Received: 11 February 2021 | Revised: 14 May 2021 | Accepted: 19 November 2021

DOI: 10.1002/evan.21930

REVIEW ARTICLE

Evolutionary Anthropology ISSUES, NEWS, AND REVIEWS WILEY

The evolutionary significance of human brown adipose tissue: Integrating the timescales of adaptation

Stephanie B. Levy[1,2] | William R. Leonard[3]

[1]Department of Anthropology, CUNY Hunter College, New York, New York, USA

[2]New York Consortium in Evolutionary Primatology, New York, New York, USA

[3]Department of Anthropology, Northwestern University, Evanston, Illinois, USA

Correspondence
Stephanie B. Levy, Department of Anthropology, CUNY Hunter College, 695 Park Ave., New York, NY 10065, USA.
Email: stephanie.levy@hunter.cuny.edu

Abstract

While human adaptability is regarded as a classical topic in anthropology, recent work provides new insight into metabolic adaptations to cold climates and the role of phenotypic plasticity in human evolution. A growing body of literature demonstrates that adults retain brown adipose tissue (BAT) which may play a role in non-shivering thermogenesis. In this narrative review, we apply the timescales of adaptation framework in order to explore the adaptive significance of human BAT. Human variation in BAT is shaped by multiple adaptive modes (i.e., allostasis, acclimatization, developmental adaptation, epigenetic inheritance, and genetic adaptation), and together the adaptive modes act as an integrated system. We hypothesize that plasticity in BAT facilitated the successful expansion of human populations into circumpolar regions, allowing for selection of genetic adaptations to cold climates to take place. Future research rooted in human energetics and biocultural perspectives is essential for understanding BAT's adaptive and health significance.

KEYWORDS
circumpolar, cold stress, development, human energetics, metabolism, phenotypic plasticity

1 | INTRODUCTION

How do humans thrive in a broad array of ecological conditions? Human adaptability, and in particular the study of biological adaptation to cold climates, is considered a classical topic in biological anthropology.[1,2] By investigating biological adaptation to cold climates, we aim to shed light on the process of adaptation in humans and the origins of our extreme adaptability.

Since the early 20th century, research has demonstrated that indigenous circumpolar populations utilize metabolic adaptations to generate body heat in order to survive in cold climates. Early studies of Inuit populations of Alaska and Canada found that their basal metabolic rates (BMR) were 25%–35% higher than reference values (see Table 1 for glossary).[3,4] These initial findings were questioned because of relatively small samples and lack of control for the potentially confounding effects of anxiety, diet, and body composition.[5] More recent research, with controlled measurement conditions, has largely confirmed the early studies in documenting elevated BMRs among indigenous arctic groups in North America, Asia and Europe.[6–8] Additionally, total energy expenditure (TEE) is significantly elevated among groups that are acclimatized to cold climates.[9,10] What remains unclear are the specific pathways through which indigenous circumpolar populations increase metabolic heat production in response to cold stress.

Non-shivering thermogenesis (NST) heat production that is not associated with muscle activity during shivering was first described in the 1950s; however, researchers continue to debate the biological mechanisms that are responsible for NST in adult humans.[11] Recent research suggests that brown adipose tissue (BAT) plays a significant role in human NST.[12] BAT is a form of adipose tissue that generates heat during exposure to cold stress. Brown fat has long been recognized as the primary source of NST in infants due to their underdeveloped musculature and inability to shiver.[13] BAT deposits were previously thought to decline to negligible amounts during development; however, during the late 2000's a series of studies using positron emission tomography (PET) and computed tomography (CT) detected BAT in adults.[14] Today, it has been demonstrated that adults that exhibit greater BAT metabolic activity during acute cold

TABLE 1 Glossary

Term	Definition
Basal metabolic rate (BMR)	The number of calories required to maintain baseline bodily functions
Total energy expenditure (TEE)	The total number calories burned by an individual including energy allocated toward BMR, thermogenesis, diet-induced thermogenesis, and physical activity
Non-shivering thermogenesis (NST)	Heat that is produced through biological mechanisms that are separate from muscle twitching during acute cold exposure
Brown adipose tissue (BAT)	A specialized type of fat that functions to produce heat in part by uncoupling oxidative phosphorylation from ATP production
Uncoupling protein 1 (UCP1)	A protein found in the inner membrane of the mitochondria of brown adipocytes and allows the proton gradient to bypass ATP production
BAT thermogenesis	Heat produced through the metabolic and endocrine action of BAT
Beige fat	A form of fat that exhibits a blend of white and brown adipocyte characteristics
White adipose tissue (WAT)	The most prevalent type of fat on the body; functions to store energy in the form of lipids within fat vacuoles
Visceral adipose tissue (VAT)	Intra-abdominal adipose tissue that surrounds the internal organs
Subcutaneous adipose tissue (SAT)	Adipose tissue located just below the skin
Homeostasis	The process of rapid change in physiology and gene expression that works to maintain a physiological set-point in response to an environmental stimulus
Allostasis	The regulation of internal biology through rapid changes in physiology and gene expression in response to an environmental stimulus and the prediction of future needs
Acclimatization	Physiological changes that occur over the course of days to weeks that work to maintain biological functions in response to a new environmental condition
Developmental adaptation	Changes in physiology or morphology that occur during development in response to environmental conditions that result in an improvement in evolutionary fitness
Epigenetic inheritance	The transmission of information about the environment across generations via the inheritance of epigenetic marks
Sensitive period	A developmental stage in which exposure to an environmental factor influences the emergence of a specific phenotype

exposure experience a larger increase in energy expenditure.[15–17] Additionally, greater BAT mass is linked to lower risk of developing cardiometabolic diseases such as diabetes and heart disease.[18]

The determinants of human variation in BAT, its evolutionary origins, and its adaptive significance remain unclear. The following review provides a brief overview of BAT's physiology, anatomical distribution and developmental origins. We then apply the timescales of adaptation framework in order to explore how multiple modes of adaptation to cold climates may shape variation in human BAT. First, we examine how BAT thermogenesis contributes to allostatic responses to acute cold stress by reviewing the relationship between BAT, NST and cold-induced energy expenditure. Next, we explore the role that BAT plays in acclimatization to seasonal cold stress by considering variation in this tissue across climates and BAT plasticity in response to repeated cold exposure. While research examining BAT thermogenesis in infants and children is limited, we explore how the process of developmental adaptation may result in population variation in adult BAT. We also review recent work in animal models that highlights potential mechanisms through which epigenetic inheritance may program offspring BAT development. Finally, we summarize recent evidence that indigenous circumpolar populations may exhibit genetic adaptations to cold climates that facilitate greater BAT mass and activity. We conclude by highlighting several topics that require further investigation. Our review highlights the degree to which the adaptive modes interact with each other and how one adaptive mode may facilitate another. We propose that as humans migrated into circumpolar regions, pre-existing phenotypic plasticity in BAT facilitated the evolution of genetic adaptations to cold climates.

2 | PHYSIOLOGY, ANATOMY AND DEVELOPMENT OF BROWN ADIPOSE TISSUE

In most mammals, BAT increases heat production during NST by uncoupling oxidative phosphorylation from ATP production so that the proton gradient is dissipated via uncoupling protein 1 (UCP1), thus generating heat (Figure 1). This process is referred to as BAT thermogenesis.[15] Current research enabled by ^{18}F-fluoro-deoxyglucose (FDG) PET/CT confirms a handful of reports from the 1980s documenting BAT deposits in adult humans.[13] Past work indicates that human BAT metabolism is acutely stimulated by exposure to low temperatures and documents a large amount of variation in both BAT volume and activity across individuals.[19]

The anatomical locations of human BAT depots vary across development. In neonates, BAT is primarily stored in the interscapular region as well as around the muscles and blood vessels of the neck, the axillae, the mediastinum between the esophagus and trachea, around the heart, and near the kidneys.[20–22] BAT volume then declines across infancy and the interscapular depot is absent in children.[23] While pediatric studies of BAT are limited, preliminary evidence suggests that BAT volume may increase around the time of puberty.[24] There are three main BAT depots in adult humans: supraclavicular, mediastinal, and infradiaphragmatic (Figure 2).[25–28] The supraclavicular depot includes BAT deposits in the neck and above the clavicle. The mediastinal depot consists of BAT deposits around the spine and heart, while the infradiaphragmatic depot includes BAT

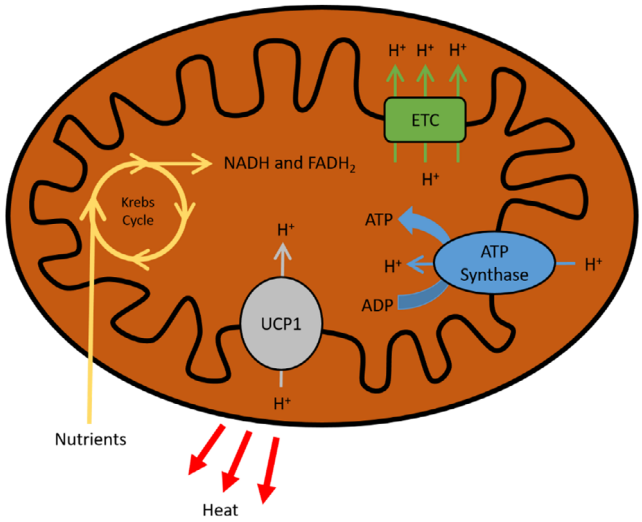

FIGURE 1 The uncoupling of oxidative phosphorylation from adenosine triphosphate (ATP) production within a brown adipocyte mitochondrion. Nutrients are transported across the inner membrane of the mitochondrion where they are used to fuel the Krebs cycle. The Krebs cycle provides electrons in the form of nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$) for the electron transport chain (ETC). The ETC uses the electrons to pump protons (H^+) across the inner membrane to produce a proton gradient. ATP synthase then uses the proton gradient to convert adenosine diphosphate (ADP) to ATP. Brown adipocyte mitochondria contain uncoupling protein 1 (UCP1) which allows protons to bypass ATP synthase and travel back across the inner membrane, leading to heat generation

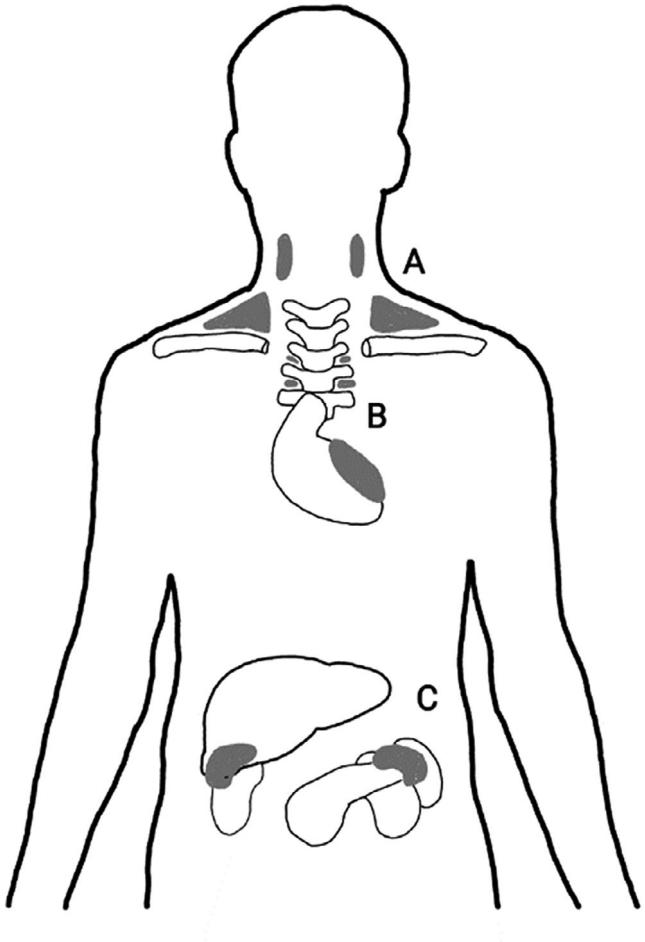

FIGURE 2 Anatomical locations of brown adipose tissue (BAT) deposits. The gray areas represent BAT deposits. (a) Supraclavicular depot: BAT located above the clavicles and in the neck. (b) Mediastinal depot: BAT located near the spine and heart. (c) Infradiaphragmatic depot: BAT located near the kidneys/adrenal glands, pancreas, liver, and spleen

near the kidneys/adrenal glands, pancreas, liver and spleen. Interestingly, the distribution of BAT exhibits a cranio-caudal gradient such that all adults with BAT in the mediastinal depot have BAT in the supraclavicular depot, and all adults with BAT in the infradiaphragmatic depot also have deposits in the mediastinal depot.[25–28]

It is possible that the cranio-caudal distribution pattern reflects the importance of maintaining warm blood flow to the brain. During cold stress exposure, supraclavicular BAT may ensure that blood traveling to the brain is an adequate temperature in order to maintain neural activity. The energy-consuming reactions of the brain are highly sensitive to reductions in core temperature.[29] BAT localized around the spinal cord, heart, kidneys, pancreas, liver and spleen may ensure adequate temperatures for the metabolic processes of these critical organs.

