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ABSTRACT

Human Energetics in a Changing Climate: Health, Lifestyle, and Adaptation among the Yakut of Northeastern Siberia

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This dissertation explores how the environment shapes energy expenditure and cardio-metabolic disease risk by investigating multiple timescales of adaptation to cold stress among the Yakut, an indigenous circumpolar population. This study pursues three main objectives. First, the adaptive and health significance of brown adipose tissue (BAT) is explored by examining its role in homeostatic responses to cold stress among Yakut adults. Second, this project examines evidence for seasonal acclimatization to a cold climate via changes in thyroid hormone dynamics. Third, the study analyzes evidence for developmental adaptation in BAT thermogenesis and discusses the timing of critical periods and their significance for understanding phenotypic plasticity.

The results of this dissertation demonstrate that BAT may play an important role in metabolic adaptation to acute exposure to low temperatures, and influences the metabolism of carbohydrates and lipids and energy balance. Yakut men and women exhibit seasonal shifts in thyroid hormone levels indicative of the "polar T3 response". Seasonal changes in thyroid hormones are structured by lifestyle such that men with greater subsistence activity participation exhibited larger reductions in thyroid hormone levels. Finally, the results provide the first

evidence for developmental plasticity in BAT in humans and indicate that critical periods for plasticity in metabolism may extend into childhood and puberty.

The results of this project highlight the critical role that the environment plays in shaping energy budgets. Furthermore, this dissertation emphasizes that the avenues through which the environment alters an individual’s metabolism will depend on the interaction of the specific social, economic, cultural and ecological characteristics the person’s environment. In order to better understand the ways in which the environment alters energy budgets and health, the timescale of the environmental stressor and the timescale of the sensitive biological mechanisms should be considered. Finally, the results of this dissertation have important implications for cardio-metabolic disease risk within the context of lifestyle change and global climate change.

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ABREVIATIONS

ATP	adenosine triphosphate
BF	body fat
BIA	bioelectrical impedance analysis
BMI	body mass index
BMR	basal metabolic rate
CV	clavicular skin temperature
DIO2	type 2 deiodinase
FFM	fat-free mass
fT3	free triiodothyronine
fT4	free thyroxine
TC	total cholesterol
TSH	thyroid stimulating hormone
HDL	high-density lipoprotein
LDL	low-density lipoprotein
NST	non-shivering thermogenesis
RMR	resting metabolic rate
RQ	respiratory quotient
SBCV	subclavicular skin temperature
SCV	maximum supraclavicular skin temperature
TN	thermoneutral condition

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CHAPTER 1

INTRODUCTION

Energetics, or the study of the use and transfer of energy, has long held a central place in biological anthropology. The study of energy dynamics provides a central vantage point into the relationships between humans and all aspects of their environment, including the social, economic, and ecological components. Thus, human energetics can serve as a tool for characterizing how the environment becomes embodied in primate biology. Pioneering research in 1960's and 70's explored human population variation in energy expenditure of groups living in diverse environments, ranging from the arctic to the tropics (Norgan et al., 1974; Rode and Shephard, 1971; Spurr et al., 1975; Thomas, 1976). Yet today, many of the sources of variation in energy expenditure remain unclear. For instance, around 26% of the total variance in basal metabolic rate (BMR) between individuals cannot be explained by differences in body composition, age, or sex (Johnstone et al., 2005). Recent investigations call into question the relative contribution of various components of total energy expenditure (TEE), such as BMR and physical activity (Pontzer et al., 2016).

Understanding the determinants of variation in metabolism is critical for addressing the growing global burden of cardio-metabolic disease. In 2012, cardiovascular diseases were the leading cause of death globally, and in 2014 over 600 million people were obese and 422 million were diabetic (WHO, 2016a, b). The "dual burden" of disease, or the presence of underweight and overweight individuals living in the same community, household, or individual is increasingly common (WHO, 2016b).

Biomedicine has generated new treatments for managing cardio-metabolic diseases, such as new medications for diabetes, blood pressure, and cholesterol and advances in bariatric surgery. However, roughly 80% of dieting Americans regain weight after one year (Wing and Hill, 2001). Public health initiatives proclaim that the key to achieving energy balance and cardio-metabolic health is to maintain a simple equation: energy in (i.e. dietary intake) must equal energy out (i.e. physical activity). The shortfall in effective solutions to cardio-metabolic disease over the last 60 years is rooted in our inability to understand and accurately quantify the two sides of this equation.

Recent work by human biologists reveals that one's energy expenditure is the result of a complex amalgamation of genetic factors and changes in gene expression, hormonal signaling, and cellular metabolism in response to shifts in diet, physical activity, and environmental conditions that occur over a wide range of timescales (Froehle, 2008; Galloway et al., 2000; Johnstone et al., 2005; Kuzawa et al. 2014; Leonard, 2012; Leonard and Katzmarzyk, 1996; Leonard and Ulijaszek, 2002; Leonard et al., 2005, 2014; Ocobock, 2016; Pontzer et al., 2016; Snodgrass, 2004; Ulijaszek and Strickland, 1993; van Marken Licthenbelt et al., 2015; Yoneshiro et al. 2011a, b, 2012). In other words, a complicated web of biological and social factors shape an individual's energy dynamics. This complex web is the reason why biological anthropology is well situated for investigating human energetics and cardio-metabolic disease risk.

Since the ability to utilize energy resources efficiently is fundamental to human survival, energetics is at the center of investigations of human evolution and adaptation (Ulijaszek, 1996; Leonard and Ulijaszek, 2002). Energy is a finite resource that must be allocated across competing biological processes, such as bodily maintenance, growth, and reproduction, over the life course. The amount of energy allocated to different biological processes varies greatly across human populations living in different environments and this has important consequences for population variation in disease risk (Leonard et al., 1996).

Additionally, energetic relationships are often altered under conditions of social, political, and economic change (Leonard et al., 1996). Thus, human energetics can act as lens for examining the social determinants of health. Leonard (1989) suggests that future work in anthropology would greatly benefit from an energetics-based approach, in which investigators examine the interaction between ecological and socio-economic factors and the ways in which they shape inter- and intra- population variation in adaptive strategies.

