthase activity, mDNA copy number, or other clinically relevant endpoints such as insulin sensitivity), and include rigorous safety monitoring. To improve the

Table 3. Consideration before cold-water immersion for health purposes

- Medical health check even for young and healthy persons
- Free of predisposing factors for heart arrhythmias (see Table 2)
- Enter the water slowly to reduce cold water shock
- Perform head-out immersion without breath holding to reduce risk of autonomic conflict
- Habituate to cold water
- Feeling comfortable in cold water may be treacherous especially when already well habituated
- Stay near the shore
- Do not perform cold-water immersion alone
- Limit the exposure to severe cold to 10 min to reduce the risk of significant neuromuscular cooling
- Consider environmental conditions during immersion and when getting out

robustness and reproducibility of the results, monitoring relevant physiological parameters will be crucial. Those may include – besides the measurement of metabolic, cardiovascular, respiratory, haematological and immunological parameters – in particular, changes in core body temperature and skin temperature. Currently there are no widely accepted guidelines regarding levels and thresholds related to these parameters in CWI.

Based on the currently low level of evidence of mechanistic underpinnings of health benefits of CWI,

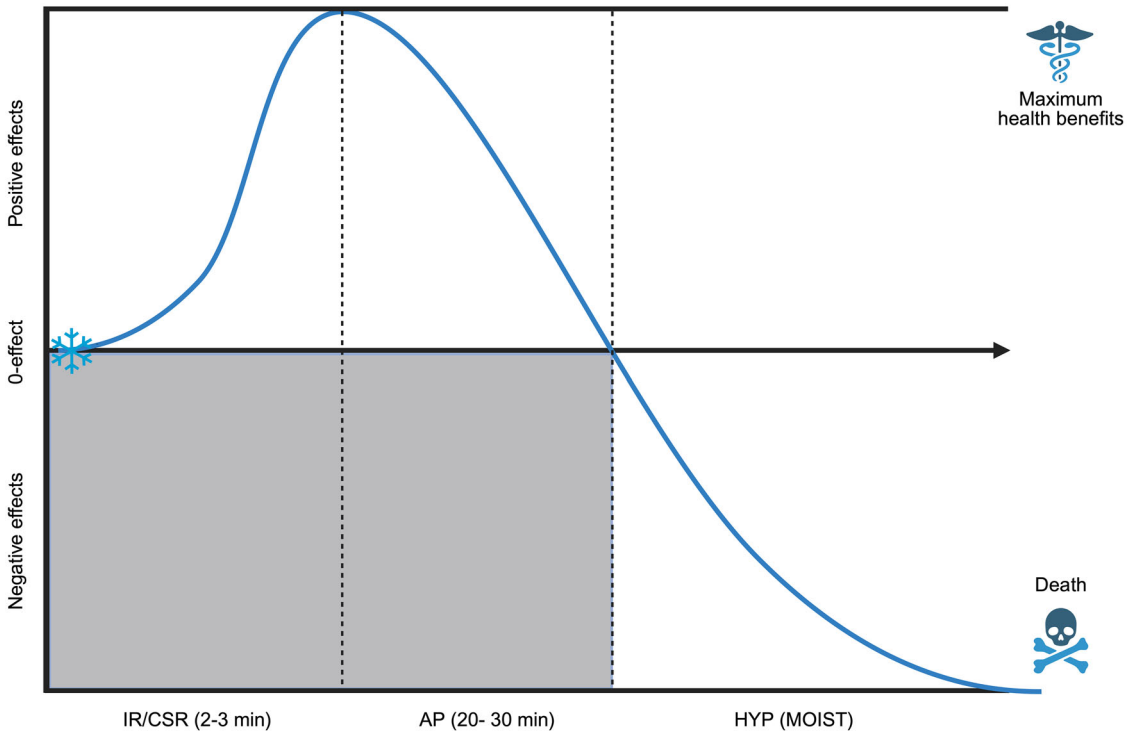

Figure 5. Assumed triphasic dose–response relationship model following cold-water immersion
The response to cold-water exposure follows a triphasic pattern. Initially, a null-effect zone is observed immediately after exposure to the thermal stimulus. This is followed by a 'therapeutic zone', characterized by physiological benefits that occur in the early phase of the cold-shock response (CSR)/initial response (IR) and the subsequent early adaptation phase (AP). The therapeutic effect peaks within these windows. Prolonged exposure beyond the body's capacity to maintain thermal homeostasis diminishes these benefits, leading to a progressive loss of therapeutic efficacy. Upon surpassing the threshold into hypothermia (HYP), cold stress induces deleterious effects, ultimately progressing toward a life-threatening state with continued exposure. The MOIST formula provides an estimate of the maximum permissible immersion time before fatal outcomes are likely, although significant health benefits are no longer present at such prolonged durations. The grey shaded area indicates that fatal reactions can already occur in the IR/CSR and AP stadium, especially if the factors listed in Table 3 are not considered.

including potential mitochondrial improvements, our synthesis should be read as a framework to identify mechanistic targets and to guide the design of future, adequately powered interventions. Moreover, we hope that the present review facilitates the development of a clearer framework and guidelines for future research on CWI.

References

Abu Shelbayeh, O., Arroum, T., Morris, S., & Busch, K. B. (2023). PGC-1α Is a master regulator of mitochondrial lifecycle and ROS stress response. *Antioxidants (Basel)*, **12**(5), 1075.

Alba, B. K., Castellani, J. W., & Charkoudian, N. (2019). Cold-induced cutaneous vasoconstriction in humans: Function, dysfunction and the distinctly counterproductive. *Experimental Physiology*, **104**(8), 1202–1214.

Allan, R., Malone, J., Alexander, J., Vorajee, S., Ihsan, M., Gregson, W., Kwiecien, S., & Mawhinney, C. (2022). Cold for centuries: A brief history of cryotherapies to improve health, injury and post-exercise recovery. *European Journal of Applied Physiology*, **122**(5), 1153–1162.

Allan, R., Sharples, A. P., Close, G. L., Drust, B., Shepherd, S. O., Dutton, J., Morton, J. P., & Gregson, W. (2017). Post-exercise cold water immersion modulates skeletal muscle PGC-1α mRNA expression in immersed and nonimmersed limbs: Evidence of systemic regulation. *Journal of Applied Physiology*, **123**(2), 451–459.

Aquilano, K., Baldelli, S., Pagliei, B., Cannata, S. M., Rotilio, G., & Ciriolo, M. R. (2013). p53 orchestrates the PGC-1α-mediated antioxidant response upon mild redox and metabolic imbalance. *Antioxid Redox Signaling*, **18**(4), 386–399.

Arany, Z., Foo, S. Y., Ma, Y., Ruas, J. L., Bommi-Reddy, A., Girnun, G., Cooper, M., Laznik, D., Chinsomboon, J., Rangwala, S. M., Baek, K. H., Rosenzweig, A., & Spiegelman, B. M. (2008). HIF-independent regulation of VEGF and angiogenesis by the transcriptional coactivator PGC-1alpha. *Nature*, **451**(7181), 1008–1012.

Arumugam, T. V., Gleichmann, M., Tang, S.-C., & Mattson, M. P. (2006). Hormesis/preconditioning mechanisms, the nervous system and aging. *Ageing Research Reviews*, **5**(2), 165–178.

Audet-walsh, É., & Giguére, V. (2015). The multiple universes of estrogen-related receptor α and γ in metabolic control and related diseases. *Acta Pharmacologica Sinica*, **36**(1), 51–61.

Baar, K., Wende, A. R., Jones, T. E., Marison, M., Nolte, L. A., Chen, M., Kelly, D. P., & Holloszy, J. O. (2002). Adaptations of skeletal muscle to exercise: Rapid increase in the transcriptional coactivator PGC-1. *Federation of American Societies for Experimental Biology Journal*, **16**(14), 1879–1886.

Bae, K. A., An, N. Y., Kwon, Y. W., Kim, C., Yoon, C. S., Park, S. C., & Kim, C. K. (2003). Muscle fibre size and capillarity in Korean diving women. *Acta Physiologica Scandinavica*, **179**(2), 167–172.

