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REVIEW

Physiology of Thermal Therapy

Examining the benefits of cold exposure as a therapeutic strategy for obesity and type 2 diabetes

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Abstract

The pathogenesis of metabolic diseases such as obesity and type 2 diabetes are characterized by a progressive dysregulation in energy partitioning, often leading to end-organ complications. One emerging approach proposed to target this metabolic dysregulation is the application of mild cold exposure. In healthy individuals, cold exposure can increase energy expenditure and whole body glucose and fatty acid utilization. Repeated exposures can lower fasting glucose and insulin levels and improve dietary fatty acid handling, even in healthy individuals. Despite its apparent therapeutic potential, little is known regarding the effects of cold exposure in populations for which this stimulation could benefit the most. The few studies available have shown that both acute and repeated exposures to the cold can improve insulin sensitivity and reduce fasting glycemia in individuals with type 2 diabetes. However, critical gaps remain in understanding the prolonged effects of repeated cold exposures on glucose regulation and whole body insulin sensitivity in individuals with metabolic syndrome. Much of the metabolic benefits appear to be attributable to the recruitment of shivering skeletal muscles. However, further work is required to determine whether the broader recruitment of skeletal muscles observed during cold exposure can confer metabolic benefits that surpass what has been historically observed from endurance exercise. In addition, although cold exposure offers unique cardiovascular responses for a physiological stimulus that increases energy expenditure, further work is required to determine how acute and repeated cold exposure can impact cardiovascular responses and myocardial function across a broader scope of individuals.

cold exposure; type 2 diabetes; obesity; thermal therapy; thermogenesis

INTRODUCTION

Human physiological responses to cold environments have historically been investigated with the aim of understanding the risks, survival odds, and occupational requirements of armed forces personnel, emergency rescue teams, outdoor workers, adventurer-explorers, and athletes. However, for centuries, there have been claims and anecdotal evidence extolling the virtues of cold exposure, particularly resulting from cold water immersion or swimming, to improve physiological and psychological health (1). Despite the mounting anecdotal evidence and growing popularity surrounding cold water swimming, experimental evidences demonstrating the physiological mechanisms that may be responsible for these health benefits have been lacking in humans. Studies performed in rodents over the course of the last century have shown that cold exposure can produce significant metabolic benefits, such as improving insulin clearance and glucose and fatty acid turnover (2–4). Many argued that these benefits were conferred through the adrenergic stimulation of brown adipose tissue (BAT) (5–9), a thermoregulatory organ that can be found in distinct depots near vital organs or as subpopulations of cells within white adipose tissue (WAT) [referred to as beige/brite/inducible/recruitable adipocytes (see Ref. 10 for more comprehensive review)]. Because BAT was thought to be absent in adult humans, there was little apparent interest in following-up the rodent experiments by examining these effects in humans. Despite indications decades earlier that cold exposure could improve the clearance of circulating glucose (11), it was the discovery that human BAT could be stimulated to produce heat and clear circulating substrates upon cold exposure (12–15) that provided the impetus to begin examining the therapeutic potential of such an environmental stimulus in humans. This short review will examine the metabolic benefits resulting from exposure to a compensable cold stimulus and the potential

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therapeutic implications for obesity and its associated metabolic complications.

THERAPEUTIC TARGETS OF OBESITY AND ITS ASSOCIATED METABOLIC COMPLICATIONS

Obesity is accompanied by several metabolic complications including the increased risk of developing type 2 diabetes (T2D), nonalcoholic fatty liver disease (NAFLD), and cardiovascular disease (CVD). Several pathophysiological factors are responsible for the progression of these diseases including a dysregulation in insulin secretion, insulin resistance, loss of incretin action, dysregulated lipid handling, increased renal glucose reabsorption, neurotransmitter/autonomic dysfunction, increased organ and systemic inflammation, and microvascular and macrovascular dysfunction (16). Given the multifactorial nature of these diseases, it is no surprise that lifestyle interventions that target several of these dysfunctions have shown the greatest therapeutic potential (17–20). Indeed, the metabolic benefits conferred by physical activity and exercise training specifically can be attributed to the simultaneous stimulation of multiple organ systems and signaling networks. It is also this characteristic feature that has limited the ability to develop pharmacological compounds that can mimic the full spectra of metabolic benefits resulting from physical activity and exercise training (21). However, we posit that perhaps in attempts to identify pharmacological compounds that mimic the benefits of exercise, we have overlooked the therapeutic potential of other nonpharmacological approaches, including harnessing one of the most fundamental evolutionary adaptations as endotherms—our ability to thermoregulate. Indeed, cold-stimulated thermoregulatory responses may be the closest exercise mimetic and, in some instances, may potentially even exceed the therapeutic potential of exercise training.