Another thermogenic adipose tissue known as beige fat or brite fat consists of adipocytes with a phenotype that is a blend of brown and white adipocyte characteristics. Beige adipocytes contain far less UCP1—about 10% of that found in classical BAT—and beige fat stores are less vascularized and innervated.[30] Recent work suggests that beige adipocytes exhibit thermogenic mechanisms that are independent of UCP1.[31] Beige adipocytes are scattered within brown adipocyte depots, such as the supraclavicular region, as well as in white adipose tissue (WAT) in adults.[30] In humans, visceral adipose tissue depots express higher levels of browning genes indicative of beige adipocytes than subcutaneous adipose tissue, while the opposite pattern is found in rodent models.[32] Some publications report that classical brown adipocytes are absent in humans after infancy and only beige adipocytes persist into adultood.[33]

Brown and beige adipocytes also differ in their developmental origins. Classical brown adipocytes originate during embryogenesis, before the development of white adipocytes, from a subpopulation of dermomyotomes that are marked by the expression of specific transcription factors.[31,34,35] Beige adipocytes, on the other hand, develop postnatally and are derived from non-dermomyotome lineage.[36] Additionally, beige adipocytes arise from multiple distinct developmental subtypes. For instance, distinct beige adipocyte progenitor cells (APCs) reside within the walls of adipose tissue capillaries and the stromal cells from human abdominal subcutaneous WAT.[37,38] In rodents, cold exposure can induce mature white adipocytes to transform into to beige adipocytes through transdifferentiation.[39,40] Furthermore, it is possible that beige adipocytes have heterogeneous origins within a single WAT depot, and that multiple subtypes of beige

adipocytes emerge depending on physiological and cellular conditions.[31,41,42] Below we utilize the timescales of adaptation framework in order to explore how multiple modes of adaptation to cold climates may shape variation in human BAT.

3 | TIMESCALES OF ADAPTATION MODEL

Building on the work of Lasker (1969) and Mazess (1975), biological anthropology recognizes multiple modes of adaptation, or adaptive processes that occur along different timescales.[43,44] These include homeostasis/allostasis, acclimatization, developmental adaptation, epigenetic inheritance, and natural selection of genes (Figure 3).[45] The timescales of adaptation framework highlights that the form, strength, and nature of an adaptive response depends not only on the type of stressor or experience, but also the timing and duration for which the perturbation exists.[46] For instance, homeostatic responses alter physiology rapidly and reversibly in reaction to environmental changes that occur in a matter of minutes, while a genetic response to environmental change through natural selection occurs over multiple generations in response to sustained selective pressure.[47] As the time length of a novel environmental challenge increases within an individual's lifetime and across generations, each adaptive mode is layered onto the next.[46] Thus, a single biological pathway can be shaped by multiple overlapping and interacting timescales of adaptation.

One advantage of the timescales of adaptation model is that it conceptualizes adaptation as an active process, rather than a final state.[48] The process of adaptation has tangible, quantifiable outcomes, but not endpoints in and of themselves. Thus, this approach allows researchers to avoid categorizing responses into a simple dichotomy of adaptive versus maladaptive states. Rather, here we define adaptation as a process of morphological, physiological, or genetic change that occurs over a range of timescales and results in enhanced evolutionary fitness at the population level.

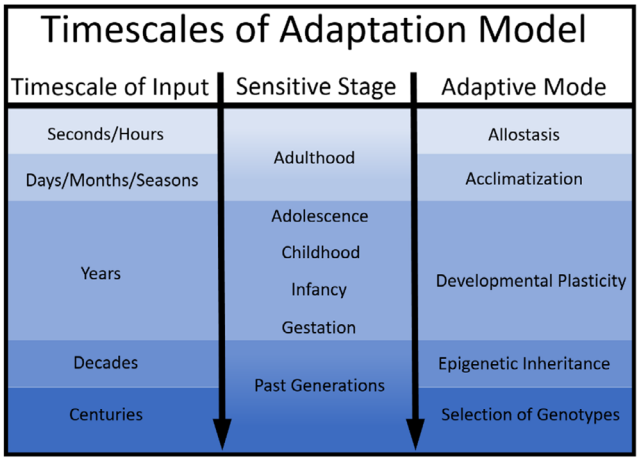

FIGURE 3 The timescales of adaptation model. Each adaptive mode represents a biological response to a change in the environment. The timescale of the environmental change will dictate the type of biological response. This model hypothesizes that as a novel environmental stressor persists in a population over time, the adaptive modes accumulate and form an integrated system

There are, however, key limitations to this definition and the timescales of adaptation model. First, the model does not assist researchers in determining whether a biological response to an environmental change is due to evolutionary constraint. For example, a trait may represent a vestige from a common ancestor. If a pathway is highly integrated into an organism's developmental infrastructure, it may be costly to remove and may therefore survive in modern lineages despite the lack of current utility.[49] Most, if not all, biological responses to environmental inputs likely have both adaptive and vestigial elements, and disentangling the relative importance of these alternative explanations is challenging.[50]

Additionally, mismatch between a phenotype and an individual's environmental conditions can occur when the timescale and/or magnitude of environmental change exceeds the combined capacity of the adaptive modes.[46] With any shift in the ecological or social environment, there may be insufficient information or the wrong environmental information may be used, thus resulting in a cost to fitness.[45] Environment-phenotype mismatch is an especially pertinent issue for species with long lifespans like humans.[51]

Nevertheless, the utility of the timescales of adaptation model is rooted in the ability to conceptualize the adaptive modes as a single integrated system of overlapping responses to a range of timescales of environmental change. Human energy allocation strategies can be viewed as the product of the interaction of all the adaptive modes. As Ellison states, deconvoluting the effects of environmental change on different timescales on a single biological system, tissue or parameter is "an exceedingly difficult task".[52] To understand how variation in a particular trait is shaped by various timescales of environmental change, measurements must be taken across a wide range of environments and across the life course. In order to examine how multiple timescales of adaptation produce variation in BAT across humans, we begin by exploring BAT's allostatic response to acute cold exposure (Box 1).

4 | BROWN ADIPOSE TISSUE, NON-SHIVERING THERMOGENESIS, AND ALLOSTASIS

NST is a critical allostatic response to acute cold stress. When thermoreceptors in the skin detect a change in ambient temperature, the sympathetic nervous system (SNS) generates norepinephrine via the sympathetic ganglia and releases norepinephrine and into the bloodstream via the adrenal glands. This increase in circulating norepinephrine quickly triggers NST, leading to an increase in whole-body energy expenditure.[54]

Studies of human NST conducted in western, educated, industrialized, rich, and democratic (WEIRD) populations as well as indigenous Siberian groups document dramatic inter-individual variability—some adults fail to mobilize NST in response to mild cold stress and do not exhibit an increase in energy expenditure, while others experience an

BOX 1 Homeostasis and allostasis

Homeostatic mechanisms represent the fastest mode of adaptation; they are thought to defend a particular set point by incorporating adjustments in physiology and gene expression on the timescale of seconds to hours in response to local feedback.[46,53] Sterling argues, however, that the homeostasis model fails to recognize that physiological systems must respond to changing environmental conditions by altering the set point.[53] If a system is designed to resist fluctuations, it cannot address changing needs. Rather, Sterling proposes that, through a process termed allostasis, physiological mechanisms change a controlled parameter by predicting what level will be needed and then overriding local feedback to meet the anticipated demand. The allostasis model is built on the assumption that organisms are designed for efficiency, and that efficiency requires reciprocal trade-offs between systems and predictive signals that anticipate future needs. Thus, the mean value of a parameter does not signify the particular set point of a system, but rather the system's most frequent demand.[53] The thermoregulatory processes that defend internal body temperature are considered a classic example of a homeostatic system because mammalian thermoregulation maintains it within a narrow range. A body temperature of around 37.0°C/98.6°F, however, is simply the most frequent optimum parameter for a majority of the human body's biological functions.

increase in resting metabolic rate of over 30%.[15,55] Some of this variation may be because thermoregulatory responses to cold, including NST, become blunted with age.[56] For instance, a sample of older men in Maryland, USA (mean age 63 years) exhibited significantly lower oxygen consumption rates than younger men (mean age 21 years) in response to a cold challenge.[56]

BAT is hypothesized to play a role in allostatic responses to cold stress via NST since it is able to quickly convert stored energy into heat. BAT is densely innervated by the SNS, thus allowing for rapid activation of BAT thermogenesis. Norepinephrine activates β2- and β3-adrenergic receptors located on the cellular membrane of brown adipocytes, stimulating the production of UCP1 and intracellular lipolysis.[12,57] Fatty acids then, fuel the respiratory chain where UCP1 dissipates the mitochondrial proton gradient as heat. To replenish lipid stores, brown adipocytes predominantly take up triglyceride-derived fatty acids from circulation in a lipoprotein lipase-dependent manner.[58] BAT also has a high glucose uptake rate per gram of tissue.[59] Additionally, BAT is highly vascularized, which facilitates the efficient transfer of oxygen and substrates toward brown adipocytes. This also allows heat and adipokines generated by BAT to be transported to the rest of the body.[12]

Adults with greater BAT metabolism exhibit a larger increase in energy expenditure during exposure to cool temperatures in both circumpolar and temperate populations.[15] For instance, Muzik et al. and u Din et al. report a significant association between the degree to which whole-body energy expenditure increases during cold exposure and BAT mass.[16,17] While estimates vary depending on the time length and severity of the cold exposure, previous work documents that adults with BAT experience an increase in energy expenditure of 3%–30% during a cold challenge.[15,60] Additionally, adults with PET/CT-detected BAT maintain significantly warmer core body temperatures during cooling and can withstand colder temperatures without shivering than those lacking BAT.[61] When study participants in Québec, Canada are given oral nicotinic acid to inhibit intracellular triglyceride lipolysis, thus suppressing cold-induced BAT oxidative metabolism, they experience a commensurate increase in shivering, suggesting a reciprocal role for BAT thermogenesis and shivering.[62]

Recent work conducted among WEIRD populations suggests that despite evidence of a significant relationship between BAT volume and cold-induced energy expenditure, the tissue-specific metabolic rate of adult human BAT may be lower than previously thought. Early estimates proposed that just 40–50 g of BAT could account for 20% of daily energy expenditure.[63] Muzik et al. used dynamic PET-CT scans with fluorodeoxyglucose (^{18}F-FDG) tracer to quantify BAT mass and used triple oxygen tracer (H_2 ^{15}O, $C^{15}O$, and $^{15}O_2$) to quantify the oxygen consumption per gram of BAT.[16] They found that the range of BAT mass found in participants with significant BAT deposits was between 32–85 g. When activated by cold, BAT contributed less than 12 kcal/100 g/day to total energy expenditure. Based on this estimate, 50 g of BAT would contribute just 0.25 kcal to total energy expenditure per hour of cold exposure. While this estimate of the tissue-specific metabolic rate of BAT is 2–10 times higher than that of WAT and skeletal muscle during mild cold exposure, the fact that BAT likely represents a very small portion of total adipose tissue diminishes its relative contribution to TEE.[11,17] Similar estimates were found by u Din et al.; however, and Leitner et al. and Martinez-Tellez et al. document higher estimates of BAT volume and metabolic activity.[17,27,64] For instance, Leitner et al. estimate that a cold-acclimatized human may generate an extra 115.5 kcal/day via BAT metabolism. Variation in estimates is likely due to differences in the PET/CT methods used to identify BAT and quantify glucose uptake.