Bartlett, J. D., Hwa Joo, C., Jeong, T. S., Louhelainen, J., Cochran, A. J., Gibala, M. J., Gregson, W., Close, G. L., Drust, B., & Morton, J. P. (2012). Matched work high-intensity interval and continuous running induce similar increases in PGC-1α mRNA, AMPK, p38, and p53 phosphorylation in human skeletal muscle. *Journal of Applied Physiology*, **112**(7), 1135–1143.

Bartlett, J. D., Louhelainen, J., Iqbal, Z., Cochran, A. J., Gibala, M. J., Gregson, W., Close, G. L., Drust, B., & Morton, J. P. (2013). Reduced carbohydrate availability enhances exercise-induced p53 signaling in human skeletal muscle: Implications for mitochondrial biogenesis. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, **304**(6), R450–R458.

Barwood, M. J., Eglin, C., Hills, S. P., Johnston, N., Massey, H., McMorris, T., Tipton, M. J., Wakabayashi, H., & Webster, L. (2024). Habituation of the cold shock response: A systematic review and meta-analysis. *Journal of Thermal Biology*, **119**, 103775.

Bertholet, A. M., Chouchani, E. T., Kazak, L., Angelin, A., Fedorenko, A., Long, J. Z., Vidoni, S., Garrity, R., Cho, J., Terada, N., Wallace, D. C., Spiegelman, B. M., & Kirichok, Y. (2019). H^+ transport is an integral function of the mitochondrial ADP/ATP carrier. *Nature*, **571**(7766), 515–520.

Bierens, J. J., Lunetta, P., Tipton, M., & Warner, D. S. (2016). Physiology of drowning: A review. *Physiology (Bethesda, Md.)*, **31**, 147–166.

Bleakley, C. M., Bieuzen, F., Davison, G. W., & Costello, J. T. (2014). Whole-body cryotherapy: Empirical evidence and theoretical perspectives. *Open Access Journal of Sports Medicine*, **5**, 25–36.

Bleakley, C., McDonough, S., Gardner, E., Baxter, G. D., Hopkins, J. T., & Davison, G. W. (2012). Cold-water immersion (cryotherapy) for preventing and treating muscle soreness after exercise. *The Cochrane Database of Systematic Reviews*, **2**, CD008262.

Blondin, D. P., Daoud, A., Taylor, T., Tingelstad, H. C., Bézaire, V., Richard, D., Carpentier, A. C., Taylor, A. W., Harper, M. E., Aguer, C., & Haman, F. (2017). Four-week cold acclimation in adult humans shifts uncoupling thermogenesis from skeletal muscles to brown adipose tissue. *The Journal of Physiology*, **595**(6), 2099–2113.

Blondin, D. P., & Haman, F. (2018). Chapter 10 - shivering and nonshivering thermogenesis in skeletal muscles. In A. A. Romanovsky (Ed.), *Handbook of clinical neurology* (pp. 153–173). Elsevier.

Bonora, M., Patergnani, S., Rimessi, A., De Marchi, E., Suski, J. M., Bononi, A., Giorgi, C., Marchi, S., Missiroli, S., Poletti, F., Wieckowski, M. R., & Pinton, P. (2012). ATP synthesis and storage. *Purinergic Signal*, **8**(3), 343–357.

Booth, F. W., Ruegsegger, G. N., Toedebusch, R. G., & Yan, Z. (2015). Chapter six - endurance exercise and the regulation of skeletal muscle metabolism. In C. Bouchard (Ed.), *Progress in molecular biology and translational science* (pp. 129–151). Academic Press.

Borniquel, S., Valle, I., Cadenas, S., Lamas, S., & Monsalve, M. (2006). Nitric oxide regulates mitochondrial oxidative stress protection via the transcriptional coactivator PGC-1alpha. *Federation of American Societies for Experimental Biology Journal*, **20**(11), 1889–1891.

Brand, M. D., Pakay, J. L., Ocloo, A., Kokoszka, J., Wallace, D. C., Brookes, P. S., & Cornwall, E. J. (2005). The basal proton conductance of mitochondria depends on adenine nucleotide translocase content. *Biochemical Journal*, **392**(2), 353–362.

Brazaitis, M., Eimantas, N., Daniuseviciute, L., Mickeviciene, D., Steponaviciute, R., & Skurvydas, A. (2014). Two strategies for response to 14°C cold-water immersion: Is there a difference in the response of motor, cognitive, immune and stress markers? *PLoS ONE*, **9**(10), e109020.

Bruton, J. D., Aydin, J., Yamada, T., Shabalina, I. G., Ivarsson, N., Zhang, S. J., Wada, M., Tavi, P., Nedergaard, J., Katz, A., & Westerblad, H. (2010). Increased fatigue resistance linked to Ca^{2+}-stimulated mitochondrial biogenesis in muscle fibres of cold-acclimated mice. *The Journal of Physiology*, **588**(21), 4275–4288.

Burtscher, J., Hohenauer, E., Burtscher, M., Millet, G. P., & Egg, M. (2023). Environmental and behavioral regulation of HIF-mitochondria crosstalk. *Free Radical Biology and Medicine*, **206**, 63–73.

Burtscher, J., Romani, M., Bernardo, G., Popa, T., Ziviani, E., Hummel, F. C., Sorrentino, V., & Millet, G. P. (2022). Boosting mitochondrial health to counteract neuro-degeneration. *Progress in Neurobiology*, **215**, 102289.

Cadenas, S. (2018). Mitochondrial uncoupling, ROS generation and cardioprotection. *Biochimica et Biophysica Acta (BBA) - Bioenergetics*, **1859**(9), 940–950.

Cai, Q., Lin, T., Kamarajugadda, S., & Lu, J. (2013). Regulation of glycolysis and the Warburg effect by estrogen-related receptors. *Oncogene*, **32**(16), 2079–2086.

Cain, T., Brinsley, J., Bennett, H., Nelson, M., Maher, C., & Singh, B. (2025). Effects of cold-water immersion on health and wellbeing: A systematic review and meta-analysis. *PLoS ONE*, **20**(1), e0317615.

Calabrese, V., Santoro, A., Monti, D., Crupi, R., Di Paola, R., Latteri, S., Cuzzocrea, S., Zappia, M., Giordano, J., Calabrese, E. J., & Franceschi, C. (2018). Aging and Parkinson's Disease: Inflammaging, neuroinflammation and biological remodeling as key factors in pathogenesis. *Free Radical Biology and Medicine*, **115**, 80–91.

Cannon, P., & Keatinge, W. R. (1960). The metabolic rate and heat loss of fat and thin men in heat balance in cold and warm water. *The Journal of Physiology*, **154**(2), 329–344.

Cao, W., Daniel, K. W., Robidoux, J., Puigserver, P., Medvedev, A. V., Bai, X., Floering, L. M., Spiegelman, B. M., & Collins, S. (2004). p38 mitogen-activated protein kinase is the central regulator of cyclic AMP-dependent transcription of the brown fat uncoupling protein 1 gene. *Molecular and Cellular Biology*, **24**(7), 3057–3067.

Carling, D. (2004). The AMP-activated protein kinase cascade–a unifying system for energy control. *Trends in Biochemical Sciences*, **29**(1), 18–24.

Castellani, J. W., & Tipton, M. J. (2016). Cold stress effects on exposure tolerance and exercise performance. In *Comprehensive Physiology* (pp. 443–469). Wiley.

Castellani, J. W., & Young, A. J. (2016). Human physiological responses to cold exposure: Acute responses and acclimatization to prolonged exposure. *Autonomic Neuroscience*, **196**, 63–74.

Chao, Y. C., Chen, C. C., Lin, Y. C., Breer, H., Fleischer, J., & Yang, R. B. (2015). Receptor guanylyl cyclase-G is a novel thermosensory protein activated by cool temperatures. *European Molecular Biology Organization Journal Journal*, **34**(3), 294–306.