METABOLIC RESPONSE TO COLD EXPOSURE

When designing experimental cold exposure studies in humans, it is important to consider the distinct metabolic, cardiovascular, and thermal perception responses elicited by different cooling stimulations. Indeed, the lack of standardization in defining the magnitude or degree of the cold exposure has raised serious challenges in the field, both for those interested in applied research as well as groups interested in understanding the metabolic and thermoregulatory responses to cold (see Ref. 22 for review). Several factors can contribute to discrepant metabolic responses, including: cooling modality [e.g., cold water immersion, cold air, liquid-conditioned suits/vests/blankets, localized cooling using blocks of ice (23)], stimulation temperature [e.g., fixed ambient temperatures (24, 25), skin temperature-clamping (26, 27), participant cold perception (28)], duration of exposure (25, 29, 30), proportion of body surface area exposed to the stimulus, participant anthropometry/body composition/morphology, and possibly training status (31, 32), acclimatization and acclimation status (28, 33–37), previous exposure experience, presence of metabolic risk factors (38, 39), and the use of certain medications (40–42). It is therefore important to clearly describe, control for, and consider the implications of these factors in future studies.

As a means of standardizing approaches and the definitions used to describe or compare the magnitude of the cold stress between studies, we have proposed that investigators report the cold stimulus according to: *1*) whether the cold stress is uncompensable (fall in core temperature) or compensable (no change in core temperature) and *2*) the relative increase in metabolic rate above resting (times above resting metabolic rate, ×RMR), commonly referred to as cold-induced thermogenesis (Fig. 1). The latter is analogous to reporting exercise intensities according to relative power outputs (% W_{max}) or maximal oxygen consumption (%$\dot{V}O_{2max}$). This approach has been preferred over the use of ambient or skin temperatures (innocuous vs. noxious cold) as the physiological response to the former is dependent upon the heat transfer and convective properties of the cooling medium whereas the latter may be influenced by interindividual differences in sensitivity, density, and responsiveness of cutaneous thermoreceptors and how this sensory stimulation is processed by the central nervous system (43).

To defend against a cold stimulus, humans adapt their behavior to optimize personal comfort. In the absence of behavioral adjustments, the stimulation of cutaneous cold-sensitive thermoreceptors results in the activation of autonomic and somatic motor responses to limit heat loss to the environment and increase metabolic heat production (22, 44–46). As in all large mammals, humans can rely on their large body mass to provide a greater thermal inertia against temperature fluctuations and their large muscle mass to provide a significant source of heat production (47, 48). Under passive cooling conditions, cold-stimulated thermogenesis increases as a function of mean skin temperature (49), ranging from mild thermogenesis [1.0- to 2.0-times resting metabolic rate, ×RMR (12, 28–30, 35, 41, 47, 50–59)], to moderate [2.0–3.0 ×RMR; (36, 57, 60–69)] or high thermogenic rates [3.0–5.0 ×RMR; (70–74)] (Fig. 1). Mild-to-moderate thermogenesis can be recruited under compensable cold conditions, whereby core temperature can be defended for prolonged periods of time (~48–72 h) (25, 29). High-thermogenic rates are typically induced only upon whole body cold-water immersion (CWI) (71) or using certain clinically developed cooling devices designed to rapidly induce hypothermia (e.g. see Ref. 75). In this context, core temperature can no longer be defended through passive thermogenesis.

The metabolic substrates used to fuel whole body heat production during cold exposure depends on the magnitude of cold-induced thermogenesis (70), endogenous substrate availability (40, 76, 77), the provision of food (25, 26, 50, 62, 64), and which thermogenic organs or metabolic pathways are recruited (24, 40, 60, 70). Although the specific metabolic rates of several major organs and tissues and their estimated contributions to resting energy expenditure under room temperature conditions has been the subject of discussion for several decades (78–82), far less is known about the relative contribution of these major organs and tissues to cold-induced thermogenesis. Studies using positron emission tomography (PET) with [^{15}O]oxygen in combination with indirect calorimetry have shown that under mild cold stimulation