If the contribution of BAT metabolism to whole-body energy expenditure is low, why do adults with greater BAT mass experience larger increases in energy expenditure during NST? BAT thermogenesis may act as an indirect biomarker of energy expended by other tissues that are also triggered by the same neuroendocrine changes during NST (see Figure 4). For instance, norepinephrine not only triggers BAT metabolism and biogenesis, but it also stimulates metabolism in skeletal muscle, heart muscle, and the liver. Thus, BAT metabolism may reflect variation in the metabolic action of norepinephrine on other tissues.[65] Alternatively, BAT

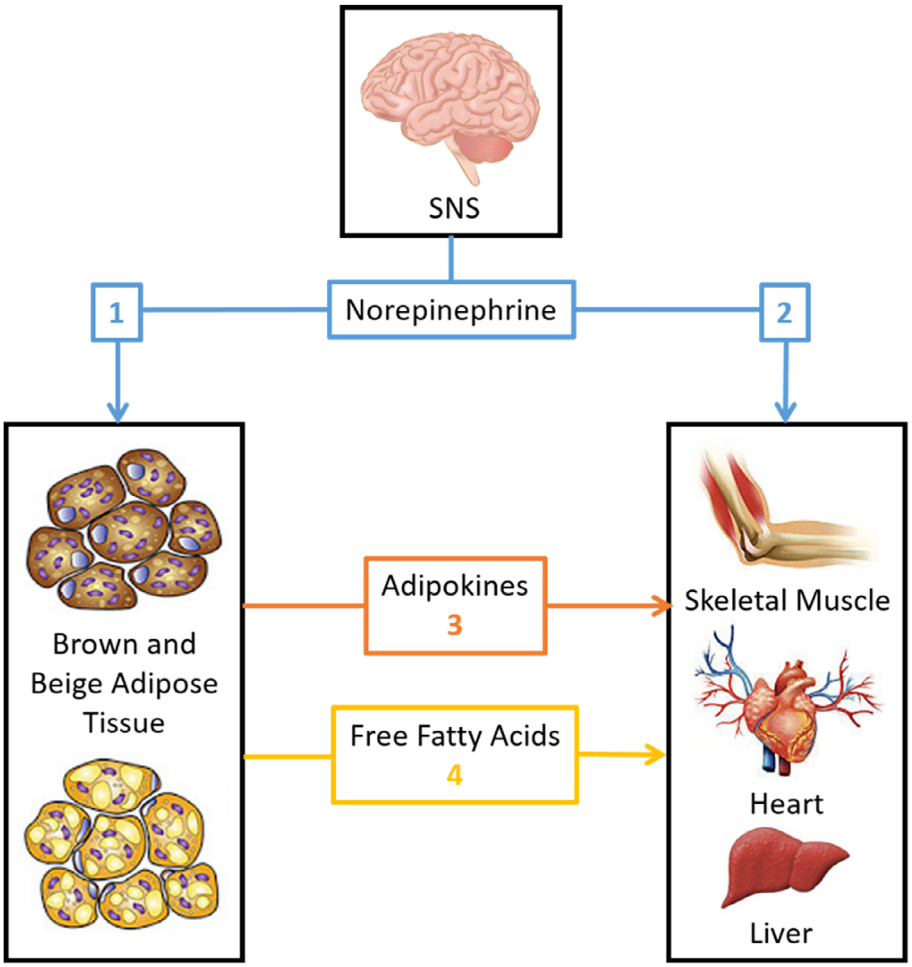

FIGURE 4 Metabolic pathways hypothesized to contribute to whole-body energy expenditure (EE) during cold stress that may correlate with BAT mass/metabolism. (1) Norepinephrine produced by the sympathetic nervous system (SNS) activates beige and brown adipocyte metabolism. This may contribute to cold-induced EE. (2) Norepinephrine produced by the SNS activates metabolism within skeletal muscle, heart, and liver, which may contribute to an increase in EE. Simultaneous metabolic activation in beige/brown fat might be correlated with the degree of activation in these other tissues. (3) During metabolic activation by the SNS, beige and/or brown adipocytes may produce adipokines, such as IL-6, which in turn activates the metabolism of skeletal muscle, heart or liver, contributing to cold-induced EE. (4) During metabolic activation by the SNS, beige and/or brown adipocytes may release free fatty acids, which act as a fuel source for metabolism in skeletal muscle, heart, and liver, contributing to cold-induced EE. Each of these four pathways require additional research in order to determine their relative contribution to whole-body EE during cold stress

may contribute to cold-induced energy expenditure through its action as an endocrine organ by triggering an increase in metabolism within other tissues during NST.[66] For instance, BAT secretes cytokines, such as interleukin-6 (IL-6), transcription factors, and other adipokines that can regulate metabolic pathways in skeletal muscle, cardiac muscle, and the pancreas.[66] Additionally, experiments suggest that up to 50% of fatty acids hydrolyzed by BAT are released into the extracellular media where they may be oxidized elsewhere, thus possibly providing fuel for thermogenesis in other tissues.[11]

Skeletal muscle has long been hypothesized to play a role in NST in humans.[67] Studies conducted in WEIRD countries have found that the degree to which skeletal muscle metabolism contributes to NST varies greatly depending on the muscle location. Muscles in the periphery, such as the trapezius and deltoid, tend not to exhibit changes in metabolism during NST, although Wijers et al. reports an increase in mitochondrial uncoupling in vastus lateralis after cooling.[68,69] Deep muscles, such as the levator scapulae, which co-locate with BAT, do exhibit an increase in metabolism during NST.[17] u Din et al. estimated that muscle of the cervico-thoracic region contributes about 86 kcal/day during cold exposure.[17] Additionally, few studies have attempted to quantify possible changes in metabolic rate during NST of the internal organs.

Finally, existing estimates of the contribution of BAT to cold-induced whole-body energy expenditure may not account for the contribution of beige adipocytes scattered within white adipose depots. Given that cold exposure can induce WAT browning in addition to recruiting new brown adipocytes, adults with larger BAT deposits may also have larger number of beige adipocytes scattered within white fat.[70] The metabolic activity of beige adipocytes located in WAT may go unnoticed depending on how PET/CT studies determine regions of interest and their threshold of detection. Virtanen et al. found that subjects with BAT exhibit a larger increase in WAT metabolism during cooling compared to subjects without BAT—perhaps due to a higher concentration of beige adipocytes in WAT.[71] In mice, the thermogenic activity of beige fat is low because UCP1 expression and mitochondrial density are reduced compared to brown adipocytes; however, the contribution of beige fat thermogenesis to energy expenditure in humans is unknown.[11]

In sum, this work suggests that BAT may play a mechanistic role in NST—a critical allostatic response to acute cold stress. NST is known to increase whole body energy expenditure, and BAT thermogenesis is correlated with elevations in energy expenditure during NST; however, the biological pathways that link BAT thermogenesis and cold-induced energy expenditure are still unclear. BAT lipid metabolism may provide fuel for increases in energy expenditure of

other tissues, it may warm local organs and facilitate faster metabolic reactions, or it may play an endocrine function by signaling to other tissues to increase their metabolic rate. A growing body of work suggests that NST requires a complex system that integrates multiple mechanisms including BAT metabolism, the conversion of white to beige/brown adipocytes, skeletal muscle metabolism, and other metabolically active organs.[67] More work is needed in order determine why some individuals exhibit NST as an allostatic response to low temperatures and others do not. The following section explores the significance of seasonal acclimatization in shaping variation in metabolic responses to cold stress and BAT thermogenesis (Box 2).

5 | BROWN ADIPOSE TISSUE AND ACCLIMATIZATION

Evidence of human acclimatization to cold stress dates back to the early 20th century; long-term elevations in resting metabolic rate were observed among circumpolar populations.[3] More recent work indicates that the Yakut, an indigenous population of northeastern Siberia, exhibit significant increases in resting metabolic rate during the winter.[77] While researchers have yet to explore the significance of BAT acclimatization for survival and reproduction in cold climates, seasonal increases in BAT thermogenesis and cold-induced energy expenditure have been documented among WEIRD populations.[78] Van der Lans et al. found that after 10 days of exposure to 15–16°C for 6 h/day, BAT volume increased significantly.[60] Similarly, Lee et al. documented significant increases in BAT metabolism after 1 month of exposure to 19°C while sleeping.[79] Efremova and colleagues collected fat cells at necropsy from individuals in Siberia and found higher UCP1 expression in cells collected from outdoor workers than indoor workers suggesting differences in acclimatization.[80]

Current research has revealed several physiological and cellular mechanisms that link sustained cold stress exposure to greater BAT mass and thermogenic potential. Acclimatizing mechanisms increase the capacity of allostatic mechanisms to manifest greater thermogenesis by increasing BAT mass and metabolic activity. For example, frequent exposure to low temperatures leads to hormonal changes that promote the proliferation of new brown adipocytes.[59] Recurrent stimulation of BAT adrenergic receptors by norepinephrine facilitates tissue growth.[59] Circumpolar populations exhibit an increase in tissue uptake of triiodothyronine (T3) from the bloodstream from summer to

BOX 2 Acclimatization

When an individual is introduced to a stressor over several days to months, for example as a result of seasonality, chronically activated allostatic mechanisms can alter their underlying baseline biology. The resulting biological response may be greater in duration, degree, or sensitivity to the environmental stimulus. This process is referred to as acclimation when the biological change is in response to a single environmental stimulus, typically within the context of an experiment. The term acclimatization is used to describe responses to complex environmental conditions outside of a laboratory setting.[72] The biological pathways that facilitate this long-acting response may include epigenetic mechanisms, hormone dynamics, or other physiological, biochemical or anatomical responses.