Charkoudian, N. (2010). Mechanisms and modifiers of reflex induced cutaneous vasodilation and vasoconstriction in humans. *Journal of Applied Physiology*, **109**(4), 1221–1228.

Chau, P. K., Ryan, E., Dalen, K. T., & Haugen, F. (2024). Timing of acute cold exposure determines UCP1 and FGF21 expression - possible interactions between the thermal environment, thermoregulatory responses, and peripheral clocks. *Journal of Thermal Biology*, **124**, 103938.

Checinska-Maciejewska, Z., Miller-Kasprzak, E., Checinska, A., Korek, E., Gibas-Dorna, M., Adamczak-Ratajczak, A., Bogdanski, P., & Krauss, H. (2017). Gender-related effect of cold water swimming on the seasonal changes in lipid profile, ApoB/ApoA-I ratio, and homocysteine concentration in cold water swimmers. *Journal of Physiology and Pharmacology*, **68**(6), 887–896.

Chen, L., Endler, A., & Shibasaki, F. (2009). Hypoxia and angiogenesis: Regulation of hypoxia-inducible factors via novel binding factors. *Experimental & Molecular Medicine*, **41**(12), 849.

Chen, T., Wang, K., & Sun, Z. (2025). New insights into the role of ubiquitination in angiogenesis (Review). *International Journal of Molecular Medicine*, **55**(2), 32.

Chinsomboon, J., Ruas, J., Gupta, R. K., Thom, R., Shoag, J., Rowe, G. C., Sawada, N., Raghuram, S., & Arany, Z. (2009). The transcriptional coactivator PGC-1alpha mediates exercise-induced angiogenesis in skeletal muscle. *Proceedings of the National Academy of Sciences of the United States of America*, **106**(50), 21401–21406.

Chung, N., Park, J., & Lim, K. (2017). The effects of exercise and cold exposure on mitochondrial biogenesis in skeletal muscle and white adipose tissue. *Journal of exercise nutrition & biochemistry*, **21**(2), 39–47.

Clarke, D. H. (1963). Effect of immersion in hot and cold water upon recovery of muscular strength following fatiguing isometric exercise. *Archives of Physical Medicine and Rehabilitation*, **44**, 565–568.

Contreras, C., Gonzalez, F., Fernø, J., Diéguez, C., Rahmouni, K., Nogueiras, R., & López, M. (2015). The brain and brown fat. *Annals of Medicine*, **47**(2), 150–168.

Craig, A. B., Jr., & Dvorak, M. (1966). Thermal regulation during water immersion. *Journal of Applied Physiology*, **21**(5), 1577–1585.

Datta, A., & Tipton, M. (2006). Respiratory responses to cold water immersion: Neural pathways, interactions, and clinical consequences awake and asleep. *Journal of Applied Physiology*, **100**(6), 2057–2064.

Davidson, S. M., & Duchen, M. R. (2007). Endothelial mitochondria: Contributing to vascular function and disease. *Circulation Research*, **100**(8), 1128–1141.

Davignon, J., & Ganz, P. (2004). Role of endothelial dysfunction in atherosclerosis. *Circulation*, **109**, (23_suppl_1), Iii27–Iii32.

Davis, T. R. (1961). Chamber cold acclimatization in man. *Report / U.S. Army Medical Research Laboratory*, **475**, 1–8.

Dempersmier, J., Sambeat, A., Gulyaeva, O., Paul, S. M., Hudak, C. S., Raposo, H. F., Kwan, H. Y., Kang, C., Wong, R. H., & Sul, H. S. (2015). Cold-inducible Zfp516 activates UCP1 transcription to promote browning of white fat and development of brown fat. *Molecular Cell*, **57**(2), 235–246.

Dhabhar, F. S. (2009). Enhancing versus suppressive effects of stress on immune function: Implications for immunoprotection and immunopathology. *Neuroimmunomodulation*, **16**(5), 300–317.

Dhabhar, F. S. (2014). Effects of stress on immune function: The good, the bad, and the beautiful. *Immunologic Research*, **58**(2–3), 193–210.

Dhabhar, F. S., & McEwen, B. S. (1997). Acute stress enhances while chronic stress suppresses cell-mediated immunity in vivo: A potential role for leukocyte trafficking. *Brain, Behavior, and Immunity*, **11**(4), 286–306.

Dhabhar, F. S., Miller, A. H., McEwen, B. S., & Spencer, R. L. (1995). Effects of stress on immune cell distribution. Dynamics and hormonal mechanisms. *Journal of Immunology*, **154**(10), 5511–5527.

Dhabhar, F., & McEwen, B. (2007). Bi-directional effects of stress on immune function: Possible explanations for salubrious as well as harmful effects. *Psychoneuroimmunology, Two-Volume Set*, **2**, 723–760.

Di, W., Lv, J., Jiang, S., Lu, C., Yang, Z., Ma, Z., Hu, W., Yang, Y., & Xu, B. (2018). PGC-1: The energetic regulator in cardiac metabolism. *Current Issues in Molecular Biology*, **28**, 29–46.

Dimicco, J. A., & Zaretsky, D. V. (2007). The dorsomedial hypothalamus: A new player in thermoregulation. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, **292**(1), R47–R63.

Donadelli, M., Dando, I., Fiorini, C., & Palmieri, M. (2014). UCP2, a mitochondrial protein regulated at multiple levels. *Cellular and Molecular Life Sciences*, **71**(7), 1171–1190.

Eastman, C. J., Ekins, R. P., Leith, I. M., & Williams, E. S. (1974). Thyroid hormone response to prolonged cold exposure in man. *The Journal of Physiology*, **241**(1), 175–181.

Eddy, S. F., & Storey, K. B. (2003). Differential expression of Akt, PPARgamma, and PGC-1 during hibernation in bats. *Biochemistry and Cell Biology*, **81**(4), 269–274.

Egan, B., Carson, B. P., Garcia-Roves, P. M., Chibalin, A. V., Sarsfield, F. M., Barron, N., McCaffrey, N., Moyna, N. M., Zierath, J. R., & O'Gorman, D. J. (2010). Exercise intensity-dependent regulation of peroxisome proliferator-activated receptor coactivator-1 mRNA abundance is associated with differential activation of upstream signalling kinases in human skeletal muscle. *The Journal of Physiology*, **588**(10), 1779–1790.

Eglin, C. M., & Tipton, M. J. (2005). Repeated cold showers as a method of habituating humans to the initial responses to cold water immersion. *European Journal of Applied Physiology*, **93**(5–6), 624–629.

Eimonte, M., Henrikas, P., Laura, D., Nerijus, E., Astra, V., Gintare, D., Rima, S., & Brazaitis, M. (2021). Residual effects of short-term whole-body cold-water immersion on the cytokine profile, white blood cell count, and blood markers of stress. *International Journal of Hyperthermia*, **38**(1), 696–707.

Esperland, D., de Weerd, L., & Mercer, J. B. (2022). Health effects of voluntary exposure to cold water - a continuing subject of debate. *International Journal of Circumpolar Health*, **81**(1), 2111789.

Fallah, A., Sadeghinia, A., Kahroba, H., Samadi, A., Heidari, H. R., Bradaran, B., Zeinali, S., & Molavi, O. (2019). Therapeutic targeting of angiogenesis molecular pathways in angiogenesis-dependent diseases. *Biomedicine & Pharmacotherapy*, **110**, 775–785.

Fedorenko, A., Lishko, P. V., & Kirichok, Y. (2012). Mechanism of fatty-acid-dependent UCP1 uncoupling in brown fat mitochondria. *Cell*, **151**(2), 400–413.

Fernandez-Marcos, P. J., & Auwerx, J. (2011). Regulation of PGC-1α, a nodal regulator of mitochondrial biogenesis. *American Journal of Clinical Nutrition*, **93**(4), 884S–90.

Ferrara, N., Gerber, H. P., & LeCouter, J. (2003). The biology of VEGF and its receptors. *Nature Medicine*, **9**(6), 669–676.