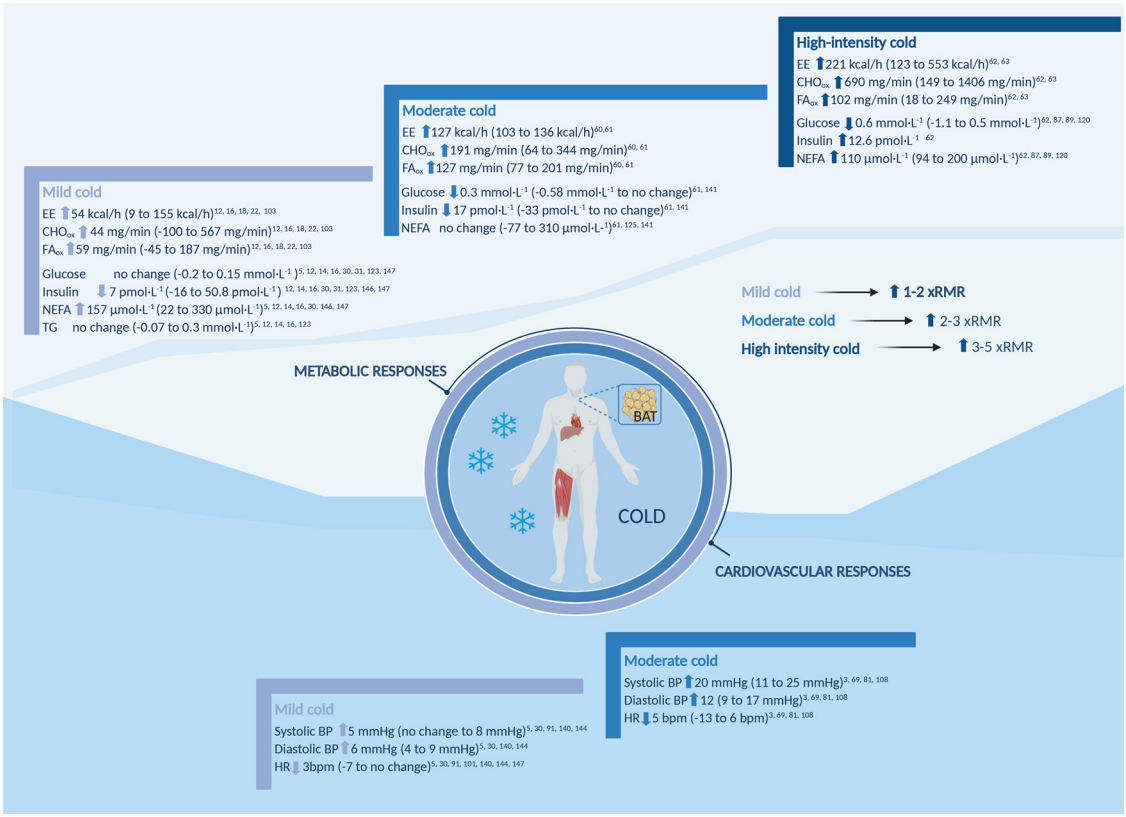

Figure 1. Metabolic and cardiovascular responses to cold exposure presented as a function of thermogenic rates (times resting metabolic rate, ×RMR) at mild (1–2 ×RMR), moderate (2–3 ×RMR), and high (>3 ×RMR) thermogenic rates. Data represent the mean (range) of responses reported in cited studies. Figure created with BioRender.com. BP, blood pressure; HR, heart rate; NEFA, nonesterified fatty acids.

(~1.13–1.20 × RMR), skeletal muscles account for 40%–70% of whole body oxygen consumption (47, 83). The contribution of skeletal muscles to whole body thermogenesis can only increase further with colder stimulations, but this has yet to be directly quantified using these complementary methods. Preclinical studies have also suggested that chronic cold exposure can result in the recruitment of beige/brite/inducible/recruitable adipocytes within white adipose tissue (WAT) depots (84), which may also contribute to cold-induced thermogenesis in rodents. In humans, there is currently no evidence for such recruitment even following repeated cold exposures (28, 37).

With skeletal muscles providing such a substantial contribution to thermogenesis, it is no surprise that many of the determinants of whole body fuel selection are largely dependent upon their impact on muscle metabolism. Skeletal muscles, however, demonstrate remarkable metabolic flexibility and as a result fuel selection can be modified through: *1*) selective recruitment of certain muscle groups (48, 85); *2*) recruitment of specific subpopulations of muscle fibers within those muscles (36, 70); and *3*) recruitment of different metabolic pathways within those muscle fibers (40, 60, 76). First, deep, centrally located muscles, many of them postural and composed of predominantly type I slow-twitch oxidative fibers, are preferentially recruited during mild cold exposure (47, 48), and the reliance on larger muscle groups such as the quadricep and pectoralis increases progressively with colder stimulations (36, 86, 87). Even within individual muscle groups, there are indications that muscle perfusion varies according to the depth of the muscle and the temperature of the cold stimulus, with the perfusion in deep muscles such as the m. vastus intermedius increasing upon 8°C cold water immersion, whereas perfusion of superficial muscles such as the m. rectus femoris decreases upon 15°C cold water immersion (85). Whether this is unique to cold water immersion or generalizable to other cold stimuli remains to be determined but can certainly be an important determinant for muscle fuel selection.

Second, although substantial interindividual variability exists in the muscle fibers recruited to shiver in larger muscles such as the quadriceps and pectoralis, a variability that is further amplified upon colder stimulations [3.3 ×RMR (88)], this may in part be determined by the innate muscle fiber-type composition of these muscles (36). Indeed, a study examining the morphological characteristics of the m. vastus lateralis in cold-acclimatized Korean breath-hold divers compared with nonacclimatized nondivers showed a greater proportion of type IIx muscle fibers and lower proportion of IIa muscle fibers in the acclimatized divers (89). Interestingly, Danish individuals undergoing a 42-day skiing expedition across polar ice demonstrated changes in fiber composition of the m. vastus lateralis, with the proportion of type I muscle fibers decreasing and type IIx increasing (90). In both instances, it is difficult to distinguish the potential impact of the breath-hold diving or daily exercise, respectively, from the daily exposure to the cold. However, in investigating the effect of daily cold

exposure in isolation we have shown that, at least in lean healthy men, the proportion of type I muscle fibers in the m. vastus lateralis tended to increase in response to daily cold exposure and that a greater proportion of type I muscle fibers was associated with a lower shivering intensity in that muscle (36). This suggests that there might have been a progressive shift toward an increased reliance on type I oxidative muscle fibers to produce heat upon daily cold exposure, ensuring a greater reliance on lipid oxidation rather than the limited glycogen stores. Such a shift toward greater lipid utilization with prolonged cold exposure has been demonstrated in men exposed to 7.5°C air for as little as 12- to 24-h (25). Clearly, further work is needed to elucidate the determinants of shivering patterns in humans and determine whether these are fixed responses or modifiable through repeated cold exposures. It is also unclear to what extent aging, ethnicity, sex, or metabolic health may influence these responses.