The adaptive significance of acclimation/acclimatization is widely debated. The beneficial acclimation hypothesis (BAH) proposes that acclimation to a particular environment gives an organism a performance advantage in that setting over other organisms that have not had the opportunity to acclimate; however, evidential support for the BAH is mixed.[73] Furthermore, many studies that advocate for the evolutionary significance of acclimatization have simply elucidated the mechanistic basis of a trait and then proposed post-hoc adaptive stories to explain their functional significance.[74] While acclimatization has the potential to improve the likelihood of survival and reproduction within the context of environmental stressors, there are several reasons why some biological changes that occur in response to weeks or months of stressor exposure may not incur a fitness advantage. For instance, in order for acclimatization to be adaptive, exposure to the sustained environmental stressor must be predictive of future stressor exposure. If certain environmental conditions provoke a long-lasting biological response but the triggering conditions are not a reliable cue for future exposure, the resulting biological changes are unlikely to improve an organism's chances of survival and reproduction.[73] The observed biological changes in response to a sustained stressor may represent unavoidable wear-and-tear on the stress-response system, and the costs may outweigh the fitness benefits.[75] Additionally, biological changes in response to a sustained environmental stressor may be due to genetic, developmental or physiological constraint and may not have an adaptive advantage.[73]

Previous work, however, has argued that studying plasticity in response to thermal stressors may be particularly valuable in understanding the adaptive significance of acclimatization for two reasons.[76] First, researchers can easily assess variation in the thermal environment over relevant timescales and estimate the predictability of changes in ambient temperature for future stressor exposure. Second, because exposure to cold or hot climates can be easily quantified, traits related to thermoregulation can be mechanistically linked to stressor exposure.[76] The challenge then lies in demonstrating that individuals that have undergone the process of acclimatization are in fact more likely to survive and reproduce within the context of the thermal stressor.

winter.[81] T3 is the biologically active form of thyroid hormone and is known to stimulate brown adipogenesis and sensitivity to adrenergic stimuli.[12,59] Additional research is needed in order to determine the minimal time length and degree of cold exposure needed to elicit a shift in BAT mass and metabolic activity via acclimatization. The severity of cold exposure required to produce an acclimatization response likely varies across individuals and populations.

When mammals are exposed to thermoneutrality for long periods of time, beige adipocytes undergo morphological "whitening".[70] Roh et al. housed mice at 4°C for 1 week to induce beige adipocyte formation, and then rewarmed by housing them at 30°C for 8 weeks. The authors found that rewarming caused the beige adipocytes to develop a unilocular morphology and downregulate thermogenic gene expression. Warmed beige adipocytes, however, appear to retain an epigenetic memory of past cold exposure.[70] Roh et al. found that cold-exposed beige fat cells that are then re-warmed exhibit an epigenetic pattern on a subset of lipid metabolism genes that is consistent with being inactive but "poised" for future activation.[70] The epigenomic memory of beige fat cells may represent an important mechanism for seasonal acclimatization to cold stress.

This work suggests that acclimatizing mechanisms modulate BAT's capacity to generate an allostatic response to acute cold stress via NST.[78] In this way, acclimatization modifies the adaptive significance of the allostatic response. Next, we will explore how BAT developmental plasticity may further fine-tune acute metabolic reactions to cold stress (Box 3).

6 | BROWN ADIPOSE TISSUE AND DEVELOPMENTAL ADAPTATION

Human development is characterized by important changes in adipose tissue mass and physiology.[85] BAT first develops in humans around the 20th gestational week.[86] The neonate experiences cold stress for

BOX 3 Developmental adaptation

Developmental stages such as gestation, infancy, childhood, and adolescence are characterized by a heightened sensitivity to environmental conditions and a greater degree of phenotypic plasticity when compared to adulthood. When developmental responses to environmental stimuli incur a fitness benefit, this process is termed developmental adaptation.[82] Developmental adaptations manifest through epigenetic, cellular, hormonal, structural, and/or behavioral changes that occur in response to environmental signals.[82]

Developmental adaptations may increase the evolutionary fitness of the organism because enhanced plasticity early in life allows the growing individual to better calibrate the phenotype compared to restricted phenotypic adjustments that occur in adulthood.[82] Additionally, developmental processes may improve allostatic mechanisms or acclimatization by either shifting or broadening the range of detectable sensory inputs or the range of feasible biological responses.[53] In this way, the modes of adaptation (allostasis, acclimatization and developmental adaptation) are interwoven into a complex system.

One important tradeoff associated with developmental plasticity is the risk of phenotype-environment mismatch in adulthood. Cues are expected to have less predictive power as the time lag between the developmental life stage and the reproductive life stage increases. Thus, the adaptive value of developmental plasticity depends on both the timescale of environmental fluctuations (i.e. how quickly is the environment changing and will the environmental alteration persist) and the organism's life history (i.e. how long does it take to reach sexual maturity).[83] Adult acclimatization and allostasis, however, may limit the potential for adult phenotype-environment mismatch generated by developmental plasticity by further modifying the phenotype so that it better fits the adult environment.

Integral to the adaptive significance of developmental plasticity is a debate regarding the timing of sensitive periods, or a time window during which exposure to environmental factors modulate the emergence of a specific phenotype.[84] Some developmental and evolutionary biologists argue that responsivity to environmental conditions is inversely related to the developmental stage of the organism, with the greatest degree of plasticity existing earlier in development (Figure 5a).[82] This pattern is thought to be due to constraints on an individual's ability to adjust its phenotype as development progresses.

Alternatively, the timing of sensitive periods may differ depending on whether the programming cue is sent via the mother's biology or the external environment (Figure 5b). It has been proposed that developmental programming during gestation and infancy is only adaptive within the niche of maternal care.[51] Previous work hypothesizes that maternal biological signals incorporate a longer time depth of environmental information, and thus developmental programming in response to maternal signals will have greater predictive power for anticipating the offspring's future environment.[50] In other words, maternal cues are calibrated by the mother's (and perhaps grandmother's) cumulative experience and are somewhat buffered from acute external conditions during gestation and lactation.[45] On the other hand, sensitivity during childhood and adolescence, life stages characterized by increasing independence, may be tuned into signals from the external environment that are divorced from maternal biology. Future studies may shed light on this issue by investigating the phenotypic consequences of cold climate exposure at different life stages.

the first time at birth, and during the first few weeks of life BAT stores increase significantly.[87] Over time, BAT mass gradually declines as the infant shifts from relying on NST toward shivering as the primary response to cold stress.[23]

The infancy-childhood transition is marked by distinct shifts in adipose tissue gene expression including an increase in the expression of thermogenic genes such as UCP1.[88] Studies that use infrared thermal imaging to quantify BAT thermogenesis in children suggest that the transition from early childhood to middle childhood is marked by a decline in BAT thermogenesis.[89] However, retrospective PET/CT studies of BAT suggest there may be an increase in brown adipogenesis during puberty.[24,90]

If developmental shifts in BAT growth and metabolism are sensitive to environmental conditions, then these transformations may represent potential sensitive periods. As described in Box 3, the timing of sensitive periods may differ depending on whether the programming cue is sent via the mother's biology or the external environment (Figure 5b). It has been proposed that developmental programming during gestation and infancy is only adaptive when signals originate from the mother's biology and possibly incorporate information across multiple generations.[50,91] As the growing child becomes more independent, developmental sensitivity may tune into environmental signals that are separate from the mother's biology.[92]

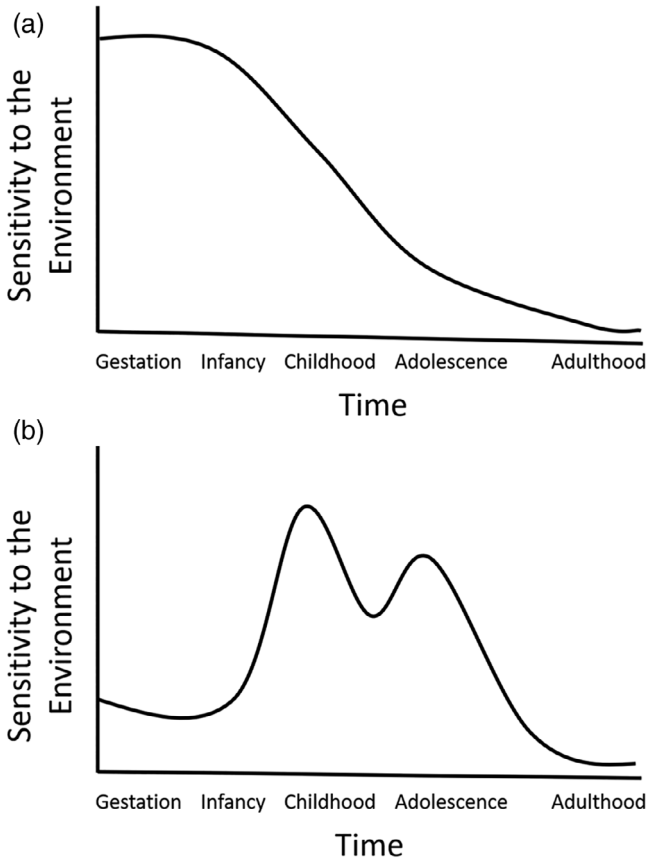

FIGURE 5 Two models depicting the potential timing of sensitive periods. (a) Sensitivity to environmental conditions may be greatest during gestation and infancy and then steadily decline over the life course. (b) Sensitivity to environmental conditions may fluctuate over the life course depending on the source of the environmental information. For instance, sensitivity to climatic conditions may be low during gestation and infancy, increase during childhood, and then decline later in life

Recent work provides preliminary support for this developmental hypothesis. The thermal environment of the fetus is tightly buffered by maternal thermoregulation. Our previous research did not detect a relationship between prenatal ambient temperature and adult supraclavicular skin temperature after cooling among indigenous Siberians.[92] Several endocrine factors that regulate brown adipogenesis, such as thyroid hormone, are sensitive to climatic conditions and pass through the placenta.[81,93] Maternal thyroid hormones may program fetal BAT development; however, this has yet to be investigated.[94]

Similarly, preliminary research did not detect a significant relationship between cold exposure during infancy and adult supraclavicular skin temperature after cooling among Siberians.[92] A recent study in Minnesota, U.S. suggests that lipids in breast milk, such as alkylglycerole-type (AKG-type) ether lipids and 12,13-dihydroxy-9Z-octadecenoic acid (12,13-diHOME), upregulate beige and brown adipocyte metabolism and are associated with infant adiposity.[95] It is interesting to note that circulating 12,13-diHOME increases after a bout of moderate exercise in humans.[96] Additional research is needed to determine the predictors of variation in breast milk lipids and whether there is a relationship between BAT metabolism during infancy and adulthood.

Our research among the Yakut documents preliminary evidence for a sensitive period of BAT plasticity during early childhood.[92] Individuals that were exposed to lower temperatures between 2 and 6 years old exhibit significantly warmer supraclavicular skin temperatures after cooling in adulthood, suggesting greater BAT thermogenesis. Similarly, Yakut adults that spent more time outside during the winter between ages five and 7 years old exhibited evidence of greater BAT activity.[92] It is possible that the systems that regulate BAT development become more sensitive to surrounding environmental conditions that are distinct from maternal biology, such as ambient temperature, as the child grows and gains independence. Alternatively, it is possible that BAT development is sensitive to ambient temperature during gestation and infancy; however, cold stress exposure during pregnancy and infancy is limited in this population due to technological adaptations and infant care practices.[92] The adaptive significance of developmental shifts in BAT mass and metabolism and their sensitivity to environmental conditions requires further investigation (Box 4).

7 | BROWN ADIPOSE TISSUE AND EPIGENETIC INHERITANCE

Key DNA methylation patterns distinguish brown and white adipocyte differentiation.[101] The DNA methylome of brown adipocytes is not only sensitive to environmental cues, it can pre-program cellular function.[102] The question then becomes, do parental signals influence the epigenetic patterns of human brown adipocytes?

BOX 4 Epigenetic inheritance

The field of developmental biology and epigenetics offer evidence of an adaptive mode that responds to environmental cues passed down from previous generations but operates on a timescale that is faster than genetic adaption via mutation and natural selection.[45] This mode involves the transmission of information about the environment across generations via the inheritance of epigenetic marks, or "stable alterations in gene expression potential that arise during development and cell proliferation."[97] There are two types of epigenetic inheritance – context-dependent and germline-dependent.