In this dissertation, I explore human energetics by examining the process of metabolic adaptation to cold stress. This approach is advantageous for two key reasons. First, investigating adaptation to cold climates serves one of the central goals of biological anthropology – to better understand human biological diversity. In an era when global climate change threatens many circumpolar lifeways, understanding the human biology of indigenous populations of the north is more pressing than ever. One primary way that circumpolar populations adapt to low temperatures is through elevations in metabolism, such as an increased BMR (Itoh, 1980; Leonard et al., 2002, 2005, 2014; Roberts, 1978). Historic work suggested that the dose-dependent effects of obesity on serum lipid and glucose levels were reduced among indigenous circumpolar groups compared to other populations across the globe (Snodgrass et al., 2006; Sorensen et al., 2005; Young, 2007). It has been hypothesized that adaptive elevations in metabolic rate in response to chronic cold stress may place a higher physiological demand for cellular substrates such as cholesterol and glucose and, therefore, may have protective effects against diabetes and cardiovascular disease (Snodgrass et al., 2007; Young and Bjerregaard 2008). In recent years, studies among circumpolar groups in North America and Greenland have documented a strong association between processes of acculturation and modernization and biomarkers of cardio-metabolic disease risk (de Knijff et al., 1992; Young et al., 1995). This dissertation sheds light on pathways that link lifestyle change, metabolism, and health that are unique to indigenous circumpolar populations with the aim of better understanding the process of adaptation in humans and its connection to health in contemporary, rapidly changing environments.

Second, investigating metabolic adaptation to cold stress will shed light on how environmental conditions shape energy budgets. A large body of research scrutinizes the pathways through which diet and physical activity alter energy budgets, yet fails to explain large portions of variability in energy expenditure across individuals and populations. For over six decades, human biologists have recognized that BMR is correlated with mean annual temperature across populations (Hart et al 1962; Heinbecker 1928; Milan et al. 1963; Milan and Evanuk 1967; Rabinowitch and Smith 1936; Rennie et al. 1962; Roberts, 1952; Rodahl 1952). Indigenous circumpolar populations, such as the Yakut of northeastern Siberia, exhibit BMRs that are higher than expected based on fat-free mass (Leonard et al., 2002, 2005; Snodgrass et al. 2005). Among the Yakut, the environmental factors that shape metabolic adaptation to cold stress include a complex interaction of ecological, social, and economic components. These components are shaped by the political history of the region, such as the rise and fall of the Soviet Union, and current patterns of lifestyle heterogeneity. The social, economic, and economic characteristics of the Siberian environment structure Yakut energy budgets by not only influencing diet and physical activity levels but also the process of metabolic adaptation to cold stress.

The discovery that brown adipose tissue (BAT) is present and active in adult humans has spurred renewed interest in how environmental inputs may alter energy balance (Enerback, 2010). BAT is a form of fat that is specialized for thermogenesis. The biological and social determinants of variation in BAT and its health significance are still largely unknown.

Objectives and Research Questions

This dissertation explores how the environment shapes energy expenditure by investigating multiple timescales of adaptation to cold stress among the Yakut, an indigenous circumpolar population. This study pursues three main objectives. First, the adaptive and health significance of BAT in Yakut adults is investigated. Second, this project examines evidence for seasonal acclimatization to cold stress via changes in thyroid hormone dynamics. Third, the study analyzes evidence for developmental adaptation in BAT thermogenesis and discusses the implications for understanding phenotypic plasticity. The study tests the following individual hypotheses:

1) Yakut adults with greater BAT thermogenesis will expend more energy during cold exposure. BAT metabolism is activated when the body is exposed to cold stress and is predicted to contribute to non-shivering thermogenesis in humans by stimulating an increase in whole body energy expenditure (Yoneshiro et al., 2011a). Additionally, participants with greater BAT thermogenesis will differ in the relative allocation of fats vs. carbohydrates used for metabolic fuel. Based on previous work, I expect that BAT activity in response to cold will result in a much

greater increase in the utilization of carbohydrates than lipids for metabolism (Vallerand and Jacobs, 1989). I predict that greater BAT activity will be associated with a higher respiratory quotient (RQ), a proxy for increased carbohydrate metabolism.

2) Yakut adults will show evidence of acclimatization to cold stress via alterations in thyroid hormone metabolism known as the "polar T3 syndrome" (Reed et al., 1990a, b). This response is characterized by reduced levels of free triiodothyronine (fT3) and free thyroxine (fT4) during the winter. Thyroid hormone dynamics regulate adaptive thermogenesis and the polar T3 response pattern has been documented among sojourners to Antarctica (Reed et al., 1990a, b; Harford et al., 1993). Lifestyle factors are expected to modify these responses such that individuals with greater subsistence activity participation will show more pronounced seasonal variation in thyroid hormone levels.

3) Yakut adults that experienced greater exposure to cold temperatures during development are predicted to exhibit greater BAT thermogenesis in adulthood. In particular, Yakut adults for which the climate was colder during development will show greater BAT activity. Additionally, adults that report spending more time participating in outdoor activities during the winter as a child will exhibit greater BAT activity.

4) The relationship between adult BAT thermogenesis and early-life cold exposure will be strongest for cold exposure experienced during the first few years of life due to the significant degree of plasticity during this period (Duffy et al., 2002; Wells, 2014). Alternatively, critical periods in BAT plasticity may extend into childhood or adolescence in order to integrate a longer time depth of environmental information into the developing phenotype and minimize the risk of phenotypic mismatch (Panchanathan and Frankenhuis, 2016).

Dissertation Overview

This thesis is composed of nine chapters. The current chapter introduces the research questions within the broader context of human energetics and frames the theoretical approach. Chapters 2, 3, and 4 provide background information for the dissertation. Chapter 2 reviews pertinent background theory while chapter 3 introduces the study location and population and provides background information on the ecological, social and health context. This project examines metabolic adaptation among Yakut adults living in the rural village Berdygestiakh and the city of Yakutsk in the Sakha Republic, Russia. The Yakut people are an indigenous population of northeastern Siberia. Chapter 3 describes the dramatic social transformations that occurred with the rise of Russian colonialism during the Tsarist and Soviet eras as well as the complex economic system that arose in the Sakha Republic after the collapse of the Soviet Union. The chapter ends with a discussion of the consequences of these political and economic transformations for cardiovascular health. Chapter 4 provides background information on BAT, a tissue of major focus in the dissertation. In particular, the function and physiology of BAT metabolism is discussed. Additionally, Chapter 4 reviews previous methods for quantifying BAT thermogenesis. Chapter 5 provides an overview of the methods used in this project.