Finally, without modifying the electromyography signature of shivering muscles (i.e., shivering pattern/muscle fiber recruitment), different metabolic pathways within the same recruited muscle fibers can be used to compensate for changes in muscle glycogen content (87), suppressed whole body lipolysis (40), or to account for the sexual dimorphism in substrate utilization (60). Much of this is likely related to the mounting evidence demonstrating the high-intracellular compartmentalization of skeletal muscle fiber organelles and cellular compartments. For instance, the development of modern electron microscopy techniques that generate high-resolution three-dimensional images to assess mitochondrial morphology has paved the way for the significant discoveries demonstrating the complex mitochondrial networks that are formed in human skeletal muscles (91, 92). These studies have shown that human mitochondrial networks are heterogeneous within each cell, between different cells in the same individual and between individuals, which likely provides tremendous flexibility to adapt to various metabolic conditions be it from exercise, cold exposure, prolonged fasting, or the oversupply of energy in metabolic diseases. Similarly, there are distinct subcellular populations of lipid droplets (93) and glycogen pools (94) that display different storage and utilization patterns according to their localization, the duration of an exercise bout, or the presence of disordered metabolism (e.g., type 2 diabetes, obesity). The subcellular skeletal muscle lipid and glycogen utilization patterns during cold exposure remains to be further explored, not only to build upon the recent work performed in response to exercise but to determine the therapeutic potential of daily cold exposure in the prevention or treatment of type 2 diabetes (T2D).

What has become clear over several decades of cold exposure research is that under fasted conditions, carbohydrates, lipids, and proteins can all provide the necessary substrates to fuel thermogenesis. Indeed, when one fuel source is depleted or restricted, others can compensate to maintain ATP production, shivering activity, and whole body thermogenesis (25, 40, 76). Carbohydrates appear to be the most important of these fuels. Although carbohydrates account for ~1% of total energy stores, its relative contribution to total heat production increases in parallel with increases in cold-induced thermogenesis (Fig. 1), accounting for up to 80% of heat production at the highest shivering intensities, whereas fatty acid oxidation increases in response to cold but remains steady at ~100–200 mg/min regardless of shivering intensity, sex, carbohydrate supplementation (95), or even the suppression of white adipose tissue lipolysis (40). In addition, hyperinsulinemic-clamp-induced hypoglycemia (glycemia < 2.8 mmol/L) suppresses or inhibits cold-induced thermogenesis (96, 97). The depletion of glycogen, however, results in a compensatory increase in the utilization of proteins (76). When given a standard liquid meal (26) or a carbohydrate-rich beverage (62–64) during a mild cold exposure, the rate of fatty acid oxidation increases by 37% but carbohydrate utilization increases by approximately threefold (26) to as much as 6.6-fold (64). This dramatic increase in glucose utilization, combined with a suppression in endogenous glucose production, results in no net change in glycemia upon ingesting these carbohydrate-rich beverages during cold exposure, in contrast to what is commonly seen under ambient conditions.

In summary, compensable cold exposure increases energy expenditure in proportion to the degree of heat lost to the environment, driven primarily by the recruitment of shivering thermogenesis. This thermogenesis is fueled by increases in carbohydrate, lipid, and protein utilization with carbohydrate utilization increasing in parallel with the increases in energy expenditure. BAT and skeletal muscles are the primary sources of this heat production, with the former demonstrating remarkable mass-specific increases in thermogenesis (47, 98), glucose and nonesterified fatty acids (NEFA) uptake (12, 48), and dietary fatty acid clearance (26). However, skeletal muscles, due to their large mass, provide the greatest source of heat production and are the most significant contributor to the clearance of circulating glucose (48), NEFA (12, 38), and triglyceride-rich lipoprotein-derived fatty acids (26). It is this growing body of evidence demonstrating the relative importance of skeletal muscle thermogenesis that suggests that cold exposure may serve as a promising adjunct therapeutic strategy to dissipate excess energy and improve the metabolic profile of individuals with metabolic syndrome. Indeed, even in young and healthy individuals, relative to ambient conditions, acute cold exposure improves insulin-sensitivity (24), reduces fasting and postprandial insulin levels (26, 48), and reduces the clearance of dietary fatty acids by the heart and liver (26), whereas 4 wk of daily cold exposure improves fasting glycemia (35). This further exemplifies the therapeutic potential of cold exposure for the prevention or treatment of metabolic disease. It should be noted that a recent study has demonstrated that when given an oral glucose load for 90 min following a 1 h mild/moderate cold exposure (2× RMR), glucose and insulin areas under the curve are increased, signifying a reduced clearance of both glucose and insulin (99). However, these results are confounded by the persistent elevation in lipolysis immediately following cold exposure as well as a reduction in muscle microvascular blood flow that presents when given an oral glucose load alone compared with a mixed-meal (100). Although cold exposure research has continued to showcase its remarkable therapeutic potential, few studies have examined the effect of cold exposure in individuals with obesity or its associated complications.