Context-dependent epigenetic inheritance, also known as intergenerational epigenetic inheritance, is when the developing fetus or infant receives biological signals that convey information about either the current environment or the parent's lived experience.[98] The parental cues alter the offspring's epigenetic patterns and developing phenotype. This type of epigenetic inheritance is considered context-dependent because the induced phenotype is not passed on to the next generation independently of the direct exposure to the parent's biological signal. Germline-dependent epigenetic inheritance, also known as transgenerational epigenetic inheritance, is when the epigenetic patterns of the germline are directly affected by an environmental input, and the modifications persist across generations in the absence of the original signal.[99]

Similar to developmental adaptation, the adaptive significance of epigenetic inheritance depends on the reliability of parental cues for predicting future environmental conditions. When an organism's developing phenotype responds to signals based on past contexts, it runs the risk of cultivating a phenotype that is discordant with adult conditions if the environment changes during its lifetime. Evolutionary theorists hypothesize that for organisms with long lifespans, such as humans, the predictive power of the parental signal will be greater if it incorporates information gathered across the parent's lifetime or across generations rather than responding to the parent's immediate conditions.[50]

Intergenerational phenotypic inertia is when the parental signal that programs the offspring's developing phenotype represents the average environmental conditions of previous generations.[50] This broadens the sampling window by diversifying the sources of environmental cues, potentially buffering the signal from stochastic environmental changes.

Evidence supporting germline-dependent epigenetic inheritance in long-lived species, however, is limited.[100] This is largely due to key mechanisms that limit the transmission of epigenetic marks across generations.[98] Despite these mechanistic constraints, there is evidence from animal models that some epigenetic marks may be buffered from these reprogramming events.

The adaptive significance of epigenetic inheritance may be enhanced by complex interactions with other modes of adaptation. Developmental adaptations (particularly those that respond to cues that are divorced from parental biology), acclimatization, and allostasis may minimize the potential for phenotypic/environmental mismatch by continuing to modify the phenotype across the life course. Future research should investigate whether the adaptive significance of epigenetic inheritance is modified by other adaptive modes.

A study conducted by Sun et al. found that male mice that are exposed to repeated cold stress exhibit differentially methylated regions in their sperm compared to mice that were raised in thermoneutral conditions.[103] When the cold-exposed male mice reproduced, their offspring showed higher UCP1 expression in interscapular BAT and inguinal WAT under thermoneutral conditions and after cold exposure compared to the offspring of mice that were not exposed to cold prior to reproducing.[103] The mechanisms through which cold stress exposure modifies sperm DNA methylation patterns and the pathways through which differentially methylated regions in sperm direct brown adipogenesis in developing offspring remain unknown.

The degree to which variation in human BAT is influenced by epigenetic inheritance in response to cold climates is largely unexplored. Sun et al. performed a retrospective analysis of PET/CT scans from adults in Zurich, Switzerland and found that individuals with active BAT were 3.2% more likely to have been conceived in the colder months of October to February.[103] The adaptive significance of these findings, however, remains unclear. Our study of BAT among Yakut adults did not find a relationship between season of conception and change in supraclavicular skin temperature after cooling (unpublished data). Thus, further research is needed to in order to address whether epigenetic inheritance influences human variation in BAT and adaptation to cold climates (Box 5).

8 | BROWN ADIPOSE TISSUE AND GENETIC ADAPTATION

Genetic studies of circumpolar populations further suggest that the process of genetic adaptation in humans is largely shaped by polygenic selection acting on pre-existing variation in multiple functionally related genes.[104] Metabolic phenotypes are shaped by complex genetic architecture. Thus, as humans dispersed into subarctic regions, it is likely that natural selection acted on multiple loci related to BAT

BOX 5 Genetic adaptation

As humans dispersed into new environments across the African continent and later into Eurasia, humans faced new selective pressures. Under a hard sweep model, geneticists hypothesize that novel mutations that were advantageous in the new environment would quickly increase in population frequency.[104] There are a few well-known examples of evidence of selective sweeps in the human genome, particularly on genes involved in pigmentation and infectious disease susceptibility; yet, recent studies suggest that such sweeps were likely rare over the past ~250,000 years of human evolution.[105] While it is challenging to identify footprints of hard selective sweeps in the genome, evidence suggests that positive selection on novel mutations likely played a nominal role in shaping human genomic diversity and adaptation to new environments.[105]

Rather, human genetic adaptations likely emerged by natural selection acting on pre-existing allelic variation in multiple genes that contribute to a trait.[104] Now that over 1000 human genome-wide association studies have been published, consensus suggests that most human traits are polygenic. Depending on population size and mutation rates, new advantageous alleles are expected to arise only rarely. Thus, natural selection of standing genetic variation may have represented a faster adaptive response.[104]

Certain polymorphisms may be beneficial depending on their interaction with other modes of adaptation. Given that most human traits are influenced by multiple genes and are sensitive to environmental conditions, the genetic background may shape the adaptive significance of altered epigenetic states and vice versa. For example, some alleles may alter the course of epigenetic inheritance by making the individual more or less sensitive to parental signals.[106] Additionally, the beneficial effects of certain alleles may be triggered by particular environmental stimuli during development.

Thus, epigenetic changes can drive genetic change, leading to genetic assimilation.[106] Through genetic assimilation, natural selection acts on genes related to a previously plastic phenotype, thus increasing its prevalence, efficiency, or reducing disadvantageous side effects.[106] As time passes, the frequency of the adaptive genetic architecture will increase within the population. This adaptive process is described as a "phenotype-first" model of evolution because novel adaptive phenotypes are first introduced through plasticity, and only later are they consolidated by gene frequency change.[47] The significance of phenotypic plasticity for human genetic evolution is currently unknown and warrants future investigation.

development and thermogenesis (Table 2). The East African environment in which humans evolved was probably heterogeneous and included habitats ranging from cloud forest to desert.[107] Early humans were likely exposed to temperatures below thermoneutrality due to seasonal and diurnal shifts in temperature, particularly in more arid environments. A majority of alleles that have been identified as potentially adaptive to cold climates are found in low frequencies among contemporary African populations. This suggests that these alleles evolved long before humans were exposed to the unique selective pressures of circumpolar environments.[108] There are, however, a couple of exceptions. The L479 variant of the *CPT1a* gene, for instance, underwent one of the strongest known selective sweeps in human history and is specific to circumpolar populations.[109] The enzyme carnitine palmitoyltransferase type 1a (CPT-1a) is the rate limiting step in hepatic fatty acid oxidation. It has been proposed that the variant may be beneficial in the context of low-carbohydrate diets common among circumpolar populations.[109] Additionally, the variant may be advantageous in cold climates due to its role in BAT metabolism. CPT-1a increases the production of acylcarnitines, which are exported from the liver to brown adipocytes and represent an energy-rich fuel source.[110] Hallmark et al. also identified a new mutation in the *PLA2G2A* gene that plays a role in mitochondrial uncoupling and is geographically limited to populations living in cold climates of Central and East Asia and Siberia.[108] *PLA2G2A* encodes secretory phospholipase A_2 group IIA, an enzyme that generates free fatty acids and influences circulating lipid levels. The protein is required to activate mitochondrial uncoupling in BAT.[111]

Variants in two genes involved in brown adipocyte lipid metabolism likely arose prior to human dispersal into subarctic regions but exhibit evidence for selection in circumpolar populations—*PLIN1* and *ANGPTL8*.[108] *PLIN1* encodes for perilipin 1, a protein that is highly expressed in adipose tissue and functions as a critical regulator of lipolysis and lipogenesis.[108] Perilipin 1 plays an essential role in lipolysis in murine BAT and can induce browning in white adipocytes.[112] The *ANGPTL8* gene encodes angiopoietin-like 8 (ANGPTL8), which plays a role in distributing triglycerides across various tissues, and is highly expressed in BAT.[108]

The leptin receptor gene (*LEPR*) is hypothesized to play a functional role in the BAT-mediated NST via interactions with the sympathetic nervous system.[113] The 109R allele of *LEPR* correlates with a principal component variable related to winter conditions across 54 world populations.[114] Additionally, there is evidence of recent positive selection for the 109R allele in populations of Eurasia.[114]

Genome-wide scans of data from Inuit populations of Greenland have identified evidence of selection in a divergent haplotype that contains two genes of interest—*WARS2* and *TBX15*.[115] *TBX15* encodes a transcription factor that plays a role in brown adipocyte differentiation.[116] *WARS2* encodes the mitochondrial protein

TABLE 2 Description of genes that play a functional role in brown adipose tissue (BAT) biogenesis and metabolism and whose polymorphisms exhibit evidence of natural selection among indigenous circumpolar populations

Gene	Function and associated phenotypes	References
ANGPTL8	Encodes angiopoietin-like 8 protein Functions to regulate the distribution of triglycerides to various tissues under different physiological conditions Variant of the gene is associated with population variation in LDL and HDL-cholesterol levels Highly expressed in BAT Expression is upregulated during cold exposure	[76]
CPT1a	Encodes the enzyme carnitine palmitoyltransferase type 1a, the rate limiting step in hepatic fatty acid oxidation Increases the production of acylcarnitines, which are exported from the liver to brown adipocytes and used as a fuel source for metabolism	[77]
LEPR	Encodes the leptin receptor Variant is associated with elevations in RMR and decreased BMI Hypothesized to play a role in NST	[80,81]
PLA2G2A	Encodes secretory phospholipase A2 group IIA, an enzyme that generates free fatty acids Influences circulating lipid levels by hydrolyzing the sn-2 ester bond of phospholipids Variants of the gene have been linked to the metabolic syndrome Enzyme is required to activate mitochondrial uncoupling in brown adipocytes	[76]
PLIN1	Encodes perilipin 1 protein, which functions as a critical regulator of lipolysis and lipogenesis Highly expressed in adipose tissue Genetic polymorphisms are associated with obesity, weight gain and hypertension Essential for norepinephrine-induced lipolysis in murine BAT Plays a role in conversion of white adipocytes to beige phenotype	[76,79]
TBX15	Encodes a transcription factor member the T-box family Plays a role in the differentiation of brown and beige adipocytes Linkage between genetic polymorphisms and body fat distribution	[82,84]
WARS2	Encodes mitochondrial tryptophanyl-tRNA synthase, which links amino acids with tRNAs Polymorphisms of the gene are associated with body fat distribution	[82,84]

tryptophanyl-tRNA synthase and is associated with variation in body fat distribution in humans.[115] Interestingly, the divergent haplotype is closely related to the Denisovan genome sequence and likely introgressed from an archaic population in Eurasia.[117] Functional genomic analyses suggest that the selected archaic haplotype may alter the regulation of *TBX15* and *WARS2* expression.[117] In addition to Greenlandic Inuit populations, the introgressed haplotype is found at high frequencies among the Yakut and the Even in Siberia and the Naxi in the Himalayan foothills.[117]

Overall, this body of work suggests that human genetic adaptations to cold climates function via multiple pathways that regulate BAT development and metabolism, and thus modulate the adaptive significance of faster-acting adaptive modes such as developmental adaptation, acclimatization, and allostasis. This research also suggests that perhaps pre-existing phenotypic plasticity in BAT and NST and its underlying genetic architecture in part facilitated the successful expansion of humans into circumpolar regions. Under this phenotype-first evolution model, more plastic adaptive modes, like allostasis, acclimatization, and developmental adaptation, enabled human populations to persist in northern latitudes for multiple generations, allowing time for natural selection to act on existing genetic variation and for new beneficial mutations to arise. Additional research is needed to test the phenotype-first evolution model and parse out how environmental conditions interact with particular genotypes and shape phenotypic responses to cold stress.