Chapter 6 explores the relationships between BAT thermogenesis, energy expenditure, and biomarkers of cardio-metabolic health. This study shows that Yakut subjects with greater BAT thermogenesis exhibit more dramatic increases in energy expenditure during cooling and a decrease in respiratory quotient suggesting greater reliance on carbohydrates as a metabolic fuel.

Adults with greater BAT activity had a higher percent body fat and blood glucose levels. This may be due to the fact that the sample is relatively young and healthy.

Chapter 7 presents data on seasonal changes in thyroid hormones collected in the summer of 2009 and the winter of 2011 in Berdygestiakh. The results indicate that Yakut adults exhibit small, significant winter declines in fT3 and fT4 indicative of the polar T3 response. Evidence of acclimatization via thyroid function to be structured by lifestyle such that individuals that spend more time participating in subsistence activities exhibit more pronounced changes in the thyroid hormone levels. This pattern is consistent with the thyroid hormone dynamics of other high latitude populations.

Chapter 8 investigates whether human BAT exhibits developmental plasticity in reaction to cold stress during development. Early life cold stress was quantified using historic weather data and by surveying subjects about their participation in childhood winter-time outdoor activities. The results show evidence for developmental plasticity in BAT thermogenesis. Mid-childhood and puberty were both identified as potential critical periods for plasticity in human BAT.

Chapter 9, the concluding chapter, summarizes the results of the dissertation. This chapter also postulates on the possible adaptive function of BAT in humans. The results of the dissertation are reviewed within the context of the timescales of adaptation model.

CHAPTER 2

BACKGROUND THEORY

This dissertation draws from past work that synthesizes biocultural and evolutionary theory in biological anthropology. By integrating evolutionary and biocultural approaches, this project attempts to explore how social, economic, and ecological factors interact to shape energy expenditure. Additionally, this research conceptualizes biological adaptation as a process and applies the timescales of adaptation model (Kuzawa and Bragg, 2012; Kuzawa and Thayer, 2011) as a theoretical framework for investigating metabolic adaptation to cold stress among the Yakut of northeastern Siberia.

Integrating Biocultural and Evolutionary Approaches

Historically, two prominent approaches to describing and explaining biological variation have been applied by and competed for authority among anthropologists interested in human health. The first is a critical biocultural perspective, in which researchers are primarily focused on how sociocultural and political-economic processes affect biological variation and how health status can further impact the social fabric (Goodman and Leatherman, 1998: 5). The second approach is built on an evolutionary perspective focused on biological adaptation to environmental stressors. Recently, biological anthropologists have begun to increasingly merge these two perspectives (Hoke and McDade, 2014; Levy et al. 2013; Snodgrass et al., 2007). While research in biological anthropology is often framed in either a biocultural or an evolutionary perspective, such a distinction is a false dichotomy that moves anthropologists away from the historic strengths of the field and limits the explanatory power of our models (Snodgrass et al., 2007).

In their pivotal book, Leatherman and Goodman (1998) outline the aims of a biocultural approach to anthropological research. The dominant focus of this approach is how sociocultural and political-economic processes affect human biology and how an individual's compromised biology further threatens their social fabric (Leatherman and Goodman, 1998: 5). Therefore, biocultural anthropologists are ultimately concerned with tracing the roots of human biological conditions to the interaction of cultural and political-economic processes and local circumstances. The authors propose that a biocultural approach should address five main interrelated issues. The first is the importance of examining biological variation in terms of social relations through which individuals gain access to basic resources and labor (Leatherman and Goodman, 1998: 19). These social processes are key to forming proximate environments. Second, a biocultural approach examines and emphasizes the links between local and global forces. Next, biocultural analysis should be couched in history and convey historical contingency. Biocultural approaches recognize that humans are active agents in constructing their environments. For example, individuals will find ways to circumvent or change social systems when they are unable to make ends meet (Thomas, 1998: 48). Finally, ideology and knowledge, of subjects and scientists alike, are key to understanding human action (Goodman and Leatherman, 1998: 20).

Recent biocultural work builds on a historic emphasis on large-scale political-economic factors, such as lifestyle change and market integration, by considering how these processes may have differential impacts on distinct groups as a result of underlying biological differences

(Cepon et al., 2011; Levy et al., 2013; Snodgrass et al., 2007). A growing volume of work describes interactions between social determinants of disease and underlying biology that was been shaped by evolutionary and adaptive processes. In particular, developmental plasticity appears to be a critical pathway for interactions between cultural and economic forces and an adaptive biological scaffolding within the body (Kuzawa and Quinn, 2009; Worthman, 1993).

An evolutionary approach to biological anthropology focuses on the ways in which evolutionary processes, such as adaptation and natural selection, shape biological variation. While the biocultural approach applies information regarding a population's political-economic history, an evolutionary approach considers the evolutionary history of a population. Many human biologists contemplate adaptive energetic trade-offs between competing processes to explain unique human life history traits. One of the most prominent human features is our ability to adjust to new conditions and the wide variety of strategies that we have for doing this (Huss-Ashmore, 2000: 11).

Applications of an evolutionary perspective to human biology research in the past have often minimized the importance of proximate causes such as political, economic and historical factors (Snodgrass et al., 2007). Thomas (1998: 50) points out that although behavior serves as our primary means of adapting, it is guided by cultural and social agendas which do not always support biological well-being. Additionally, the evolutionary approach often ignores the ways in which humans not only experience or fit into an environment, but also construct it (Lewontin and Levins, 2007: 33). Finally, the tendency for evolutionary approaches to focus on adaptive responses to conditions rather than on the alteration of poor environments has been heavily critiqued as having a passive orientation and even reifying disease status (Singer, 1989; Thomas, 1998: 66). For instance, Waterlow (1986) states, “it is impossible to discuss adaptation without making value judgements and without using indefinable concepts such as ‘normal’, ‘healthy’, etc.”

Conceptualizing Adaptation as a Process

In response to these arguments and as an avenue for integrating biocultural and evolutionary approaches, Goodman and Leatherman (2003) propose that researchers conceptualize adaptation as an ongoing process rather than a collection of measures. 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 simplistic dichotomy of adaptive vs. maladaptive states.