COLD AS ADJUNCT THERAPEUTIC STRATEGY IN THE MANAGEMENT OF OBESITY AND T2D

Obesity is widely considered to result largely from a chronic imbalance between the overconsumption of energy relative to energy demands (101). However, the metabolic complications resulting from obesity are driven by energy being redirected away from energy storing organs like white adipose tissue and toward lean organs like the heart, skeletal muscles, pancreas, and liver (102–104). Indeed, the inability of white adipose tissue to regulate fatty acid flux in the fasted and fed condition, through an impairment in catecholamine-stimulated intracellular lipolysis and insulin-mediated storage of dietary fatty acids, respectively, is the hallmark of the progression toward impaired glucose tolerance (IGT) and T2D (105). Simultaneously targeting several energy homeostatic mechanisms through lifestyle interventions involving continuous, moderate-intensity endurance exercise and modest nutritional changes has been shown to be advantageous for the treatment of obesity (106), thereby reducing the risk of developing T2D and CVD (19). Epidemiological studies have shed some light on the potential impact of living in a cold climate on metabolic health, particularly on the prevalence of T2D. In the continental United States, the predicted prevalence of T2D of individuals who lived in a county with a mean annual outdoor temperature of 25°C was 1.6-times higher (12.1%) than individuals who lived in a county with a mean annual temperature of 5°C (7.6%) (107). It is unclear, however, whether these effects are independent of county variations in physical activity. In addition, the incidence of gestational diabetes rises by 6% for every 10°C increase in mean 30-day outdoor environmental temperature (108). Living in a mildly cold environment can increase resting energy expenditure by ~20% over a span of 6 wk (109) and whole body insulin sensitivity by ~50% within a month (37), even in young healthy individuals. Together, these epidemiological and ecological studies lend support for cold exposure as an adjunct therapeutic strategy in the prevention of T2D, but prospective studies investigating the effects of acute and repeated mild cold exposure in T2D have been lacking.

To date, few studies have examined the metabolic impact of cold exposure in individuals with obesity or T2D. Recently, we showed that acute mild cold exposure increases energy expenditure by an additional 60 kcal/h of exposure, reduces glycemia by ~10%, and insulinemia by 28% over the 3 h of exposure in men with well-controlled T2D (38) **(**Fig. 2**)**. This magnitude of change in glycemia is consistent with what is commonly observed during or immediately following a single bout of moderate-intensity endurance exercise (range: 1%–18%) (110–114), at a metabolic rate that is more than 2.5-times greater (50%–85% $\dot{V}O_{2max}$ during exercise vs. 10%–17% $\dot{V}O_{2max}$ during cold). Furthermore, at least in healthy individuals, the effect of cold exposure on glycemia and insulinemia appears to be temperature-dependent, with colder stimulations eliciting greater decreases in glycemia and insulinemia (Fig. 1). This cold exposure also stimulated catecholamine-induced intracellular triglyceride lipolysis in white adipose tissue, leading to an increased rate of fatty acid oxidation of 31 kcal/h.

The most significant knowledge gap in our understanding of the therapeutic benefits of cold exposure is in fact the lack of data examining the metabolic effects of repeated exposures to the cold in individuals with obesity or T2D. To date, only two studies have examined the effects of daily cold exposure in these populations (115, 116). Using an individualized cooling

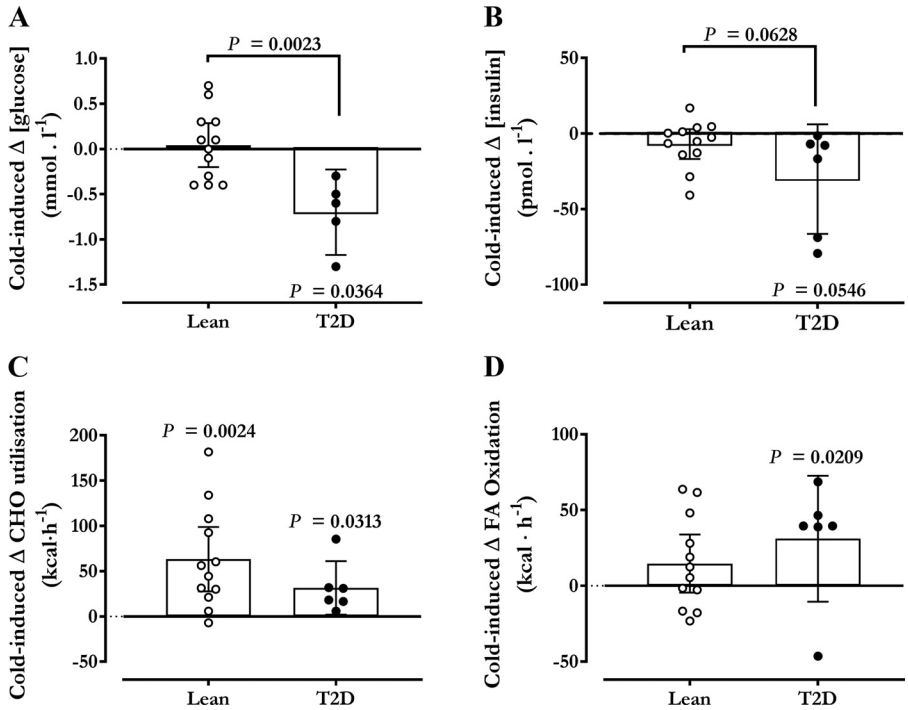

Figure 2. Cold-induced changes in plasma glucose (*A*), insulin (*B*), carbohydrate (CHO) utilization (*C*), and fatty acid (FA) oxidation (*D*) in lean young men and overweight individuals with type 2 diabetes (T2D) (38).