9 | TOPICS FOR FURTHER INVESTIGATION

Human BAT is a burgeoning research topic and many key questions remain unanswered regarding its adaptive, energetic, and health significance. Future research should investigate the ways in which human variation in BAT is shaped by each of the timescales of adaptation. For instance, the biological pathways that link BAT with allostatic increases in energy expenditure during acute cold exposure are still unclear. Researchers have yet to characterize seasonal changes in BAT among circumpolar populations. How might slower modes of adaptation, such as genetic adaptation, epigenetic inheritance, and developmental adaptation, modulate BAT's action during allostasis or acclimatization? In what ways do social, cultural, and political-economic contexts shape the process of biological adaptation and human BAT variation? How do the energy costs of thermogenesis influence energy allocation toward physical activity, growth, reproduction, and other components of the energy budget? How do nutritional environments across the life course influence BAT development and metabolism?

Additional research is needed to parse out the relationship between under- and over-nutrition and human variation in BAT mass and activity. In rodent models, caloric restriction stimulates the development of functional beige adipocytes within subcutaneous and

visceral WAT; however, this pattern has yet to be replicated in humans. In fact, preliminary research suggests that weight loss may be associated with changes in subcutaneous WAT gene expression that promote a more white than brown adipocyte phenotype.[118] Future research should consider why the relationship between caloric restriction and adipose tissue plasticity may differ between humans and rodent models and the possible evolutionary significance of these differences. While many researchers have hypothesized that there will be a negative relationship between BAT thermogenesis and body fatness, investigations of the relationship between BAT and BMI have produced mixed results.[119,120]

Research in animal models suggests that maternal nutrition during gestation and lactation may influence the development of BAT in offspring. When female mice are supplemented with ω-3 polyunsaturated fatty acid during gestation and lactation, their offspring exhibit significantly greater thermogenic gene expression and whole-body energy expenditure.[121] The consequences of maternal nutrition for offspring BAT programming are dependent on the timing of the nutritional intervention.[94]

Physical activity may modify the endocrine cross talk between adipose tissue and skeletal muscle, leading to shifts in BAT metabolism. In particular, studies in rodent models suggest that an exercise intervention may upregulate mitochondrial biogenesis and activity in brown adipocytes and stimulate the trans differentiation of white adipocytes to beige adipocytes.[122,123] Exercise also alters epigenetic regulation of brown and beige adipocyte gene expression (check out Rodrigues et al. for a review).[124] The functional significance of exercise-induced activation of BAT thermogenesis is unclear, especially given that both exercise and BAT activity can trigger an increase in core temperature. It has been hypothesized that oxidative phosphorylation in UCP1-expressing adipocytes may reduce the detrimental effects of reactive oxygen species (ROS) that are generated during exercise.[125] Whether exercise leads to greater BAT thermogenesis in humans remains an open question. One of the few studies to investigate human BAT activation by exercise documents that BAT volume and metabolic activity are not associated with physical activity levels quantified using accelerometry; however, quantifying exercise-induced energy expenditure using accelerometry presents significant limitations.[126,127] Previous studies of exercise-induced shifts in BAT volume and activity do not control for shifts in energy balance, and prolonged negative energy balance during exercise interventions may downregulate brown adipocyte metabolism.

Preliminary research conducted in wealthy nations suggests there may be a positive association between BAT thermogenesis and bone growth. BAT mass (measured using ^{18}F-FDG PET/CT scans) is positively associated with femoral cross-sectional area and cortical bone area in children and adolescents.[128] Similarly, MRI data suggests that children with a lower fat-fraction in the supraclavicular depot (indicative of more brown adipocytes) have higher levels of circulating osteocalcin, a biomarker of osteoblast activity and bone formation produced by bone cells.[129] It is possible that children and adolescents with more energy available for growth also have more energy available for thermogenesis.[130]

The process of human biological adaptation is not only shaped by ecological and climatic stressors, but also social, cultural and political-economic components of the environment as well.[48] When studying adaptation, it is critical to consider the complex ways humans not only biologically respond to their environment, but also how they actively construct it. Social, cultural, and political-economic contexts will structure the degree to which a population is exposed to a particular stressor and whether a biological response to that stressor affects evolutionary fitness. The social, cultural, and political-economic factors that shape variation in stressor exposure also interact across local, state, and global scales. Based on our investigations of the adaptive significance of human BAT, we argue that investigating biological adaptation to cold stress is a useful approach to studying how the process of adaptation interacts with social contexts on a range of scales. For example, individual-level factors such as dietary preferences, occupation(s), and income, household-level characteristics like kin networks and subsistence practices, community-level economic policies, and country-wide trends in market integration and economic development will all interact and structure low-temperature exposure among circumpolar populations. On the global level, climate change patterns may directly and indirectly influence energy allocation and thermogenesis by directing economic decisions, lifestyle choices, and disease risk. Future research is needed to better understand how social, cultural and political-economic factors at the local, state, and global level influence the degree, timing and duration of stressor exposure and thus the process of biological adaptation.

Strong claims have been made regarding the importance of BAT metabolism for preventing cardiometabolic disease.[94] The removal of free fatty acids and glucose from the blood stream through BAT metabolism may have important implications for population variation in cardiometabolic disease risk. A retrospective study of over 130,000 ^{18}FDG PET scans generated in New York found that the presence of active BAT deposits was independently correlated with lower odds of several cardiometabolic diseases including type 2 diabetes, coronary heart disease, cerebrovascular disease, congestive heart failure and hypertension.[18] Furthermore, patients with BAT had improved blood glucose, triglyceride, and high-density lipoprotein levels.[18] Iwen et al. report that adults in northern Germany with active BAT stores exhibit enhanced insulin sensitivity after mild cooling.[131] Among the Yakut of northeastern Siberia, we found that fasting blood glucose levels are positively associated with change in supraclavicular skin temperature after cooling, and participants with greater BAT activity are more likely to preferentially metabolize carbohydrates during cold exposure.[15] Most investigations of NST, however, do not report a significant change in respiratory quotient. Previous investigations of human BAT have been limited to populations living in temperate and arctic climates. Future research should investigate BAT among populations living in tropical and arid climates in order to clarify BAT's contribution to population variation in cardiometabolic health. Currently, the causal mechanisms that link BAT activity and biomarkers of cardiometabolic health remain unclear and there may be bidirectional pathways. Additional research is needed to determine the degree to which BAT mass may play an active role in glucose metabolism in humans or whether it

may act as a biomarker for other pathways that regulate insulin dynamics.

10 | CONCLUSION

Since the emergence of a general consensus in the late 2000s that many adult humans have active BAT depots, the study of human brown and beige adipocytes has been a fruitful avenue in the investigation of biological adaptation to cold climates. Our review of the existing literature suggests that variation in human BAT is shaped by each of the timescales of adaptation and that the adaptive modes act as an integrated system. Preliminary research suggests that BAT plays an important role in allostatic responses to cold stress via its contribution to NST; however, further research is needed to delineate its functional significance. Humans acclimatize to seasonal cold stress by amplifying the metabolic pathways that control allostatic responses via BAT-mediated NST. Furthermore, longer-acting adaptive modes, such as developmental adaptation, epigenetic inheritance, and genetic adaptations, appear to modify BAT's contribution to allostatic responses to cold stress by promoting mitochondrial biogenesis, lipid metabolism, and brown adipogenesis. Thus, the modes of adaptation are not mutually exclusive. Rather, as the timescale of an environmental challenge increases within an individual's lifetime and across generations, each adaptive mode is layered onto the next.[46] When novel conditions are confronted, more plastic modes of adaptation are the original sources of phenotypic novelty and functional adjustment.[106] As the amount of time a population is exposed to the novel stressor increases, longer-acting, more durable adaptive modes accumulate.[47] The adaptive significance of longer-acting adaptive modes may be rooted in the ways in which they modify and interact with the fast-acting adaptive modes.

When adaptation is conceptualized as a dynamic process that integrates multiple adaptive modes, the significance of phenotypic plasticity cannot be ignored. Anthropologists have long recognized the essential role of phenotypic plasticity in producing human variation beginning with the foundational work of Boas.[132] Recent advancements in developmental biology and epigenetic research within molecular biology have sparked a renewed appreciation for the importance of plasticity in generating phenotypic variation. This work largely rejects a model of adaptation in which genes are viewed as the blueprint for constructing an organism and that environmental inputs present interfering "noise" for carrying out the genetic plan. Rather, the body is understood as inseparably integrated with environmental forces (both macro and micro) which play a critical role in normal development.

Based on our review of the literature, we hypothesize that phenotypic plasticity in human BAT generated by allostatic mechanisms, acclimatization, developmental plasticity, and epigenetic inheritance facilitated the successful expansion of humans into circumpolar climates and the evolution of genetic adaptations. Additional research is needed to test this application of the phenotype-first evolution hypothesis. Existing research characterizing population variation in human BAT is largely limited to populations living in temperate and subarctic climates, and future research should describe variation in human BAT among populations living in warmer climates.

Finally, future research should situate the adaptive significance of human BAT within the context of competing energy demands, social conditions, and cardiometabolic health disparities. How does energy allocation toward BAT thermogenesis change in the context of competing energy demands? How do nutritional patterns shape variation in human BAT? How do social, cultural, and political-economic factors structure stressor exposure and the process of adaptation? Integrating perspectives from biocultural and evolutionary anthropology will be critical for not only defining the adaptive significance of human variation in BAT but also its influence on cardiometabolic health.

ACKNOWLEDGMENTS

The authors would like to thank M. Uddin, M. Hoke, R. Fried, and K. McCabe for their helpful feedback on the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Stephanie B. Levy https://orcid.org/0000-0003-2828-2014
William R. Leonard https://orcid.org/0000-0002-6233-604X

REFERENCES

[1] Leonard WR. Centennial perspective on human adaptability. Am J Phys Anthropol. 2018;165:813-833.
[2] Steegmann AT. Human cold adaptation: an unfinished agenda. Am J Hum Biol. 2007;19:218-227.
[3] Heinbecker P. Studies on the metabolism of Eskimos. J Biol Chem. 1928;16:461-475.
[4] Crile GW, Quiring DP. Indian and Eskimo metabolisms. J Nutr. 1939; 18:361-368.
[5] Rodahl K, Edwards J Jr. Basal metabolism of the Eskimo. J Nutr. 1952;48:359-368.
[6] Leonard WR, Snodgrass JJ, Sorensen MV. Metabolic adaptation in indigenous Siberian populations. Annu Rev Anthropol. 2005;34: 451-471.
[7] Rode A, Shephard RJ. Basal metabolic rate of inuit. Am J Hum Biol. 1995;7:723-729.
[8] Ocobock C, Soppela P, Turunen MT, Stenbäck V, Herzig K-H. Elevated resting metabolic rates among female, but not male, reindeer herders from subarctic Finland. Am J Hum Biol. 2020;32:e23432.
[9] Ocobock C. Human energy expenditure, allocation, and interactions in natural temperate, hot, and cold environments. Am J Phys Anthropol. 2016;161:667-675.
[10] Snodgrass JJ, Leonard WR, Tarskaia LA, Schoeller DA. Total energy expenditure in the Yakut (Sakha) of Siberia as measured by the doubly labeled water method. Am J Clin Nutr. 2006;84:798-806.
[11] Carpentier AC, Blondin DP, Virtanen KA, Richard D, Haman F, Turcotte ÉE. Brown adipose tissue energy metabolism in humans. Front Endocrinol. 2018;9:447.