Integrating evolutionary and biocultural approaches can provide a better understanding of the adaptive options available to human populations (Snodgrass et al., 2007). Evolutionary theory dictates that processes of adaptation are inherently imperfect due to constant changes in the environment (Van Valen, 1978; Liow et al., 2011). Furthermore, the costs that arise as a consequence of the process of adaptation are not negated by the benefits, and these costs often create biological constraints on future adaptive change. Political-economic relationships construct new stressors to respond to and constrain adaptive capacity as well, and people will attempt to circumvent or counter the social conditions that cause them (Thomas 1998: 44). Contextualizing social, cultural and economic factors within their biological effects will improve our understanding of how these factors function and are perpetuated.

When adaptation is conceptualized as a dynamic process, 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 (1911). 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 (Leonard and Hicks, 2014; Leatherman and Hoke, 2014). 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 (Leonard and Hicks, 2014; Lock, 2015).

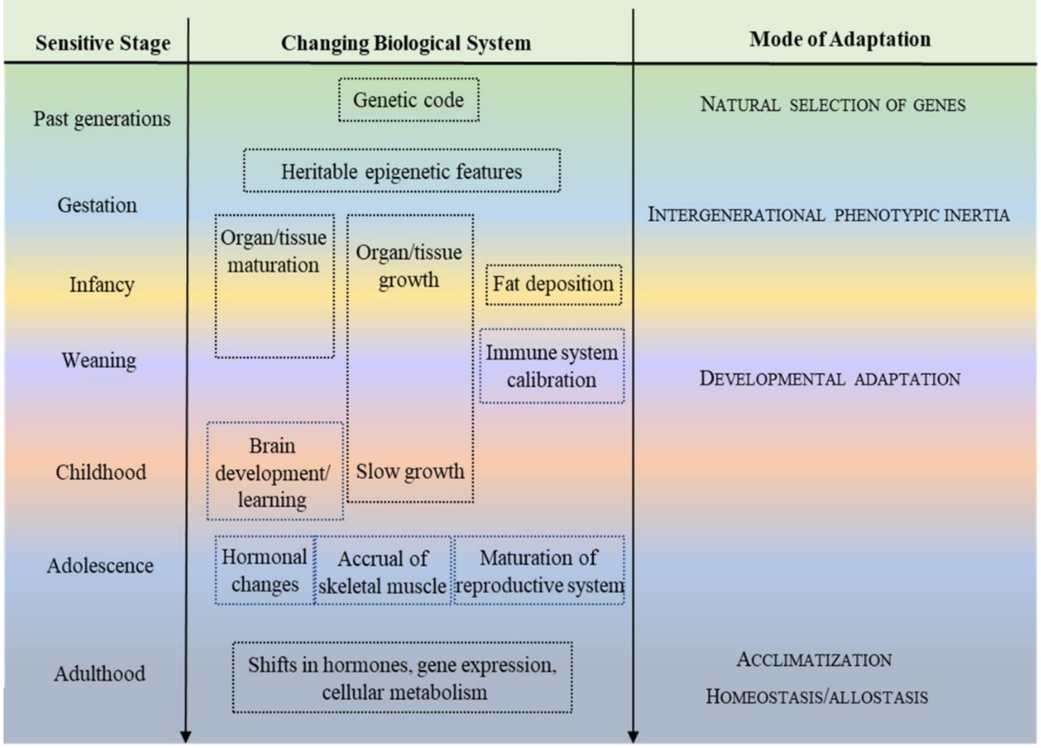
In this dissertation, adaptation is defined as a process of morphological, physiological or genetic change that occurs over a range of timescales and results in an improvement in evolutionary fitness at the population level. I use the timescales of adaptation model as a framework for investigating how energy budgets adapt to environmental inputs over the life course.

Timescales of Adaptation

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 (see Figure 1.1). These include homeostasis/allostasis, acclimatization, developmental adaptation, intergenerational phenotypic inertia, and natural selection of genotypes (Kuzawa and

Bragg, 2012; Kuzawa and Thayer, 2011). The form, strength and nature of an adaptive response depends not only on the type of stressor or experience, but also the duration for which the perturbation exists (Kuzawa and Thayer, 2011; Raubenheimer et al., 2012). In other words, the time-depth of a biological response should match the time-depth of the stressor. 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 (Kuzawa and Thayer, 2011).

Figure 2.1 Timescales of adaptation model. Figure modified from Kuzawa and Bragg (2012)



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 (Ellison, 2005; Raubenheimer et al., 2012). When novel conditions are confronted, more plastic modes of adaptation are the original sources of phenotypic novelty and functional adjustment (West-Eberhard, 2003). As the amount of time a population is exposed to the novel stressor increases, longer-acting, more durable adaptive modes accumulate (Ghalambor et al., 2007; Kuzawa and Bragg, 2012).

For example, homeostatic and allostatic mechanisms are sensitive to rapid environmental changes on the timescale of seconds to hours and buffer against their effect by continuously modifying physiology in order to maintain an adjustable “set-point” (Nijout, 1994; Sterling, 2004). When an individual is introduced to a stressor over several days to months, for example as a result of seasonality, chronically-activated homeostatic mechanisms can alter the underlying baseline biology and thus change the “set-point” (Young, 1988; Jansky et al., 1996). The biological pathways that facilitate this change may include epigenetic mechanisms or shifts in hormone dynamics. This process is called acclimatization (Frisancho, 1993).

Widespread acclimatization allows a population to withstand a stressor on a longer timescale. With each additional year of exposure, the number of individuals in a population exposed during formative early stages will increase. 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 (Frisancho. 1993). One potential advantage is that developmental adaptation may allow the growing individual to better calibrate the phenotype to environmental inputs than responses derived in adulthood (Frisancho, 2009; Kuzawa and Quinn, 2009). Alternatively, developmental processes may improve allostatic mechanisms by either shifting or broadening the range of detectable sensory inputs or the range of feasible biological responses (Sterling, 2004). In this way, these modes of adaptation (allostasis/acclimatization and developmental adaptation) become interwoven into a complex system.