Fliers, E., Kalsbeek, A., & Boelen, A. (2014). Beyond the fixed setpoint of the hypothalamus-pituitary-thyroid axis. *European Journal of Endocrinology*, **171**(5), R197–R208.

Fuchs, C. J., Kouw, I. W. K., Churchward-Venne, T. A., Smeets, J. S. J., Senden, J. M., Lichtenbelt, W., Verdijk, L. B., & van Loon, L. J. C. (2020). Postexercise cooling impairs muscle protein synthesis rates in recreational athletes. *The Journal of Physiology*, **598**(4), 755–772.

Gibas-Dorna, M., Chęcińska, Z., Korek, E., Kupsz, J., Sowińska, A., & Krauss, H. (2016). Cold water swimming beneficially modulates insulin sensitivity in middle-aged individuals. *Journal of Aging and Physical Activity*, **24**(4), 547–554.

Gilde, A. J., van der Lee, K. A., Willemsen, P. H., Chinetti, G., van der Leij, F. R., van der Vusse, G. J., Staels, B., & van Bilsen, M. (2003). Peroxisome proliferator-activated receptor (PPAR) alpha and PPARbeta/delta, but not PPARgamma, modulate the expression of genes involved in cardiac lipid metabolism. *Circulation Research*, **92**(5), 518–524.

Glancy, B., Kane, D. A., Kavazis, A. N., Goodwin, M. L., Willis, W. T., & Gladden, L. B. (2021). Mitochondrial lactate metabolism: History and implications for exercise and disease. *The Journal of Physiology*, **599**(3), 863–888.

Gong, D. W., He, Y., Karas, M., & Reitman, M. (1997). Uncoupling protein-3 is a mediator of thermogenesis regulated by thyroid hormone, beta3-adrenergic agonists, and leptin. *Journal of Biological Chemistry*, **272**(39), 24129–24132.

Gong, J., Liu, J., Ronan, E. A., He, F., Cai, W., Fatima, M., Zhang, W., Lee, H., Li, Z., Kim, G. H., Pipe, K. P., Duan, B., Liu, J., & Xu, X. Z. S. (2019). A cold-sensing receptor encoded by a glutamate receptor gene. *Cell*, **178**(6), 1375–1386.e1311.

Gordon, K., Blondin, D. P., Friesen, B. J., Tingelstad, H. C., Kenny, G. P., & Haman, F. (2019). Seven days of cold acclimation substantially reduces shivering intensity and increases nonshivering thermogenesis in adult humans. *Journal of Applied Physiology*, **126**(6), 1598–1606.

Gunnar, M., & Quevedo, K. (2007). The neurobiology of stress and development. *Annual Review of Psychology*, **58**, 145–173.

Haman, F., & Blondin, D. P. (2017). Shivering thermogenesis in humans: Origin, contribution and metabolic requirement. *Temperature (Austin)*, **4**(3), 217–226.

Haman, F., Souza, S. C. S., Castellani, J. W., Dupuis, M.-P., Friedl, K. E., Sullivan-Kwantes, W., & Kingma, B. R. M. (2022). Human vulnerability and variability in the cold: Establishing individual risks for cold weather injuries. *Temperature*, **9**(2), 158–195.

Handschin, C., & Spiegelman, B. M. (2006). Peroxisome proliferator-activated receptor gamma coactivator 1 coactivators, energy homeostasis, and metabolism. *Endocrine Reviews*, **27**(7), 728–735.

Hanssen, M. J., Broeders, E., Samms, R. J., Vosselman, M. J., van der Lans, A. A., Cheng, C. C., Adams, A. C., van Marken Lichtenbelt, W. D., & Schrauwen, P. (2015). Serum FGF21 levels are associated with brown adipose tissue activity in humans. *Scientific Reports*, **5**, 10275.

Hardie, D. G. (2003). Minireview: The AMP-activated protein kinase cascade: The key sensor of cellular energy status. *Endocrinology*, **144**(12), 5179–5183.

Hayashi, T., Hirshman, M. F., Kurth, E. J., Winder, W. W., & Goodyear, L. J. (1998). Evidence for 5' AMP-activated protein kinase mediation of the effect of muscle contraction on glucose transport. *Diabetes*, **47**(8), 1369–1373.

Heck, D. E., Shakarjian, M., Kim, H. D., Laskin, J. D., & Vetrano, A. M. (2010). Mechanisms of oxidant generation by catalase. *Annals of the New York Academy of Sciences*, **1203**, 120–125.

Hensel, H., & Boman, K. K. A. (1960). Afferent impulses in cutaneous sensory nerves in human subjects. *Journal of Neurophysiology*, **23**(5), 564–578.

Herzig, S., & Shaw, R. J. (2018). AMPK: Guardian of metabolism and mitochondrial homeostasis. *Nature Reviews Molecular Cell Biology*, **19**(2), 121–135.

Huss, J. M., Garbacz, W. G., & Xie, W. (2015). Constitutive activities of estrogen-related receptors: Transcriptional regulation of metabolism by the ERR pathways in health and disease. *Biochimica Et Biophysica Acta*, **1852**(9), 1912–1927.

Huttunen, P., Rintamäki, H., & Hirvonen, J. (2001). Effect of regular winter swimming on the activity of the sympathoadrenal system before and after a single cold water immersion. *International Journal of Circumpolar Health*, **60**(3), 400–406.

Iacovelli, J., Rowe, G. C., Khadka, A., Diaz-Aguilar, D., Spencer, C., Arany, Z., & Saint-Geniez, M. (2016). PGC-1α induces Human RPE oxidative metabolism and antioxidant capacity. *Investigative Ophthalmology & Visual Science*, **57**(3), 1038.

Ihsan, M., Markworth, J. F., Watson, G., Choo, H. C., Govus, A., Pham, T., Hickey, A., Cameron-Smith, D., & Abbiss, C. R. (2015). Regular postexercise cooling enhances mitochondrial biogenesis through AMPK and p38 MAPK in human skeletal muscle. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, **309**(3), R286–R294.

Ihsan, M., Watson, G., & Abbiss, C. (2014). PGC-1α mediated muscle aerobic adaptations to exercise, heat and cold exposure. *Cellular and Molecular Exercise Physiology*, **3**(1), e7.

Ihsan, M., Watson, G., Choo, H. C., Lewandowski, P., Papazzo, A., Cameron-Smith, D., & Abbiss, C. R. (2014). Post-exercise muscle cooling enhances gene expression of PGC-1α. *Medicine and Science in Sports and Exercise*, **46**(10), 1900–1907.

Irrcher, I., Ljubicic, V., Kirwan, A. F., & Hood, D. A. (2008). AMP-activated protein kinase-regulated activation of the PGC-1alpha promoter in skeletal muscle cells. *PLoS ONE*, **3**(10), e3614.

Ivanova, Y. M., & Blondin, D. P. (2021). Examining the benefits of cold exposure as a therapeutic strategy for obesity and type 2 diabetes. *Journal of Applied Physiology*, **130**(5), 1448–1459.

Iwen, K. A., Backhaus, J., Cassens, M., Waltl, M., Hedesan, O. C., Merkel, M., Heeren, J., Sina, C., Rademacher, L., Windjäger, A., Haug, A. R., Kiefer, F. W., Lehnert, H., & Schmid, S. M. (2017). Cold-induced brown adipose tissue activity alters plasma fatty acids and improves glucose metabolism in men. *The Journal of Clinical Endocrinology and Metabolism*, **102**(11), 4226–4234.

Janský, L., Pospísilová, D., Honzová, S., Ulicný, B., Srámek, P., Zeman, V., & Kamínková, J. (1996). Immune system of cold-exposed and cold-adapted humans. *European Journal of Applied Physiology and Occupational Physiology*, **72–72**(5–6), 445–450.

Ji, L. L., & Kang, C. (2015). Role of PGC-1α in sarcopenia: Etiology and potential intervention - a mini-review. *Gerontology*, **61**(2), 139–148.