[12] Betz MJ, Enerbäck S. Human brown adipose tissue: what we have learned So far. Diabetes. 2015;65:2352-2360.
[13] Lean ME, James WP, Jennings G, Trayhurn P. Brown adipose tissue uncoupling protein content in human infants, children and adults. Clin Sci (Lond). 1986;1979(71):291-297.
[14] Enerbäck S. Human brown adipose tissue. Cell Metab. 2010;11: 248-252.
[15] Levy SB, Klimova TM, Zakharova RN, et al. Brown adipose tissue, energy expenditure, and biomarkers of cardio-metabolic health among the Yakut (Sakha) of northeastern Siberia. Am J Hum Biol. 2018;30:e23175.
[16] Muzik O, Mangner TJ, Leonard WR, Kumar A, Janisse J, Granneman JG. 15O PET measurement of blood flow and oxygen consumption in cold-activated human brown fat. J Nucl Med. 2013; 54:523-531.
[17] u Din M, Raiko J, Saari T, et al. Human brown adipose tissue [15O] O2 PET imaging in the presence and absence of cold stimulus. Eur J Nucl Med Mol Imaging. 2016;43:1878-1886.
[18] Becher T, Palanisamy S, Kramer DJ, et al. Brown adipose tissue is associated with cardiometabolic health. Nat Med. 2021;27:58-65.
[19] Devlin MJ. The "skinny" on brown fat, obesity, and bone. Am J Phys Anthropol. 2015;156:98-115.
[20] Gilsanz V, Hu HH, Kajimura S. Relevance of brown adipose tissue in infancy and adolescence. Pediatr Res. 2013;73:3-9.
[21] Aherne W, Hull D. Brown adipose tissue and heat production in the newborn infant. J Pathol Bacteriol. 1966;91:223-234.
[22] Itoh S, Kuroshima A. Distribution of brown adipose tissue in Japanese new-born infants. J Physiol Soc-Jpn. 1967;29:660-661.
[23] Naeye RL. Hypoxemia and the sudden infant death syndrome. Science. 1974;186:837-838.
[24] Gilsanz V, Smith ML, Goodarzian F, Kim M, Wren TAL, Hu HH. Changes in brown adipose tissue in boys and girls during childhood and puberty. J Pediatr. 2012;160:604-609.
[25] Becker AS, Nagel HW, Wolfrum C, Burger IA. Anatomical grading for metabolic activity of brown adipose tissue. PLoS One. 2016;11: e0149458.
[26] Heaton JM. The distribution of brown adipose tissue in the human. J Anat. 1972;112:35-39.
[27] Leitner BP, Huang S, Brychta RJ, et al. Mapping of human brown adipose tissue in lean and obese young men. Proc Natl Acad Sci. 2017;114:8649-8654.
[28] Fletcher LA, Kim K, Leitner BP, et al. Sexual dimorphisms in adult human brown adipose tissue. Obesity. 2020;28:241-246.
[29] Erecinska M, Thoresen M, Silver IA. Effects of hypothermia on energy metabolism in mammalian central nervous system. J Cereb Blood Flow Metab. 2003;23:513-530.
[30] Symonds ME, Pope M, Budge H. The ontogeny of brown adipose tissue. Annu Rev Nutr. 2015;35:295-320.
[31] Ikeda K, Maretich P, Kajimura S. The common and distinct features of brown and beige adipocytes. Trends Endocrinol Metab. 2018;29: 191-200.
[32] Zuriaga MA, Fuster JJ, Gokce N, Walsh K. Humans and mice display opposing patterns of "browning" gene expression in visceral and subcutaneous white adipose tissue depots. Front Cardiovasc Med. 2017;4:27.
[33] Wu J, Boström P, Sparks LM, et al. Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. Cell. 2012;150: 366-376.
[34] Atit R, Sgaier SK, Mohamed OA, et al. β-Catenin activation is necessary and sufficient to specify the dorsal dermal fate in the mouse. Dev Biol. 2006;296:164-176.
[35] Seale P, Bjork B, Yang W, et al. PRDM16 controls a brown fat/-skeletal muscle switch. Nature. 2008;454:961-967.
[36] Cohen P, Kajimura S. The cellular and functional complexity of thermogenic fat. Nat Rev Mol Cell Biol. 2021;22:393-409. doi: 10.1038/s41580-021-00350-0
[37] Min SY, Kady J, Nam M, et al. Human 'brite/beige' adipocytes develop from capillary networks, and their implantation improves metabolic homeostasis in mice. Nat Med. 2016;22:312-318.
[38] Raajendiran A, Ooi G, Bayliss J, et al. Identification of metabolically distinct adipocyte progenitor cells in human adipose tissues. Cell Rep. 2019;27:1528-1540.e7.
[39] Barbatelli G, Murano I, Madsen L, et al. The emergence of cold-induced brown adipocytes in mouse white fat depots is determined predominantly by white to brown adipocyte transdifferentiation. Am J Physiol-Endocrinol Metab. 2010;298:E1244-E1253.
[40] Himms-Hagen J, Melnyk A, Zingaretti MC, Ceresi E, Barbatelli G, Cinti S. Multilocular fat cells in WAT of CL-316243-treated rats derive directly from white adipocytes. Am J Physiol-Cell Physiol. 2000;279:C670-C681.
[41] Wang H, Liu L, Lin JZ, Aprahamian TR, Farmer SR. Browning of white adipose tissue with roscovitine induces a distinct population of UCP1 + adipocytes. Cell Metab. 2016;24:835-847.
[42] Sanchez-Gurmaches J, Guertin DA. Adipocytes arise from multiple lineages that are heterogeneously and dynamically distributed. Nat Commun. 2014;5:4099.
[43] Lasker GW. Human biological adaptability. Science. 1969;166: 1480-1486.
[44] Mazess RB. Biological adaptation: aptitudes and acclimatization. Biosocial Interrelations in Population Adaptation 918. Mouton Publishers; 1975.
[45] Kuzawa CW, Thayer ZM. Timescales of human adaptation: the role of epigenetic processes. Epigenomics. 2011;3:221-234.
[46] Raubenheimer D, Simpson SJ, Tait AH. Match and mismatch: conservation physiology, nutritional ecology and the timescales of biological adaptation. Philos Trans R Soc B Biol Sci. 2012;367:1628-1646.
[47] Kuzawa CW, Bragg JM. Plasticity in human life history strategy: implications for contemporary human variation and the evolution of genus *Homo*. Curr Anthropol. 2012;53:S369-S382.
[48] Goodman AH, Leatherman TL. Building a New Biocultural Synthesis: Political-Economic Perspectives on Human Biology. University of Michigan Press; 2010.
[49] Gould SJ, Lewontin RC. The spandrels of San Marco and the Panglossian paradigm: a critique of the adaptationist programme. Proc R Soc Lond B Biol Sci. 1979;205:581-598.
[50] Kuzawa CW. Fetal origins of developmental plasticity: are fetal cues reliable predictors of future nutritional environments? Am J Hum Biol. 2005;17:5-21.
[51] Wells JCK. Adaptive variability in the duration of critical windows of plasticity: implications for the programming of obesity. Evol Med Public Health. 2014;2014:109-121.
[52] Ellison PT. Evolutionary perspectives on the fetal origins hypothesis. Am J Hum Biol. 2005;17:113-118.
[53] Sterling P. Principles of allostasis: optimal design, predictive regulation, pathophysiology, and rational therapeutics. In: Schulkin J, ed. Allostasis, Homeostasis, and the Costs of Physiological Adaptation. Cambridge University Press; 2004:17-64. doi:10.1017/CBO9781316257081.004
[54] Lesná I, Vybííral S, Janský L, Zeman V. Human nonshivering thermogenesis. J Therm Biol. 1999;24:63-69.
[55] Sanchez-Delgado G, Alcantara JMA, Acosta FM, et al. Estimation of non-shivering thermogenesis and cold-induced nutrient oxidation rates: impact of method for data selection and analysis. Clin Nutr. 2019;38:2168-2174.
[56] Frank SM, Raja SN, Bulcao C, Goldstein DS. Age-related thermoregulatory differences during core cooling in humans. Am J Physiol-Regul Integr Comp Physiol. 2000;279:R349-R354.
[57] Blondin DP, Nielsen S, Kuipers EN, et al. Human brown adipocyte thermogenesis is driven by β2-AR stimulation. Cell Metab. 2020;32: 287-300.
[58] Khedoe PPS, Hoeke G, Kooijman S, et al. Brown adipose tissue takes up plasma triglycerides mostly after lipolysis. J Lipid Res. 2015;56:51-59.