This interwoven system is reflected in developing biological systems and their sensitivity to environmental stressors. During gestation, the process of organ and tissue specialization and growth is sensitive to external signals conveyed through the maternal phenotype. As altricial mammals, human neonates continue to be sensitive to maternal and environmental cues. For instance, the growth and development of organs and tissues, particularly fat deposition, is sensitive to environmental inputs. Weaning represents a time when babies are increasingly interacting with their environment, and in turn, developing systems like the immune system are responsive external stressors. Brain growth and learning during childhood can be conceptualized as a biological mechanism through which the developing organism responds to both social and ecological aspects of the environment. Finally, hormonal changes that mediate the accrual of skeletal muscle and maturation of the reproductive system are likely sensitive to environmental inputs. Thus, the particular biological pathways that are likely to be sensitive to environmental inputs at any given time will depend on the stage of development.

One inherent trade-off of developmental adaptation is that the developing individual risks modifying its trajectory in response to environmental cues that do not reflect future environmental conditions. This risk can be mitigated, however, by incorporating information about the conditions experienced by ancestors into the developmental response (Kuzawa, 2005; Raubenheimer et al., 2012). In other words, a developing organism may be able to distinguish signals from stochastic environmental stimuli and better predict future conditions by incorporating information about the past (Kuzawa, 2005). This mode of adaptation is known as intergenerational phenotypic inertia (Kuzawa, 2005). While both developmental adaptation and intergenerational phenotypic inertia are both actualized during early, impressionable life stages, they differ in the time-depth of the information to which the body is responding (Kuzawa, 2005).

Non-genetic inheritance is an essential mechanism for facilitating intergenerational phenotypic inertia because it is sensitive to environmental cues on an intermediate temporal scale. Epigenetic modifications may provide a biological “memory” of experiences across generations, thus allowing organisms to adapt their biology in response to rapid environmental changes (Non and Thayer, 2015). In humans, transmission can be facilitated through biological pathways such as the transmission of nutrients, microbiome, growth factors, metabolites, hormones and immune factors through the placenta or lactation (Kuzawa and Quinn, 2009; Hoke & McDade, 2014). Non-genetic inheritance can also take place via social and structural pathways that reinforce biological outcomes (Hoke and McDade, 2014). The potential benefits of this strategy are likely to be greatest when new environmental conditions are introduced fairly rapidly, but then persist, at least on average, over multiple generations (Kuzawa, 2005).

As the number of generations exposed to an environmental stressor increases, genetic accommodation via natural selection is more likely to occur. Through genetic accommodation, natural selection acts on genes related to a previously plastic phenotype, thus increasing its prevalence, enhancing its efficiency, adjusting its form or reducing disadvantageous side effects (Gottleib, 1991; West-Eberhard, 2003). Additionally, genetic change can improve developmental adaptations by adjusting regulation to change the frequency of expression of the trait or the conditions in which it is expressed (West-Eberhard. 2003). In this way, genetic adaptations can provide the infrastructure for a wide diversity of phenotypic plasticity. Concurrently, constancy of the phenotype must be constructed through an interaction between components of the developmental system (Oyama et al., 2001). Thus, the adaptive significance of natural selection is inextricably tied to the other adaptive modes. As time passes, the frequency of the adaptive genetic architecture will increase within the population (Aubret and Shine, 2009). 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 (Kuzawa and Bragg, 2012).

Thus, the modes of adaptation are all integrated into a complex system of biological responses that are sensitive to a wide range of timescales of environmental change. In other words, the timescales of adaptation model asserts that the body integrates environmental information that ranges in time-depth from a few milliseconds ago to many generations in the past in an attempt to accurately generate an adaptive phenotype (Figure 2.1). Niewöhner (2011) argues that such a body is “heavily impregnated by its own past and by the social and material environment within which it dwells. It is a body that is imprinted by evolutionary and transgenerational time, by ‘early-life’ and a body that is highly susceptible to changes in social and material environments.”

Limitations of the Model

Of course, not all biological variation reflects adaptation to environmental conditions. A trait may also become widespread not because it is adapted to the current environment, but for many other reasons. For example, a trait may be 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 a modern lineage despite the lack of current utility (Gould and Lewontin, 1979). 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 far from straightforward (Kuzawa, 2005).

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 (Rubenheim et al., 2012). 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 health and wellbeing (Piersma and Drent, 2003). The negative effects of toxicants on the body at various life stages can be re-interpreted as a failure in the responsive system to adequately buffer or appropriately interpret an environmental input (Kuzawa and Thayer, 2011). Environment-phenotype mismatch is an especially pertinent issue for long-lived species like humans (Wells, 2012).

Nevertheless, since the modes of adaptation are integrated into a single system of overlapping responses to a range of timescales of environmental change, human variation in metabolism can be viewed as the product of the interaction of all of the adaptive modes. As Ellison (2005) states, that deconvoluting the effects of environmental change on different timescales on a single biological system, tissue, or parameter is an exceedingly difficult task. To understand how variation in energy expenditure is shaped by various timescales of environmental change, measurements must be taken across a wide range of environments and across the life course.

Summary

In conclusion, the research presented in this dissertation draws from and integrates evolutionary and biocultural approaches to biological anthropology by investigating how the process of biological adaptation interacts with ongoing political-economic trends to shape biological variation and health. This dissertation conceptualizes adaptation as a dynamic process that proceeds on multiple simultaneous timescales in order to investigate how biological adaptation to cold climates influences the energy budgets of Yakut people. Furthermore, this research aims to examine how multiple dimension of the environment, including ecological, social, and economic factors, interact and structure stressor exposure over various timescales.

CHAPTER 3

ECOLOGICAL, SOCIAL, AND HEALTH CONTEXT

This chapter provides a description of the region, the history of Yakut people, and their cardiovascular health. First, I describe the climate and population of the Sakha Republic. I then review hypotheses regarding the process of human migration into the region. Yakut lifeways changed drastically with Russian contact, especially after the formation of the Soviet Union. After the collapse of the Soviet Union, these changes had lasting effects on the economic and health conditions of Yakut people. The chapter discusses lifestyle heterogeneity among the Yakut, a pattern first described Snodgrass (2004) in which there exists a diversity of economic strategies within a community, household or even an individual. While participation in subsistence activities, such as raising cattle and horses, picking berries, herbs and mushrooms, growing vegetable gardens, fishing, and hunting, are not ubiquitous across Yakut people, these practices are integral to life in northeastern Siberia. The chapter ends by contextualizing trends in cardiovascular health within ongoing lifestyle change.