Johnson, C. D., Melanaphy, D., Purse, A., Stokesberry, S. A., Dickson, P., & Zholos, A. V. (2009). Transient receptor potential melastatin 8 channel involvement in the regulation of vascular tone. *American Journal of Physiology-Heart and Circulatory Physiology*, **296**(6), H1868–H1877.

Johnson, J. M. (2007). Mechanisms of vasoconstriction with direct skin cooling in humans. *American Journal of Physiology Heart and Circulatory Physiology*, **292**(4), H1690–H1691.

Joo, C. H., Allan, R., Drust, B., Close, G. L., Jeong, T. S., Bartlett, J. D., Mawhinney, C., Louhelainen, J., Morton, J. P., & Gregson, W. (2016). Passive and post-exercise cold-water immersion augments PGC-1α and VEGF expression in human skeletal muscle. *European Journal of Applied Physiology*, **116**(11–12), 2315–2326.

Joseph-Bravo, P., Jaimes-Hoy, L., Uribe, R. M., & Charli, J. L. (2015). 60 Years of neuroendocrinology: TRH, the first hypophysiotropic releasing hormone isolated: Control of the pituitary-thyroid axis. *Journal of Endocrinology*, **227**(3), X3.

Kadlec, A. O., Chabowski, D. S., Ait-Aissa, K., & Gutterman, D. D. (2016). Role of PGC-1α in vascular regulation: Implications for atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **36**(8), 1467–1474.

Karvinen, H., Pasanen, E., Rissanen, T. T., Korpisalo, P., Vähäkangas, E., Jazwa, A., Giacca, M., & Ylä-Herttuala, S. (2011). Long-term VEGF-A expression promotes aberrant angiogenesis and fibrosis in skeletal muscle. *Gene Therapy*, **18**(12), 1166–1172.

Kelly, D. P., & Scarpulla, R. C. (2004). Transcriptional regulatory circuits controlling mitochondrial biogenesis and function. *Genes & Development*, **18**(4), 357–368.

Kim, J. C., Yi, H. K., Hwang, P. H., Yoon, J. S., Kim, H. J., Kawano, F., Ohira, Y., & Kim, C. K. (2005). Effects of cold-water immersion on VEGF mRNA and protein expression in heart and skeletal muscles of rats. *Acta Physiologica Scandinavica*, **183**(4), 389–397.

Kluge, M. A., Fetterman, J. L., & Vita, J. A. (2013). Mitochondria and endothelial function. *Circulation Research*, **112**(8), 1171–1188.

Knechtle, B., Waśkiewicz, Z., Sousa, C. V., Hill, L., & Nikolaidis, P. T. (2020). Cold water swimming-benefits and risks: A narrative review. *International Journal of Environmental Research and Public Health*, **17**(23), 8984.

Kong, X., Banks, A., Liu, T., Kazak, L., Rao, R. R., Cohen, P., Wang, X., Yu, S., Lo, J. C., Tseng, Y. H., Cypess, A. M., Xue, R., Kleiner, S., Kang, S., Spiegelman, B. M., & Rosen, E. D. (2014). IRF4 is a key thermogenic transcriptional partner of PGC-1α. *Cell*, **158**(1), 69–83.

Kong, X., Yao, T., Zhou, P., Kazak, L., Tenen, D., Lyubetskaya, A., Dawes, B. A., Tsai, L., Kahn, B. B., Spiegelman, B. M., Liu, T., & Rosen, E. D. (2018). Brown adipose tissue controls skeletal muscle function via the secretion of myostatin. *Cell Metabolism*, **28**(4), 631–643.e3.

Kralova Lesna, I., Rychlikova, J., Vavrova, L., & Vybiral, S. (2015). Could human cold adaptation decrease the risk of cardiovascular disease? *Journal of Thermal Biology*, **52**, 192–198.

Kubo, S. H., Rector, T. S., Bank, A. J., Williams, R. E., & Heifetz, S. M. (1991). Endothelium-dependent vasodilation is attenuated in patients with heart failure. *Circulation*, **84**(4), 1589–1596.

Kurth-Kraczek, E. J., Hirshman, M. F., Goodyear, L. J., & Winder, W. W. (1999). 5' AMP-activated protein kinase activation causes GLUT4 translocation in skeletal muscle. *Diabetes*, **48**(8), 1667–1671.

Kwan, K. Y., Allchorne, A. J., Vollrath, M. A., Christensen, A. P., Zhang, D. S., Woolf, C. J., & Corey, D. P. (2006). TRPA1 contributes to cold, mechanical, and chemical nociception but is not essential for hair-cell transduction. *Neuron*, **50**(2), 277–289.

Ledesma, A., de Lacoba, M. G., & Rial, E. (2002). The mitochondrial uncoupling proteins. *Genome Biology*, **3**(12), reviews3015.1.

Lee, P., Brychta, R. J., Linderman, J., Smith, S., Chen, K. Y., & Celi, F. S. (2013). Mild cold exposure modulates fibroblast growth factor 21 (FGF21) diurnal rhythm in humans: Relationship between FGF21 levels, lipolysis, and cold-induced thermogenesis. *The Journal of Clinical Endocrinology & Metabolism*, **98**(1), E98–E102.

Leppäluoto, J., Westerlund, T., Huttunen, P., Oksa, J., Smolander, J., Dugué, B., & Mikkelsson, M. (2008). Effects of long-term whole-body cold exposures on plasma concentrations of ACTH, beta-endorphin, cortisol, catecholamines and cytokines in healthy females. *Scandinavian Journal of Clinical and Laboratory Investigation*, **68**(2), 145–153.

Liang, H., & Ward, W. F. (2006). PGC-1alpha: A key regulator of energy metabolism. *Advances in Physiology Education*, **30**(4), 145–151.

Lima, T. I., Guimarães, D., Sponton, C. H., Bajgelman, M. C., Palameta, S., Toscaro, J. M., Reis, O., & Silveira, L. R. (2019). Essential role of the PGC-1α/pparβ axis in Ucp3 gene induction. *The Journal of Physiology*, **597**(16), 4277–4291.

Lin, J., Wu, H., Tarr, P. T., Zhang, C. Y., Wu, Z., Boss, O., Michael, L. F., Puigserver, P., Isotani, E., Olson, E. N., Lowell, B. B., Bassel-Duby, R., & Spiegelman, B. M. (2002). Transcriptional co-activator PGC-1 alpha drives the formation of slow-twitch muscle fibres. *Nature*, **418**, 797–801.

Lira, V. A., Benton, C. R., Yan, Z., & Bonen, A. (2010). PGC-1alpha regulation by exercise training and its influences on muscle function and insulin sensitivity. *American Journal of Physiology-Endocrinology and Metabolism*, **299**, E145–E161.

Liu, C. T., & Brooks, G. A. (2012). Mild heat stress induces mitochondrial biogenesis in C2C12 myotubes. *Journal of Applied Physiology*, **112**(3), 354–361.

Liu, F., Xiao, Y., Ji, X. L., Zhang, K. Q., & Zou, C. G. (2017). The cAMP-PKA pathway-mediated fat mobilization is required for cold tolerance in C. elegans. *Scientific Reports*, **7**(1), 638.

Liu, J., Wang, Y., & Lin, L. (2019). Small molecules for fat combustion: Targeting obesity. *Acta pharmaceutica Sinica. B*, **9**(2), 220–236.

Liu, L., Liu, J., Gao, Y., Yu, X., Xu, G., & Huang, Y. (2014). Uncoupling protein-2 mediates the protective action of berberine against oxidative stress in rat insulinoma INS-1E cells and in diabetic mouse islets. *British Journal of Pharmacology*, **171**(13), 3246–3254.

Liu, M., Sun, X., Chen, B., Dai, R., Xi, Z., & Xu, H. (2022). Insights into Manganese superoxide dismutase and Human diseases. *International Journal of Molecular Sciences*, **23**(24), 15893.

López, M. (2018). Hypothalamic AMPK and energy balance. *European Journal of Clinical Investigation*, **48**(9), e12996.