protocol designed to restrict participant-reported shivering in men with obesity, very mild cold exposure increased energy expenditure by ~10% which resulted in a 6%–8% decrease in glycemia and no effect on insulinemia both before and after 10 days of daily mild cold exposure (14–15°C for 2–6 h/day; cold acclimation) (116). In contrast, using the same acute cold stimulation and cold acclimation intervention protocol in overweight men with T2D, daily cold exposure increased insulin-stimulated glucose disposal, with most of this additional clearance being directed toward oxidation rather than storage (115). In both studies, daily cold exposure increased basal glucose transporter (GLUT) 4 translocation in the m. vastus lateralis. This suggests that much of the cold-induced improvements in glycemia and glucose clearance are a result of shivering/contraction-mediated GLUT4 translocation resulting in an enhanced capacity to transport glucose into skeletal muscles. These two critical studies have set a valuable platform to further examine the therapeutic potential of cold exposure in individuals with metabolic dysfunctions. Further studies are needed to examine the effects of a longer intervention (at least consistent with exercise interventions), slightly colder stimulations that recruit a larger proportion of muscle groups and with a higher shivering intensity to further increase contraction-mediated GLUT4 translocation, and thereby increasing glucose transport/clearance, as well as examining these responses in women.

COLD EXPOSURE ON CARDIOVASCULAR RESPONSES AND RISK FACTORS

In addition to the described metabolic responses, cold exposure also elicits unique cardiovascular responses that contrast with the dose-dependent increase in thermogenesis, such as modest increases in systolic blood pressure and a paradoxical decrease in heart rate. Some cross-sectional epidemiological studies have reported that while decreases in environmental temperature below 18°C are associated with increased all-cause mortality, the increased mortality risk is greatest in regions with warmer winters (117). However, only a few studies address some of the factors that may account for these associations. In the Eurowinter study (117), the cold-associated mortality risks were lower in cities with milder winters and where protective measures against cold were more commonly used. For instance, the study reported lower mortality indices with wearing of hats, anoraks (warm winter jacket), and gloves, and with those who performed more physical activity outdoors. A more recent prospective cohort study found negative correlations between BAT activity, likely a reflection of regular cold exposure, and cardiovascular risk factor levels both cross-sectionally (between low- and high-BAT activity) and longitudinally after a 5-yr follow-up (118). Using [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) and [^{15}O]H_2O PET, the study reports negative correlations between BAT activity and future subclinical atherosclerosis, and these associations were independent of BMI. This study was the first prospective study to correlate functional measures of atherosclerosis to cold-stimulated BAT activity. Higher mortality and hospitalizations due to natural, cardiovascular, and respiratory causes were also reported in a more recent Finnish population-based study aimed at investigating whether cold-related cardiac and respiratory symptoms predict future morbidity and mortality (119). This study reports that the development of cold-related cardiorespiratory symptoms, such as shortness of breath/coughing bouts/wheezing/increased mucus in respiratory tract or chest pain or cardiac arrhythmia, increases the risk of dying from natural causes by 38%, from cardiovascular causes by 77% (i.e., CVD, ischemic heart disease, myocardial infarction, cerebrovascular event), and from respiratory causes by 119% [i.e., chronic obstructive pulmonary disease (COPD) and bronchial asthma]). Although such studies provide valuable insight into the associations between cold temperatures and mortality risks, it is impossible to determine the causal relationship as the adverse events occurring at these environmental temperatures appear to be independent of cold-stimulated thermoregulatory responses (120). It may be, however, that underlying respiratory and cardiovascular symptoms are exacerbated by cold dry air or cold-specific activities (e.g., exertion from shoveling, cold water immersion, contrasting thermal stimuli between saunas/cold exposure).