[59] Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance. Physiol Rev. 2004;84:277-359.
[60] van der Lans AAJJ, Hoeks J, Brans B, et al. Cold acclimation recruits human brown fat and increases nonshivering thermogenesis. J Clin Invest. 2013;123:3395-3403.
[61] Chondronikola M, Volpi E, Børsheim E, et al. Brown adipose tissue is linked to a distinct thermoregulatory response to mild cold in people. Front Physiol. 2016;7:129.
[62] Blondin DP, Frisch F, Phoenix S, et al. Inhibition of intracellular triglyceride lipolysis suppresses cold-induced brown adipose tissue metabolism and increases shivering in humans. Cell Metab. 2017;25:438-447.
[63] Rothwell NJ, Stock MJ. Influence of carbohydrate and fat intake on diet-induced thermogenesis and brown fat activity in rats fed low protein diets. J Nutr. 1987;117:1721-1726.
[64] Martinez-Tellez B, Nahon KJ, Sanchez-Delgado G, et al. The impact of using BARCIST 1.0 criteria on quantification of BAT volume and activity in three independent cohorts of adults. Sci Rep. 2018;8:8567.
[65] Muzik O, Diwadkar VA. Regulation of brown adipose tissue activity by interoceptive CNS pathways: the interaction between brain and periphery. Front Neurosci. 2017;11:640.
[66] Bal NC, Maurya SK, Pani S, et al. Mild cold induced thermogenesis: are BAT and skeletal muscle synergistic partners? Biosci Rep. 2017;37:BSR20171087.
[67] Bal NC, Periasamy M. Uncoupling of sarcoendoplasmic reticulum calcium ATPase pump activity by sarcolipin as the basis for muscle non-shivering thermogenesis. Philos Trans R Soc B. 2020;375:20190135.
[68] Blondin DP, Daoud A, Taylor T, et al. Four-week cold acclimation in adult humans shifts uncoupling thermogenesis from skeletal muscles to brown adipose tissue: cold-acclimation increases muscle efficiency. J Physiol. 2017;595:2099-2113.
[69] Wijers SLJ, Schrauwen P, Saris WHM, van Marken Lichtenbelt WD. Human skeletal muscle mitochondrial uncoupling is associated with cold induced adaptive thermogenesis. PLoS One. 2008;3:e1777.
[70] Roh HC, Tsai LTY, Shao M, et al. Warming induces significant reprogramming of beige, but not brown adipocyte cellular identity. Cell Metab. 2018;27:1121-1137.
[71] Virtanen KA, Lidell ME, Orava J, et al. Functional brown adipose tissue in healthy adults. N Engl J Med. 2009;360:1518-1525.
[72] Muehlenbein MP. Human Evolutionary Biology. Cambridge University Press; 2010.
[73] Woods HA, Harrison JF. Interpreting rejections of the beneficial acclimation hypothesis: when is physiological plasticity adaptive? Evolution. 2002;56:1863-1866.
[74] Wilson RS, Franklin CE. Testing the beneficial acclimation hypothesis. Trends Ecol Evol. 2002;17:66-70.
[75] McEwen BS, Stellar E. Stress and the individual: mechanisms leading to disease. Arch Intern Med. 1993;153:2093-2101.
[76] Kingsolver JG, Huey RB. Evolutionary analyses of morphological and physiological plasticity in thermally variable environments. Integr Comp Biol. 1998;38:545-560.
[77] Leonard WR, Levy SB, Tarskaia LA, et al. Seasonal variation in basal metabolic rates among the yakut (Sakha) of northeastern Siberia: seasonality in BMR in the Yakut. Am J Hum Biol. 2014;26:437-445.
[78] Yoneshiro T, Matsushita M, Nakae S, et al. Brown adipose tissue is involved in the seasonal variation of cold-induced thermogenesis in humans. Am J Physiol-Regul Integr Comp Physiol. 2016;310:R999-R1009.
[79] Lee P, Smith S, Linderman J, et al. Temperature-acclimated brown adipose tissue modulates insulin sensitivity in humans. Diabetes. 2014;63:3686-3698.
[80] Efremova A, Senzacqua M, Venema W, et al. A large proportion of mediastinal and perirenal visceral fat of Siberian adult people is formed by UCP1 immunoreactive multilocular and paucilocular adipocytes. J Physiol Biochem. 2020;76:185-192.
[81] Levy SB, Leonard WR, Tarskaia LA, et al. Seasonal and socioeconomic influences on thyroid function among the Yakut (Sakha) of eastern Siberia: seasonal thyroid changes in the Yakut. Am J Hum Biol. 2013;25:814-820.
[82] Frisancho AR. Developmental adaptation: where we go from here. Am J Hum Biol. 2009;21:694-703.
[83] Bonamour S, Chevin L-M, Charmantier A, Teplitsky C. Phenotypic plasticity in response to climate change: the importance of cue variation. Philos Trans R Soc B Biol Sci. 2019;374:20180178.
[84] Meredith RM. Sensitive and critical periods during neurotypical and aberrant neurodevelopment: a framework for neurodevelopmental disorders. Neurosci Biobehav Rev. 2015;50:180-188.
[85] Kuzawa CW. Adipose tissue in human infancy and childhood: an evolutionary perspective. Am J Phys Anthropol off Publ Am Assoc Phys Anthropol. 1998;107:177-209.
[86] Velickovic K, Cvoro A, Srdic B, et al. Expression and subcellular localization of estrogen receptors α and β in human fetal brown adipose tissue. J Clin Endocrinol Metab. 2014;99:151-159.
[87] Symonds ME, Lomax MA. Maternal and environmental influences on thermoregulation in the neonate. Proc Nutr Soc. 1992;51:165-172.
[88] Rockstroh D, Landgraf K, Wagner IV, et al. Direct evidence of brown adipocytes in different fat depots in children. PLoS One. 2015;10:e0117841.
[89] Robinson L, Ojha S, Symonds ME, Budge H. Body mass index as a determinant of brown adipose tissue function in healthy children. J Pediatr. 2014;164:318-322.
[90] Drubach LA, Palmer EL III, Connolly LP, Baker A, Zurakowski D, Cypess AM. Pediatric brown adipose tissue: detection, epidemiology, and differences from adults. J Pediatr. 2011;159:939-944.
[91] Kuzawa CW, Quinn EA. Developmental origins of adult function and health: evolutionary hypotheses. Annu Rev Anthropol. 2009;38:131-147.
[92] Levy SB, Klimova TM, Zakharova RN, et al. Evidence for a sensitive period of plasticity in brown adipose tissue during early childhood among indigenous Siberians. Am J Phys Anthropol. 2021;ajpa.24297:834-846. doi:10.1002/ajpa.24297
[93] Loubière LS, Vasilopoulou E, Bulmer JN, et al. Expression of thyroid hormone transporters in the human placenta and changes associated with intrauterine growth restriction. Placenta. 2010;31:295-304.
[94] Symonds M, Mostyn A, Pearce S, Budge H, Stephenson T. Endocrine and nutritional regulation of fetal adipose tissue development. J Endocrinol. 2003;179:293-299.
[95] Wolfs D, Lynes MD, Tseng YH, et al. Brown fat–activating lipokine 12,13-diHOME in human milk is associated with infant adiposity. J Clin Endocrinol Metab. 2020;106:e943-e956. doi:10.1210/clinem/dgaa799
[96] Stanford KI, Lynes MD, Takahashi H, et al. 12,13-diHOME: an exercise-induced lipokine that increases skeletal muscle fatty acid uptake. Cell Metab. 2018;27:1111-1120.e3.
[97] Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. Nat Genet. 2003;33:245-254.
[98] Ryan CP, Kuzawa CW. Germline epigenetic inheritance: challenges and opportunities for linking human paternal experience with offspring biology and health. Evol Anthropol Issues News Rev. 2020;29:180-200. doi:10.1002/evan.21828
[99] Burggren WW, Crews D. Epigenetics in comparative biology: why we should pay attention. Integr Comp Biol. 2014;54:7-20.

[100] Thayer ZM, Non AL. Anthropology meets epigenetics: current and future directions: anthropology meets epigenetics. Am Anthropol. 2015;117:722-735.
[101] Sun W, von Meyenn F, Peleg-Raibstein D, Wolfrum C. Environmental and nutritional effects regulating adipose tissue function and metabolism across generations. Adv Sci. 2019;6:1900275. doi: 10.1002/advs.201900275
[102] Lim YC, Chia SY, Jin S, Han W, Ding C, Sun L. Dynamic DNA methylation landscape defines brown and white cell specificity during adipogenesis. Mol Metab. 2016;5:1033-1041.
[103] Sun W, Dong H, Becker AS, et al. Cold-induced epigenetic programming of the sperm enhances brown adipose tissue activity in the offspring. Nat Med. 2018;24:1372-1383.
[104] Hancock AM, Alkorta-Aranburu G, Witonsky DB, Rienzo AD. Adaptations to new environments in humans: the role of subtle allele frequency shifts. Philos Trans Biol Sci. 2010;365:2459-2468.
[105] Hernandez RD, Kelley JL, Elyashiv E, et al. Classic selective sweeps were rare in recent human evolution. Science. 2011;331:920-924.
[106] West-Eberhard MJ. Developmental Plasticity and Evolution. Oxford University Press; 2003.
[107] Maslin MA, Brierley CM, Milner AM, Shultz S, Trauth MH, Wilson KE. East African climate pulses and early human evolution. Quat Sci Rev. 2014;101:1-17.
[108] Hallmark B, Karafet TM, Hsieh PH, Osipova LP, Watkins JC, Hammer MF. Genomic evidence of local adaptation to climate and diet in indigenous Siberians. Mol Biol Evol. 2019;36:315-327.
[109] Hale N. Inuit metabolism revisited: what drove the selective sweep of CPT1a L479? Mol Genet Metab. 2020;129:255-271.
[110] Simcox J, Geoghegan G, Maschek JA, et al. Global analysis of plasma lipids identifies liver-derived acylcarnitines as a fuel source for brown fat thermogenesis. Cell Metab. 2017;26:509-522.
[111] Kuefner MS, Pham K, Redd JR, et al. Secretory phospholipase A2 group IIA modulates insulin sensitivity and metabolism. J Lipid Res. 2017;58:1822-1833.
[112] Souza SC, Christoffolete MA, Ribeiro MO, et al. Perilipin regulates the thermogenic actions of norepinephrine in brown adipose tissue. J Lipid Res. 2007;48:1273-1279.
[113] Brown EA. Genetic explorations of recent human metabolic adaptations: hypotheses and evidence. Biol Rev. 2012;87:838-855.
[114] Hancock AM, Witonsky DB, Gordon AS, et al. Adaptations to climate in candidate genes for common metabolic disorders. PLoS Genet. 2008;4:e32.
[115] Fumagalli M, Moltke I, Grarup N, et al. Greenlandic Inuit show genetic signatures of diet and climate adaptation. Science. 2015; 349:1343-1347.
[116] Gburcik V, Cawthorn WP, Nedergaard J, Timmons JA, Cannon B. An essential role for Tbx15 in the differentiation of brown and "brite" but not white adipocytes. Am J Physiol-Endocrinol Metab. 2012;303:E1053-E1060.
[117] Racimo F, Gokhman D, Fumagalli M, et al. Archaic adaptive introgression in TBX15/WARS2. Mol Biol Evol. 2017;34(3):509-524.
[118] Barquissau V, Léger B, Beuzelin D, et al. Caloric restriction and diet-induced weight loss do not induce browning of human subcutaneous white adipose tissue in women and men with obesity. Cell Rep. 2018;22:1079-1089.
[119] Matsushita M, Yoneshiro T, Aita S, Kameya T, Sugie H, Saito M. Impact of brown adipose tissue on body fatness and glucose metabolism in healthy humans. Int J Obes. 2014;38:812-817.
[120] Hanssen MJ, van der Lans AA, Brans B, et al. Short-term cold acclimation recruits brown adipose tissue in obese humans. Diabetes. 2015;65:1179-1189.
[121] Fan R, Toney AM, Jang Y, Ro S-H, Chung S. Maternal n-3 PUFA supplementation promotes fetal brown adipose tissue development through epigenetic modifications in C57BL/6 mice. Biochim Biophys Acta Mol Cell Biol Lipids. 1863;2018:1488-1497.
[122] Dewal RS, Stanford KI. Effects of exercise on brown and beige adipocytes. Biochim Biophys Acta Mol Cell Biol Lipids. 2019;1864: 71-78.
[123] De Matteis R, Lucertini F, Guescini M, et al. Exercise as a new physiological stimulus for brown adipose tissue activity. Nutr Metab Cardiovasc Dis. 2013;23:582-590.
[124] Rodrigues AC, Prímola-Gomes TN, Peluzio MCG, Hermsdorff HHM, Natali AJ. Aerobic exercise and lipolysis: a review of the β-adrenergic signaling pathways in adipose tissue. Sci Sports. 2021; 36:16-26.
[125] Peppler WT, Townsend LK, Knuth CM, Foster MT, Wright DC. Subcutaneous inguinal white adipose tissue is responsive to, but dispensable for, the metabolic health benefits of exercise. Am J Physiol-Endocrinol Metab. 2018;314:E66-E77.
[126] Acosta FM, Martinez-Tellez B, Sanchez-Delgado G, et al. Association of objectively measured physical activity with brown adipose tissue volume and activity in young adults. J Clin Endocrinol Metab. 2018;104:223-233. doi:10.1210/jc.2018-01312
[127] Plasqui G, Westerterp KR. Physical activity assessment with accelerometers: an evaluation against doubly labeled water. Obesity. 2007; 15:2371-2379.
[128] Ponrartana S, Aggabao PC, Hu HH, Aldrovandi GM, Wren TAL, Gilsanz V. Brown adipose tissue and its relationship to bone structure in pediatric patients. J Clin Endocrinol Metab. 2012;97:2693-2698.
[129] Andersson J, Roswall J, Kjellberg E, Ahlström H, Dahlgren J, Kullberg J. MRI estimates of brown adipose tissue in children—associations to adiposity, osteocalcin, and thigh muscle volume. Magn Reson Imaging. 2019;58:135-142.
[130] Devlin MJ. Why does starvation make bones fat? Am J Hum Biol. 2011;23:577-585.
[131] Iwen KA, Backhaus J, Cassens M, et al. Cold-induced brown adipose tissue activity alters plasma fatty acids and improves glucose metabolism in men. J Clin Endocrinol. 2017;16:4226-4234.
[132] Boas F. Changes in the bodily form of descendants of immigrants. Am Anthropol. 1912;14:530-562.

AUTHOR BIOGRAPHIES

Stephanie B. Levy is an Assistant Professor in the Department of Anthropology at Hunter College. She investigates human evolution, adaptation, and health by integrating tools from energetics and endocrinology. She is an investigator with the Indigenous Siberian Health and Adaptation Project, an international collaboration between scholars in the Russian Federation and United States.

William R. Leonard is the Abraham Harris Professor of Anthropology and Director of the Global Health Studies Program at Northwestern University. His research explores human adaptation to environmental and social stressors among contemporary and prehistoric populations. He has conducted research among indigenous populations of Siberia and South America.

How to cite this article: Levy SB, Leonard WR. The evolutionary significance of human brown adipose tissue: Integrating the timescales of adaptation. Evolutionary Anthropology. 2021;1–17. https://doi.org/10.1002/evan.21930