López, M., & Tena-Sempere, M. (2017). Estradiol effects on hypothalamic AMPK and BAT thermogenesis: A gateway for obesity treatment? *Pharmacology & Therapeutics*, **178**, 109–122.

Loria, P., Ottoboni, S., Michelazzi, L., Giuria, R., Ghisellini, P., & Rando, C. (2014). Salivary cortisol in an extreme non-competitive sport exercise: Winter swimming. *Natural Science*, **06**(06), 387–398.

Lott, C., Truhlář, A., Alfonzo, A., Barelli, A., González-Salvado, V., Hinkelbein, J., Nolan, J. P., Paal, P., Perkins, G. D., Thies, K. C., Yeung, J., Zideman, D. A., & Soar, J. (2021). European Resuscitation Council Guidelines 2021: Cardiac arrest in special circumstances. *Resuscitation*, **161**, 152–219.

Lubos, E., Loscalzo, J., & Handy, D. E. (2011). Glutathione peroxidase-1 in health and disease: From molecular mechanisms to therapeutic opportunities. *Antioxid Redox Signaling*, **15**(7), 1957–1997.

Lunt, H. C., Barwood, M. J., Corbett, J., & Tipton, M. J. (2010). 'Cross-adaptation': Habituation to short repeated cold-water immersions affects the response to acute hypoxia in humans. *The Journal of Physiology*, **588**(18), 3605–3613.

Manolis, A. S., Manolis, S. A., Manolis, A. A., Manolis, T. A., Apostolaki, N., & Melita, H. (2019). Winter swimming: Body hardening and cardiorespiratory protection via sustainable acclimation. *Current Sports Medicine Reports*, **18**(11), 401–415.

Martinez de Mena, R., Scanlan, T. S., & Obregon, M. J. (2010). The T3 receptor beta1 isoform regulates UCP1 and D2 deiodinase in rat brown adipocytes. *Endocrinology*, **151**(10), 5074–5083.

Mattson, M. P. (2008). Awareness of hormesis will enhance future research in basic and applied neuroscience. *Critical Reviews in Toxicology*, **38**(7), 633–639.

Medicine, I. O. (1996). *Nutritional Needs in Cold and High-Altitude Environments: Applications for Military Personnel in Field Operations*. National Academies Press.

Miller, B. F., & Hamilton, K. L. (2012). A perspective on the determination of mitochondrial biogenesis. *American Journal of Physiology-Endocrinology and Metabolism*, **302**(5), E496–E499.

Miura, S., Kawanaka, K., Kai, Y., Tamura, M., Goto, M., Shiuchi, T., Minokoshi, Y., & Ezaki, O. (2007). An increase in murine skeletal muscle peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) mRNA in response to exercise is mediated by β-adrenergic receptor activation. *Endocrinology*, **148**(7), 3441–3448.

Miura, S., Tadaishi, M., Kamei, Y., & Ezaki, O. (2014). Mechanisms of exercise- and training-induced fatty acid oxidation in skeletal muscle. *The Journal of Physical Fitness and Sports Medicine*, **3**(1), 43–53.

Morrison, S. F. (2016). Central neural control of thermoregulation and brown adipose tissue. *Autonomic Neuroscience*, **196**, 14–24.

Mulligan, J. D., Gonzalez, A. A., Stewart, A. M., Carey, H. V., & Saupe, K. W. (2007). Upregulation of AMPK during cold exposure occurs via distinct mechanisms in brown and white adipose tissue of the mouse. *The Journal of Physiology*, **580**(2), 677–684.

Nakamura, K. (2024). Central mechanisms of thermoregulation and fever in mammals. *Advances in Experimental Medicine and Biology*, **1461**, 141–159.

News, P. (2023). Ice baths are hot on social media. Here's how they affect your body.

Olesen, J., Kiilerich, K., & Pilegaard, H. (2010). PGC-1alpha-mediated adaptations in skeletal muscle. *Pflugers Archiv: European Journal Of Physiology*, **460**(1), 153–162.

Oliveira, R. L., Ueno, M., de Souza, C. T., Pereira-da-Silva, M., Gasparetti, A. L., Bezzera, R. M., Alberici, L. C., Vercesi, A. E., Saad, M. J., & Velloso, L. A. (2004). Cold-induced PGC-1alpha expression modulates muscle glucose uptake through an insulin receptor/akt-independent, AMPK-dependent pathway. *American Journal of Physiology-Endocrinology and Metabolism*, **287**(4), E686–E695.

Oliveira, R., Ueno, M., de Souza, C. T., Pereira-da-Silva, M., Gasparetti, A. L., Bezzera, R. M. N., Alberici, L. C., Vercesi, A. E., Saad, M. J. A., & Velloso, L. A. (2004). Cold-induced PGC-1α expression modulates muscle glucose uptake through an insulin receptor/akt-independent, AMPK-dependent pathway. *American Journal of Physiology-Endocrinology and Metabolism*, **287**(4), E686–E695.

Onyango, I. G., Bennett, J. P., & Stokin, G. B. (2021). Regulation of neuronal bioenergetics as a therapeutic strategy in neurodegenerative diseases. *Neural Regeneration Research*, **16**(8), 1467.

Ouellet, V., Labbé, S. M., Blondin, D. P., Phoenix, S., Guérin, B., Haman, F., Turcotte, E. E., Richard, D., & Carpentier, A. C. (2012). Brown adipose tissue oxidative metabolism contributes to energy expenditure during acute cold exposure in humans. *Journal of Clinical Investigation*, **122**(2), 545–552.

Park, E.-H., Choi, S.-W., & Yang, Y.-K. (2021). Cold-water immersion promotes antioxidant enzyme activation in elite taekwondo athletes. *Applied Sciences*, **11**(6), 2855.

Patel, R. P., Levonen, A., Crawford, J. H., & Darley-Usmar, V. M. (2000). Mechanisms of the pro- and anti-oxidant actions of nitric oxide in atherosclerosis. *Cardiovascular Research*, **47**(3), 465–474.

Pawłowska, M., Mila-Kierzenkowska, C., Boraczyński, T., Boraczyński, M., Szewczyk-Golec, K., Sutkowy, P., Wesołowski, R., Smoguła, M., & Woźniak, A. (2021). The effect of submaximal exercise followed by short-term cold-water immersion on the inflammatory State in healthy recreational athletes: A cross-over study. *Journal of Clinical Medicine*, **10**(18), 4239.

Peretti, D., Bastide, A., Radford, H., Verity, N., Molloy, C., Martin, M. G., Moreno, J. A., Steinert, J. R., Smith, T., Dinsdale, D., Willis, A. E., & Mallucci, G. R. (2015). RBM3 mediates structural plasticity and protective effects of cooling in neurodegeneration. *Nature*, **518**(7538), 236–239.

Perry, C. G., Lally, J., Holloway, G. P., Heigenhauser, G. J., Bonen, A., & Spriet, L. L. (2010). Repeated transient mRNA bursts precede increases in transcriptional and mitochondrial proteins during training in human skeletal muscle. *The Journal of Physiology*, **588**(Pt 23), 4795–4810.

Pidoux, G., & Taskén, K. (2010). Specificity and spatial dynamics of protein kinase A signaling organized by A-kinase-anchoring proteins. *Journal of Molecular Endocrinology*, **44**(5), 271–284.

Puigserver, P., & Spiegelman, B. M. (2003). Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1 alpha): Transcriptional coactivator and metabolic regulator. *Endocrine Reviews*, **24**(1), 78–90.

Puigserver, P., Wu, Z., Park, C. W., Graves, R., Wright, M., & Spiegelman, B. M. (1998). A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. *Cell*, **92**(6), 829–839.

Ranasinghe, N., Chen, W. Z., Hu, Y. C., Gamage, L., Lee, T. H., & Ho, C. W. (2023). Regulation of PGC-1α of the mitochondrial energy metabolism pathway in the gills of Indian medaka (Oryzias dancena) under hypothermal stress. *International Journal of Molecular Sciences*, **24**(22), 16187.