Investigations focused primarily on cardiovascular changes during cold exposure have remained somewhat limited and even fewer have reported the long-term effects of daily exposure. The cold-stimulated cardiovascular changes are largely influenced by the cooling medium (air, water, liquid-conditioned suit, and cold air inhalation), the temperature of that medium, and whether facial cooling is present. With a sufficiently strong stimulus, cold exposure increases autonomic activity, increasing peripheral vasoconstriction and in turn increasing arterial blood pressure (BP) and mean arterial pressure (MAP) while decreasing heart rate (HR). The changes in cardiovascular responses during cold exposure follow a dose-response relationship, with mild cold eliciting smaller changes in responses than more moderate cold exposures (Fig. 1). For example, mild cold increases systolic BP by ~4–8 mmHg (or ~3%–6%) (41, 58, 121–124), whereas moderate cold exposure increases systolic BP by ~11–25 mmHg (or ~9%–20%) (125–128). Mild cold also increases diastolic BP by ~4–9 mmHg (or ~6%–14%) (41, 52, 58, 121–124, 129, 130), whereas moderate cold exposure increases diastolic BP by ~9–17 mmHg (or ~12%–20%) (125–128). Furthermore, although data from different populations is limited, studies suggest that this increase in blood pressure is more pronounced in some populations. For example, in older and hypertensive individuals who are exposed to mild cold, systolic BP increases by ~11%–15% (123, 130, 131), whereas diastolic BP increases by ~9%–10% (130, 131). Such an increase in systolic and diastolic BP may be perceived as potentially increasing the risks of experiencing acute cardiovascular events; however, it is important to note that these increases are of the same magnitude as what is observed during low-intensity aerobic exercise (132), a cornerstone in cardiac rehabilitation. In addition, although regular physical activity is associated with significant reductions in resting blood pressure (133), studies investigating the long-term effects of cold exposure on resting blood pressure are currently lacking.

Although exercise and cold exposure are often seen as analogous metabolic processes (134), one of the most profound differences between the two metabolic conditions is reflected in the heart rate response. For instance, in contrast to exercise, heart rate either does not change (52, 58, 122, 130,

131) or decreases by ~3–7 beats/min (~3%–9% decrease) in response to mild cold exposure in either young or older individuals (121, 123, 124). During cold exposure that elicits a moderate increase in thermogenesis, heart rate decreases even further, falling by ~5–13 beats/min (~8%–22%) in both healthy and hypertensive individuals (125, 127, 128). Whereas exercise-induced increases in cardiac output is primarily driven by increases in heart rate, cold-induced increases in cardiac output appears to be driven primarily by increases in stroke volume. For example, mild cold exposure (ambient temperature, 10°C) results in a ~10% increase in cardiac output (135) regardless of age or sex, whereas a more moderate cold exposure (ambient temperature, 4–6°C) increases cardiac output by ~65%–150% (126, 136). The temperature-dependent increase in cardiac output is driven primarily by the temperature-dependent increases in stroke volume, which increases by ~15%–20% under mild cold exposure and by up to ~40%–77% at a more moderate cold (126, 135, 136), as a result of the redistribution of blood from the periphery to the central circulation (126) increasing the central venous pressure (137). Whether the cold-induced decrease in HR is driven by these changes in stroke volume, baroreceptor reflex, or a combination of both remains to be fully elucidated.

In summary, although there has been considerable interest in understanding the effects of cold exposure on cardiovascular responses, much of the currently available data is derived from epidemiological studies that fail to account for many of the important confounding factors associated with cooler environmental temperatures. These include potential changes in lifestyle behaviors such as reduced physical activity patterns but may also include changes in domestic responsibilities that accompany colder environmental temperatures, such as shoveling, which may expose individuals with a higher-risk of cardiorespiratory complications (i.e., at risk of myocardial infarctions, CVD, COPD, arrhythmias, asthma, cerebrovascular events) to activities that may exacerbate their condition. Controlled, prospective studies which show very limited increases in blood pressure and even decreases in heart rate in response to cold exposure suggest that cold per se is unlikely to be the primary cause of the seasonal associations with increases