Geography and Demographics

The Sakha Republic, also known as Yakutia, is a semi-autonomous state within the Russian Federation, located in northeastern Siberia (see Figure 3.1). The Sakha Republic has a population of over 958,000 people and spans 3,103,200 km^2, and 40% of this area falls above the Arctic Circle (Russian Census, 2010). The territory consists of boreal forest and arctic tundra, and is known for its many natural resources. For example, ~25% of the world’s diamonds come from the Sakha Republic (Alrosa Annual Report, 2016). There are also large reserves of oil, natural gas, gold, silver, tin, tungsten, and other rare minerals.

The Sakha Republic is home to the coldest human inhabited places on Earth (Crate, 2006: 7). Temperatures can range from -60ºC (-76ºF) in the winter to 40ºC (104ºF) in the summer. The winter months are characterized by an annual “anti-cyclone” consisting of extreme temperature inversions, persistent fog, and windlessness. The lack of winter wind allows inhabitants to conserve heat at extremely low temperatures (Crate 2006: 8). During the spring, temperatures rise but blizzards are common. The summer is typically dry with sudden bouts of torrential rainfall. Despite dramatic annual temperature fluctuations, the permafrost remains frozen throughout the year while the topsoil thaws in the summer (Crate 2006: 8).

A majority of the population of the Sakha Republic is Yakut, an indigenous population of over 450,000 people (Russian Census, 2010). Ethnic Russians make up 37.8% of the population. Other indigenous Siberian groups make up a minority of the population, including the Evenki, Evens, Tatars, and Buryat people. There are three ethnographically defined groups of Yakut people based on subsistence patterns and clan origins: Northern Reindeer herders, Viliui Valley Cattle-breeders, and Central Sakha (Kangalas) (Sorensen, 2003). A majority of households consist of a nuclear family, though intergenerational households are not uncommon. For this study, data collection took place in the capital city Yakutsk and in a small rural village called Berdygestiakh (see Figure 3.1).

Figure 3.1 Map of the Sakha Republic, Russia

Human Migration into Northeastern Siberia

Humans were the first hominid species to successfully colonize latitudes above 55ºN during the late Pleistocene (Pavlov et al., 2001; Ulijaszek and Strickland, 1993). The successful settlement of subarctic regions represents an unprecedented adaptive shift that likely included cultural, behavioral and biological dimensions (Snodgrass et al., 2007). Archaeological evidence suggests that humans may have occupied Arctic Siberia before the Last Glacial Maximum (LGM), or at least 27,000 years before present (YBP) (Lee et al., 2016; Pitulko et al., 2004). It is possible that as northern Siberia transformed from boreal forest to a steppe, hunter-gatherers followed the mammoth migration north into the Siberian Arctic (Lee et al., 2016). The LGM likely led to depopulation of northern Siberia as groups congregated in more southern regions (Forster, 2004). Population studies suggest that Tungusic language groups, such as the ancestors of the Evenki and Evens, likely expanded into northern Siberia after the LGM and introduced reindeer herding to the region (Foster, 2004; Lee et al., 2016; Schurr et al., 2010; Simchenko, 1976).

The Yakut people are thought to be one of the northernmost Turkic-speaking populations in the world (Zlojutro et al., 2009). Comparative linguistics have revealed close similarities between the Yakut language and Turkic languages spoken in the Altai-Sayan region (Ruhlen, 1987). Archaeological evidence suggests that the Yakut people stem from a Kurkan exodus that trekked north along the Lena River system in order to escape Mongolian incursions during the 11th to 13th centuries (Alekseev, 1996; Konstantinov, 1975; Okladnikov, 1970). Genetic studies of the Yakut claim that a small population migrated northwards approximately 1,000 YBP and experienced significant admixture with neighboring populations in northeastern Siberia (Fedorova et al., 2003; Pakendorf et al., 2006; Zlojutro et al., 2009).

Yakut Lifeways Prior to Russian Colonialism

The Yakut people practiced complex and variable subsistence strategies depending on the season and the local ecological conditions (Tokarev and Gurvich, 1964). According to archaeological evidence, the Yakut were the first inhabitants of a subarctic ecosystem to introduce cattle and horse husbandry (Crate, 2006: 16-17). Traditionally, the horse played a central role in Yakut spiritual beliefs and folklore (Tokarev and Gurvich, 1964). In the Lena River Valley, Yakut people practiced a semi-nomadic transhumant pastoralism (Forsyth, 1992). Groups would travel between a summer camp made up of birch-bark tents and a winter hamlet consisting of earth-covered log structures. Both summer and winter dwellings were located in grasslands (*alaas*) near lakes or rivers and the seasonal camps could be anywhere from 5 to 50 km apart. In the more northern regions, Yakut people practiced a nomadic reindeer herding lifestyle similar to neighboring groups such as the Evenki and Yukagir (Forsyth, 1992). Hunting, fishing and foraging were also important subsistence practices throughout the region (Tokarev and Gurvich, 1964; Wrangel, 1842).

Yakutia During Tsarist Russia

The Russian Cossacks arrived in Yakutia to extend Tsarist rule in the 17th century (Forsyth, 1992). Russian contact had a profound effect on the social organization of the Yakut. The Russian expedition exploited the lack of political unity between the largest Yakut clans by appointing clan leaders, which were responsible for collecting fur tribute in return for status and privileges among the Russians (Forsyth, 1992; Sorensen, 2003: 16). This led to economic stratification between clans. Some clans escaped tribute obligations by migrating north and adopting a nomadic reindeer herding and fishing lifestyle (Forsyth, 1992; Sorensen, 2003:16).

In 1633, a Russian expedition established a fort near the Lena River which served as a center for fur trade (Forsyth, 1992: 60). This fort became an administrative capital of great importance for the further annexation of eastern Siberia as wealthy fur merchants established trapping and trading business in the area (Forsyth, 1992: 61). By 1650, the district of Yakutsk had almost 2000 Russian inhabitants due to attractive sable and other fur sales (Forsyth 1992: 61). Later, the city would become the capitol of the Sakha Republic, Yakutsk.

The Soviet Era

After the Russian Revolution in 1917, Yakutia remained under the control of loyalists of the Tsar that had fled eastward until the mid-1920's (Sorensen, 2003: 18). Through collectivization and extensive planning, the Soviet economy became tightly integrated (Kempton, 1996). Certain components of the Soviet Union became specialized as factory or production centers while other regions specialized as agricultural areas. The result of this economic interdependence was that political leaders in Moscow maintained considerable economic leverage over Russia's outer components including Siberia (Kempton, 1996).