Rennie, D. W., Covino, B. G., Howell, B. J., Song, S. H., Kang, B. S., & Hong, S. K. (1962). Physical insulation of Korean diving women. *Journal of Applied Physiology*, **17**(6), 961–966.

Ricquier, D. (2017). UCP1, the mitochondrial uncoupling protein of brown adipocyte: A personal contribution and a historical perspective. *Biochimie*, **134**, 3–8.

Rius-Pérez, S., Torres-Cuevas, I., Millán, I., Ortega, Á. L., & Pérez, S. (2020). PGC-1α, inflammation, and oxidative stress: An integrative view in metabolism. *Oxidative Medicine and Cellular Longevity*, **2020**, 1452696.

Rodríguez-Moreno, A., & Lerma, J. (1998). Kainate receptor modulation of GABA release involves a metabotropic function. *Neuron*, **20**(6), 1211–1218.

Romanovsky, A. A. (2014). Skin temperature: Its role in thermoregulation. *Acta physiologica (Oxford, England)*, **210**(3), 498–507.

Rowe, G. C., Jiang, A., & Arany, Z. (2010). PGC-1 coactivators in cardiac development and disease. *Circulation Research*, **107**(7), 825–838.

Rowe, G. C., Raghuram, S., Jang, C., Nagy, J. A., Patten, I. S., Goyal, A., Chan, M. C., Liu, L. X., Jiang, A., Spokes, K. C., Beeler, D., Dvorak, H., Aird, W. C., & Arany, Z. (2014). PGC-1α induces SPP1 to activate macrophages and orchestrate functional angiogenesis in skeletal muscle. *Circulation Research*, **115**(5), 504–517.

Sahebnasagh, A., Eghbali, S., Saghafi, F., Sureda, A., & Avan, R. (2022). Neurohormetic phytochemicals in the pathogenesis of neurodegenerative diseases. *Immunity & Ageing : I & A*, **19**(1), 36.

Sephton, S., & Spiegel, D. (2003). Circadian disruption in cancer: A neuroendocrine-immune pathway from stress to disease? *Brain, Behavior, and Immunity*, **17**(5), 321–328.

Severinsen, M. C. K., & Pedersen, B. K. (2020). Muscle-organ crosstalk: The emerging roles of myokines. *Endocrine Reviews*, **41**(4), 594–609.

Shattock, M. J., & Tipton, M. J. (2012). 'Autonomic conflict': A different way to die during cold water immersion? *The Journal of Physiology*, **590**(14), 3219–3230.

Shevchuk, N. A. (2007). Possible use of repeated cold stress for reducing fatigue in Chronic Fatigue Syndrome: A hypothesis. *Behavioral and Brain Functions*, **3**, 55.

Shi, F., & Collins, S. (2017). Second messenger signaling mechanisms of the brown adipocyte thermogenic program: An integrative perspective. *Hormone Molecular Biology and Clinical Investigation*, **31**(2), https://doi.org/10.1515/hmbci-2017-0062

Slivka, D. R., Dumke, C. L., Tucker, T. J., Cuddy, J. S., & Ruby, B. (2012). Human mRNA response to exercise and temperature. *International Journal of Sports Medicine*, **33**(2), 94–100.

Slivka, D., Heesch, M., Dumke, C., Cuddy, J., Hailes, W., & Ruby, B. (2013). Effects of post-exercise recovery in a cold environment on muscle glycogen, PGC-1α, and downstream transcription factors. *Cryobiology*, **66**(3), 250–255.

Smith, B. W., Tooley, E. M., Montague, E. Q., Robinson, A. E., Cosper, C. J., & Mullins, P. G. (2009). The role of resilience and purpose in life in habituation to heat and cold pain. *The Journal of Pain*, **10**(5), 493–500.

Sramek, P., Simeckova, M., Jansky, L., Savlikova, J., & Vybiral, S. (2000). Human physiological responses to immersion into water of different temperatures. *European Journal of Applied Physiology*, **81**(5), 436–442.

Stancic, A., Buzadzic, B., Korac, A., Otasevic, V., Jankovic, A., Vucetic, M., Markelic, M., Velickovic, K., Golic, I., & Korac, B. (2013). Regulatory role of PGC-1α/PPAR signaling in skeletal muscle metabolic recruitment during cold acclimation. *Journal of Experimental Biology*, **216**(Pt 22), 4233–4241.

Stephens, D. P., Aoki, K., Kosiba, W. A., & Johnson, J. M. (2001). Nonnoradrenergic mechanism of reflex cutaneous vasoconstriction in men. *American Journal of physiology Heart and Circulatory Physiology*, **280**(4), H1496–H1504.

Stocks, J. M., Taylor, N. A., Tipton, M. J., & Greenleaf, J. E. (2004). Human physiological responses to cold exposure. *Aviation, Space, and Environmental Medicine*, **75**(5), 444–457.

Story, G. M., Peier, A. M., Reeve, A. J., Eid, S. R., Mosbacher, J., Hricik, T. R., Earley, T. J., Hergarden, A. C., Andersson, D. A., Hwang, S. W., McIntyre, P., Jegla, T., Bevan, S., & Patapoutian, A. (2003). ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures. *Cell*, **112**(6), 819–829.

Swerlick, R. A. (1995). Angiogenesis. *The Journal of Dermatology*, **22**(11), 845–852.

Tahergorabi, Z., & Khazaei, M. (2012). A review on angiogenesis and its assays. *Iranian Journal of Basic Medical Sciences*, **15**(6), 1110–1126.

Thompson-Torgerson, C. S., Holowatz, L. A., & Kenney, W. L. (2008). Altered mechanisms of thermoregulatory vasoconstriction in aged human skin. *Exercise and Sport Sciences Reviews*, **36**(3), 122–127.

Tian, X. Y., Ma, S., Tse, G., Wong, W. T., & Huang, Y. (2018). Uncoupling protein 2 in cardiovascular health and disease. *Frontiers in Physiology*, **9**, 1060.

Tikuisis, P., Gonzalez, R. R., & Pandolf, K. B. (1988). Thermoregulatory model for immersion of humans in cold water. *Journal of Applied Physiology*, **64**(2), 719–727.

Tipton, M. J. (1989). The initial responses to cold-water immersion in man. *Clinical Science (London, England: 1979)*, **77**(6), 581–588.

Tipton, M. J., Collier, N., Massey, H., Corbett, J., & Harper, M. (2017). Cold water immersion: Kill or cure? *Experimental Physiology*, **102**(11), 1335–1355.

Tipton, M. J., Eglin, C. M., & Golden, F. S. (1998). Habituation of the initial responses to cold water immersion in humans: A central or peripheral mechanism? *The Journal of Physiology*, **512**(2), 621–628.

Tipton, M. J., Kelleher, P. C., & Golden, F. S. (1994). Supraventricular arrhythmias following breath-hold submersions in cold water. *Undersea & Hyperbaric Medicine: Journal of the Undersea and Hyperbaric Medical Society, Inc*, **21**(3), 305–313.

Tipton, M. J., Mekjavic, I. B., & Eglin, C. M. (2000). Permanence of the habituation of the initial responses to cold-water immersion in humans. *European Journal of Applied Physiology*, **83**(1), 17–21.

Tipton, M. J., Stubbs, D. A., & Elliott, D. H. (1991). Human initial responses to immersion in cold water at three temperatures and after hyperventilation. *Journal of Applied Physiology*, **70**(1), 317–322.

Tipton, M. (2019). Drifting into unconsciousness: Jason Zirganos and the mystery of undetected hypothermia. *British Journal of Sports Medicine*, **53**(17), 1047–1047.

Tipton, M., & Bradford, C. (2014). Moving in extreme environments: Open water swimming in cold and warm water. *Extreme Physiology & Medicine*, **3**(1), 12.

Tipton, M., & Golden, F. (2006). The Physiology of Cooling in Cold Water. *Handbook on drowning* (pp. 485–490). Springer.