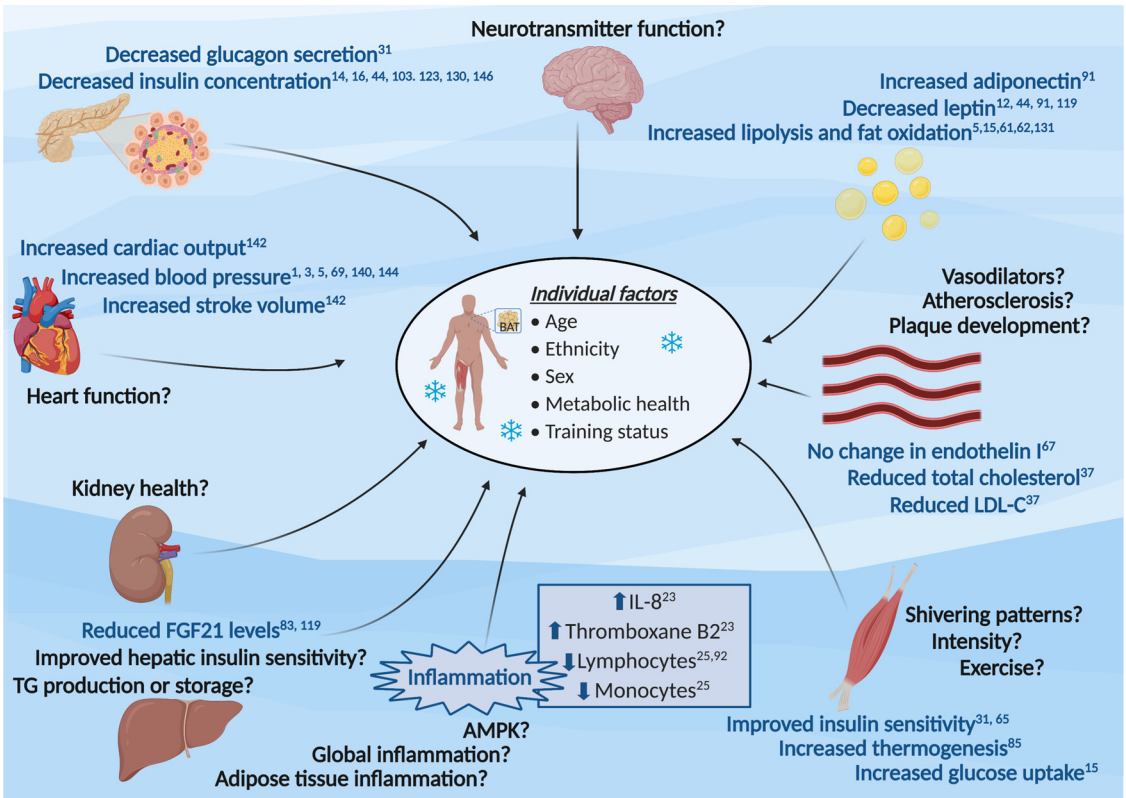

Figure 3. Therapeutic benefits of cold exposure according to the pathophysiological factors responsible for the progression of metabolic diseases. Previously reported evidence of responses to an acute bout of cold exposure is shown in blue whereas as research gaps are shown in black. A small body of literature suggests that cold exposure decreases leptin and increases adiponectin levels (40, 124, 138–141). Cold exposure also increases whole body lipolysis and fatty acid oxidation (40, 61, 67, 70, 140). Limited data suggest that cold exposure has no effect on angiotensin II (140) or endothelin I (142), one of the most potent vasoconstrictors, but whether cold impacts atherosclerosis and plaque development remains unclear (143). Cold exposure is shown to increase peripheral insulin sensitivity (115) as well as thermogenesis and glucose uptake in muscles (38, 48). However, it is not known what the determinants of shivering patterns are or whether they are modifiable through repeated exposures. It is also not clear to what extent individual factors such as aging, ethnicity, sex, metabolic health, or training status impact these responses. Cold exposure impacts inflammation but whether this results in a reduction in global or tissue-specific inflammation remains unknown (144–146). Furthermore, it remains unclear whether cold exposure affects triglyceride production or storage in the liver. There is a small body of literature that suggests that cold exposure leads to changes in the secretion of several hormones including insulin (139), glucagon (147), ghrelin (40, 147), and FGF21 (138, 148). Whether cold exposure has any effects on kidney, heart (135), and neurotransmitter function remains to be elucidated. Figure created with BioRender.com.

in cardiovascular complications and all-cause mortality. Clearly, further work is needed with controlled experimental conditions to more carefully assess how cold exposure influences cardiovascular responses and myocardial function.

CONCLUSIONS

Historically, cold exposure research has been driven primarily by interests and concerns identified in the field by armed forces, emergency rescue teams, and generally outdoor workers and adventurers. Consequently, until recently, our understanding of the metabolic and cardiovascular impact of cold exposure has been limited to more extreme cold conditions. The (re)discovery of BAT in adult humans in 2007–2009 shifted the focus of cold exposure research toward examining the potential metabolic benefits of mild exposures to the cold. In that time, the field has grown dramatically and there has been mounting evidence demonstrating that cold exposure, through the stimulation of thermogenic processes and in particular the recruitment of shivering skeletal muscles, can improve glucose homeostasis and insulin sensitivity, increase the rate of glucose and fatty acid oxidation, and modify the organ-specific handling of dietary fatty acids compared with ambient conditions. Although the findings to date have been quite remarkable, there is also very limited scope largely focusing on young, lean, and healthy men. There is a significant gap in understanding the role of age, sex, race, and training status on these metabolic and cardiovascular responses to cold exposure (Fig. 3). In addition, although the evidence points strongly toward cold exposure being a promising adjunct or complementary therapeutic strategy to counteract the development of obesity or the progression of T2D, very few studies have examined acute cold-induced metabolic responses in these populations. Even fewer have investigated the impact of daily cold exposure as an intervention in these populations, despite the various claims strongly suggesting its therapeutic potential. Further work is needed to determine the frequency, minimal intensity, duration, and type of cold exposure required to elicit meaningful metabolic changes in individuals with metabolic syndrome and whether there may by any contraindications to performing such interventions in certain populations. Future work should also broaden the characterization of cold responses in order to better appreciate its therapeutic potential in targeting several of the pathophysiological factors responsible for the progression of metabolic diseases. The integrative simultaneous stimulation of multiple organ systems resulting from cold exposure makes it ideally suited as a nonpharmacological exercise mimetic. This could thereby further expand the choices available in our movement menu to treat or prevent obesity and its associated metabolic complications.

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DISCLOSURES

D. P. Blondin holds the GSK Chair in Diabetes of Université de Sherbrooke. None of the other authors has any conflicts of interest, financial or otherwise, to disclose.

AUTHOR CONTRIBUTIONS

Y.M.I. and D.P.B. conceived and designed research; Y.M.I. and D.P.B. prepared figures; Y.M.I. and D.P.B. drafted manuscript; Y.M.I. and D.P.B. edited and revised manuscript; Y.M.I. and D.P.B. approved final version of manuscript.

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