In the 1930's, the Soviet Union forcibly organized Yakut families into herding and farming collectives in order to end “backward” nomadism and promote “civilization” (Forsyth, 1992). Relocation policies also sought to sever Yakut place-based identity ties to the land in order to foster Soviet nationalism (Fondahl, 1997: 71). However, government attempts at assimilation failed, both due to Russians' frequent unwillingness to accept indigenous populations as equals and due to indigenous groups unwillingness to renounce their place-based identity (Fondahl, 1997: 72). Collectivization and relocation continued through the 1950's, as the Soviet government resettled the Yakut living in villages and hamlets onto large farm complexes in order to improve the agricultural output through mechanization (Sorensen, 2003: 19). By the mid-1980s, nearly all residents of Yakutia were either employed by the state or dependent upon government welfare (Slezkine, 1994).

While collectivization improved food availability and dietary stability and brought greater access to market goods, many of the Soviet era promises of modernization were never filled (Leonard et al., 1996; Snodgrass, 2004). For example, by the 1990s, very few homes in rural villages had running water or electricity (Sorensen, 2003:19). Pika (1999: 9-10) identifies 5 critical consequences of Soviet collectivization among the Yakut: loss of economic self-sufficiency and increased reliance on the Soviet government; a decline in the number of individuals participating in traditional subsistence with an increase in unskilled labor; increased alcoholism, isolation, and psychological stress; demographic decline; and deterioration of the health care infrastructure.

Lifestyle changes during the Soviet Era were particularly dramatic for women (Forsyth, 1992). Before Soviet collectivization, there was a relatively unstructured division of labor between the sexes, and the entire family participated in subsistence activities. The Soviet Union, however, created all-male herding brigades and charged men with hay-cutting responsibilities while women were forced to relocate to villages in order to focus on raising children and conducting wage labor (Forsyth, 1992).

Along with major social, political, and economic changes, Siberia witnessed a rapid growth in industrial development with few precautions taken to protect the subarctic environment (Fondahl, 1997: 74). By 1989, 68% of the population of the Sakha Republic lived in a few large cities (Kempton, 1996). The progressive concentration of the population in Yakutsk has led to devastating chemical pollution of the air, land and water (Fohndal, 1997: 75). For example, unsafe levels of polychlorobiphenyls (PCBs) and toxaphens, which leach into water sources and then bio-accumulate as they pass through the food chain, have been detected (Shephard and Rode, 1996: 98). Furthermore, the published ceilings for PCB levels are based on the assumption that people consume an average of 48 g of meat per day; however, many Yakut individuals rely on a diet high in meat (Shephard and Rode, 1996: 99). Other harmful chemicals, such as pheonl and thallium, have also been identified in water sources like the Viliui River (Crate, 2006: 204).

The Post-Soviet Era

After the collapse of the Soviet Union, the Sakha Republic declared autonomy in 1991. Initially, the Sakha Republic was relatively successful at negotiating sovereignty from Russia and in seeking recognition for the region's indigenous populations (Kempton, 1996). This is in large part due to the region's valuable natural resources – in particular the diamond caches, but also oil and natural gas – as well as the leadership and political maneuverings of Mikhail Nikolaev, the first president of the Sakha Republic. Mikhail Nikolaev is ethnically Yakut and an articulate and ardent supporter of greater economic and political autonomy of the Sakha Republic (Kempton, 1996).

Nikolaev used the power struggle in Moscow toward the end of *perestroika* and after the collapse of the Soviet Union between Boris Yeltsin and the Russian Parliament to maximize the Sakha Republic's control over the diamond industry. Due to Nikolaev's political maneuvers, Yakutia was no longer viewed as a passive empty frontier on the margins but an important player in the struggle for power in Moscow (Kempton, 1996). While Nikolaev clearly favored Yeltsin, he remained open to Khasbulatov's courtship and his promises of parliamentary support. This strategy proved successful in not just the struggle for control of the diamond mines, but also in more general efforts to maximize the Sakha Republic's political and economic autonomy (Kempton, 1996).

An increase in economic and political independence also meant that the Yakut people were suddenly without support from the central government. The collapse of the Soviet Union dramatically altered the lives of rural Siberians, many of whom were dependent on government wages and deliveries of food and other essential goods (Fondahl, 1998). By 1994, nearly all collective farms that operated during the Soviet period were dismantled (Jordan and Jordan-Bychkov, 2001: 140). Thus, Yakut villagers faced a variety of both challenges and opportunities related to defining new subsistence strategies (Crate, 2006: 141).

Lifestyle Heterogeneity

Some households have chosen to adopt a lifestyle that relies heavily on subsistence strategies such as cattle and horse breeding, hunting, fishing, and farming. For example, after state farms were dismantled, the 1990 Russian Law on Peasant Farms attempted to establish a system of privately-owned Western-style farms (Takakura, 2015: 74-92). The peasant farm system includes farms that consist of two or three households, usually related by blood or marriage, who engage in farming and animal husbandry as their primary business. Like other farms built on Western models, they are believed to run on market principles. While the number of peasant farms has increased, the production volume has remained stagnant and they represent only about 16% of meat and 21% of milk produced in the Sakha Republic (Takakura, 2015: 166-202).

On the other hand, neotraditionalism has been rejected by many in rural Yakutia and not everyone wishes to return to subsistence lifestyles practiced prior to the Soviet era (Jordan and Jordan-Bychkov, 2001). Fondahl (1997: 72) argues that the lack of Soviet respect for traditional land-based knowledge has translated into a declining prestige of traditional practices within Yakut communities. In addition, many do not have the appropriate knowledge required to participate in subsistence activities (Snodgrass, 2004: 48). Some households rely completely on private salaries and government pensions (Crate, 2006: 101). A majority of wage earning positions in rural Yakutia are state-subsidized white collar positions in administration, health care and education (Crate, 2006: 101).