Tipton, M., McCormack, E., Elliott, G., Cisternelli, M., Allen, A., & Turner, A. C. (2022). Survival time and search time in water: Past, present and future. *Journal of Thermal Biology*, **110**, 103349.

Tirpe, A. A., Gulei, D., Ciortea, S. M., Crivii, C., & Berindan-Neagoe, I. (2019). Hypoxia: Overview on Hypoxia-mediated mechanisms with a focus on the role of HIF genes. *International Journal of Molecular Sciences*, **20**(24), 6140.

Toner, M. M., & McArdle, W. D. (2011). Human thermoregulatory responses to acute cold stress with special reference to water immersion. In *Comprehensive physiology* (pp. 379–397). Wiley.

Tsibulnikov, S., Maslov, L., Voronkov, N., & Oeltgen, P. (2020). Thyroid hormones and the mechanisms of adaptation to cold. *Hormones (Athens)*, **19**(3), 329–339.

Tsoucalas, G., Sgantzos, M., Karamanou, M., Gritzalis, K., & Androutsos, G. (2015). Hydrotherapy: Historical landmarks of a cure all remedy. *Archives of the Balkan Medical Union*, **50**, 430–432.

van Dam, A. D., Kooijman, S., Schilperoort, M., Rensen, P. C. N., & Boon, M. R. (2015). Regulation of brown fat by AMP-activated protein kinase. *Trends in Molecular Medicine*, **21**(9), 571–579.

van der Lans, A. A., Hoeks, J., Brans, B., Vijgen, G. H., Visser, M. G., Vosselman, M. J., Hansen, J., Jörgensen, J. A., Wu, J., Mottaghy, F. M., Schrauwen, P., & van Marken Lichtenbelt, W. D. (2013). Cold acclimation recruits human brown fat and increases nonshivering thermogenesis. *Journal of Clinical Investigation*, **123**(8), 3395–3403.

van der Spek, A. H., Fliers, E., & Boelen, A. (2017). The classic pathways of thyroid hormone metabolism. *Molecular and Cellular Endocrinology*, **458**, 29–38.

van der Vaart, J. I., Boon, M. R., & Houtkooper, R. H. (2021). The role of AMPK signaling in brown adipose tissue activation. *Cells*, **10**(5), 1122.

van Tulleken, C., Tipton, M., Massey, H., & Harper, C. M. (2018). Open water swimming as a treatment for major depressive disorder. *British Medical Journal case reports*, **2018**, bcr2018225007.

Ventura-Clapier, R., Garnier, A., & Veksler, V. (2008). Transcriptional control of mitochondrial biogenesis: The central role of PGC-1alpha. *Cardiovascular Research*, **79**(2), 208–217.

Villarroya, F., Peyrou, M., & Giralt, M. (2017). Transcriptional regulation of the uncoupling protein-1 gene. *Biochimie*, **134**, 86–92.

Wang, H., Olivero, W., Wang, D., & Lanzino, G. (2006). Cold as a therapeutic agent. *Acta Neurochirurgica*, **148**(5), 565–570.

Wang, S., Wan, T., Ye, M., Qiu, Y., Pei, L., Jiang, R., Pang, N., Huang, Y., Liang, B., Ling, W., Lin, X., Zhang, Z., & Yang, L. (2018). Nicotinamide riboside attenuates alcohol induced liver injuries via activation of SirT1/PGC-1α/mitochondrial biosynthesis pathway. *Redox Biology*, **17**, 89–98.

Wei, Z., Chigurupati, S., Bagsiyao, P., Henriquez, A., & Chan, S. L. (2009). The brain uncoupling protein UCP4 attenuates mitochondrial toxin-induced cell death: Role of extracellular signal-regulated kinases in bioenergetics adaptation and cell survival. *Neurotoxicity Research*, **16**(1), 14–29.

Werner, J. (2010). System properties, feedback control and effector coordination of human temperature regulation. *European Journal of Applied Physiology*, **109**(1), 13–25.

Wesołowski, R., Mila-Kierzenkowska, C., Pawłowska, M., Szewczyk-Golec, K., Saletnik, Ł., Sutkowy, P., & Woźniak, A. (2023). The influence of winter swimming on oxidative stress indicators in the blood of healthy males. *Metabolites*, **13**(2), 143.

White, G. E., & Wells, G. D. (2013). Cold-water immersion and other forms of cryotherapy: Physiological changes potentially affecting recovery from high-intensity exercise. *Extreme Physiology & Medicine*, **2**(1), 26.

Wojtczak, L., & Wieckowski, M. R. (1999). The mechanisms of fatty acid-induced proton permeability of the inner mitochondrial membrane. *Journal of Bioenergetics and Biomembranes*, **31**(5), 447–455.

Wu, Z., Puigserver, P., Andersson, U., Zhang, C., Adelmant, G., Mootha, V., Troy, A., Cinti, S., Lowell, B., Scarpulla, R. C., & Spiegelman, B. M. (1999). Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. *Cell*, **98**(1), 115–124.

Xiao, R., & Xu, X. Z. S. (2021). Temperature sensation: From molecular thermosensors to neural circuits and coding principles. *Annual Review of Physiology*, **83**(1), 205–230.

Xu, Y., Yu, T., Ma, G., Zheng, L., Jiang, X., Yang, F., Wang, Z., Li, N., He, Z., Song, X., Wen, D., Kong, J., Yu, Y., & Cao, L. (2021). Berberine modulates deacetylation of pparγ to promote adipose tissue remodeling and thermogenesis via AMPK/SIRT1 pathway. *International journal of biological sciences*, **17**(12), 3173–3187.

Yamaguchi, T., Suzuki, T., Arai, H., Tanabe, S., & Atomi, Y. (2010). Continuous mild heat stress induces differentiation of mammalian myoblasts, shifting fiber type from fast to slow. *American Journal of Physiology-Cell Physiology*, **298**(1), C140–C148.

Yankouskaya, A., Williamson, R., Stacey, C., Totman, J. J., & Massey, H. (2023). Short-term head-out whole-body cold-water immersion facilitates positive affect and increases interaction between large-scale brain networks. *Biology (Basel)*, **12**(2), 211.

Zak, R. B., Shute, R. J., Heesch, M. W., La Salle, D. T., Bubak, M. P., Dinan, N. E., Laursen, T. L., & Slivka, D. R. (2017). Impact of hot and cold exposure on human skeletal muscle gene expression. *Applied Physiology, Nutrition and Metabolism*, **42**(3), 319–325.

Zhang, Y., Uguccioni, G., Ljubicic, V., Irrcher, I., Iqbal, S., Singh, K., Ding, S., & Hood, D. A. (2014). Multiple signaling pathways regulate contractile activity-mediated PGC-1α gene expression and activity in skeletal muscle cells. *Physiological Reports*, **2**(5), e12008.

Zhang, Z., Boelen, A., Kalsbeek, A., & Fliers, E. (2018). TRH neurons and thyroid hormone coordinate the hypothalamic response to cold. *European Thyroid Journal*, **7**(6), 279–288.

Zhang, Z. W., Bi, M. Y., Yao, H. D., Fu, J., Li, S., & Xu, S. W. (2014). Effect of cold stress on expression of ampkα–PPARα pathway and inflammation genes. *Avian Diseases*, **58**(3), 415–426.

Zimmermann, K., Lennerz, J. K., Hein, A., Link, A. S., Kaczmarek, J. S., Delling, M., Uysal, S., Pfeifer, J. D., Riccio, A., & Clapham, D. E. (2011). Transient receptor potential cation channel, subfamily C, member 5 (TRPC5) is a cold-transducer in the peripheral nervous system. *Proceedings of the National Academy of Sciences of the United States of America*, **108**(44), 18114–18119.

Additional information

Competing interests

The authors declare no conflicts of interest.

Author contributions

E.H. and J.B. were responsible for the concept of the article. E.H. wrote the first draft of the article. J.B. and W.D. contributed to drafting the article and critically revising it for important intellectual content. All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

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