However, a majority of Yakut people depend on a mixed cash economy that consists of a combination of subsistence practices and cash inputs (Crate, 2006: 101). As of 2002, 36% of Yakut people live in urban areas and 64% live in rural farming villages (Takakura, 2015: 24-39). Snodgrass (2004) uses the term lifestyle heterogeneity to describe the diversity of lifeways within a Yakut community, a single household, or even an individual. Common subsistence practices include raising cattle and horses, picking berries, herbs and other naturally growing foods, growing vegetables, hunting and fishing (Crate, 2006; Snodgrass, 2004; Sorensen, 2003; Takakura, 2015). Villagers will store meat, vegetables and ice for drinking water in either a *ongkuchakh*, a small cellar dug into the permafrost within the house, or in a *buluus*, a shed built over a larger cellar in the yard (Takakura, 2015: 56-73). The degree of participation in these activities ranges across a wide spectrum and subsistence activity patterns often shift with the season. Food produced from subsistence activities not only supplements the needs of the household, but also serves in the development of social relationships (Takakura, 2015: 74-92).

In addition to subsistence activities, many households depend on income from a salaried position or on “freelance” or self-employed income, such as odd jobs, home crafts, selling plant and animal products, and income from hauling hay, wood, or ice by tractor or truck (Crate, 2006:

101). Villagers typically consider their primary work in terms of their place of employment or their own business, while subsistence activities are done during the remaining down time (Takakura 2015: 74-92).

As state farms were dismantled, the distribution of livestock was not equitable. Differences in livestock ownership have had profound consequences on socioeconomic status and have led to an increase in economic inequality (Snodgrass, 2004: 45). This trend is reflected in recent household income data for the Viliui Valley, which show a new trend of income disparity between households that was not present during the Soviet period (Crate, 2006: 101).

The description of various subsistence activities below demonstrates how lifestyle heterogeneity is the result of an economic system unique to the Sakha Republic that blends a reciprocal kin-based subsistence system, characteristics of Soviet collectivization, and recent privatization initiatives (Takakura, 2015). Additionally, lifestyle heterogeneity is also a result of the extreme seasonality in the region and the specific ecological characteristics of subsistence activities like cattle and horse husbandry (Takakura, 2015). This system has allowed the Yakut to maintain their cultural networks while adapting to privatization initiatives under the Russian government (Takakura, 2015: 166-202).

Raising Cows

In 2004, 68% of all meat and 67% of all milk was produced by individual households for which animal husbandry was not their only source of income (Takakura, 2015: 174). Households that own cattle are visibly marked by the allocation of cow space, including cows roaming in the front yard and an adjoining corral or *khoton* (Crate, 2006: 94). Cow milk is used to make *taar*, a fermented mash of milk and leftovers, and *khaiahk*, which is similar to *taar* but with butter and soured cream (Crate, 2006: 28-29).

Cows depend on hay that is harvested from naturally growing grassy meadows, or *alaas*. *Alaas* are grass-covered gaps in the forest that usually contain a small lake (Takakura, 2015: 24-39). There are 16,000 alaas in the Sakha Republic and they were created by a process of permafrost degradation, called thermokarst, during the early Holocene (Crate et al., 2017). After the collapse of the Soviet Union, each person was allocated one hectare of space within an *alaas* for harvesting hay. Ownership of this land is restricted to the hay cutting season, and this land can be used by others for fishing, berry picking, hunting and by horse herding enterprises (Takakura, 2015: 74-92).

For a week to 10 days during the summer or the beginning of fall, villagers that own cows, their neighbors that do not own cows, and their relatives living in urban centers will come together to cut hay (Takakura, 2015:74-92). Children will also help during their summer break from school. In return, the cow owners will provide their neighbors and relatives with meat and milk (Crate, 2003; Takakura, 2015: 166-202). Store bought meat and milk is expensive and Yakut people report a preference for local cow products (Holt and Amilien 2007; Stammler and Sidorova 2014).

Breeding Horses

In contrast to cows, horses require year-round grazing away from the village (Takakura, 2015: 166-202). With the exception of homestead gardens and barns, individual ownership of farmland or pastures is not recognized under current laws of the Russian Federation and the

Sakha Republic. Only peasant farms and corporations such as agricultural enterprises are allowed land rights. For this reason, horse production, which requires access to large swaths of land for grazing, is typically controlled by large agricultural enterprises that succeeded the state farms.

In recent decades, foal meat has grown in popularity as a food important to Yakut culture and is regularly consumed on holidays and special occasions; however, store-bought foal meat is very expensive. Private citizens, or even institutions like schools, can own horses that are managed by these enterprises and make money on the foal meat market (Takakura, 2015: 166-202). People living in both rural villages and Yakutsk own horses and entrust them to a herder that is part of a larger enterprise in return for an annual fee. Horse owners will use the foal meat produced during the fall slaughter for their own consumption, to give to friends and family, and to sell on the foal meat market. Thus, horse breeding and consumption has been adapted to the market economy in its own unique way (Takakura, 2015: 166-202).

Picking Berries and Other Forest Items

Picking berries and other naturally growing foods in the forest represents not only an important subsistence practice but also an important social gathering. Women bring their children and collect berries together with friends, neighbors and family visiting from Yakutsk (Takakura 2015: 74-92). From the middle of summer to the middle of fall, one can find strawberries, blue lingonberries, red lingonberries, Sakhalin currants, black currants, red currants, and blueberries. Some Yakut families also harvest wild roots and herbs, such as horseradish, wild onions, and garlic for consumption or to be sold in local markets (Crate 2006:

29; Sorensen 2003: 252). Berries are eaten fresh with curds and candied and stored in jars for the winter.

Gardening

Gardening is perhaps the most common subsistence activity among Yakut people. Crate (2006: 102, 190) found that 70% of households in the Viliui region grow their own food in home gardens, including potatoes, cabbage, turnips, carrots, and cucumbers. In Yakutsk, over 70% of the population has access to a dacha, or a summer cottage located outside of the city center where people grow food and spend their free time (Stammler and Sidorova, 2014). City authorities transfer the administration of plots of land around the city's periphery to cooperatives of plot holders. The cooperative is then responsible for common infrastructure, utilities and their fees, conflict resolution and all other issues on the dacha area. Oftentimes, the residents of Yakutsk will not know the names of their neighbors in their apartment buildings but will have close friendships with the members of their dacha cooperative (Stammler and Sidorova, 2014).

Perestroika made growing ones' food a necessity for many. Even though the supply chain of imported foods has since stabilized, maintaining a home vegetable garden is still a popular subsistence activity in the Sakha Republic (Stammler and Sidorova, 2014). Perishable items like fresh produce are sold at a very high price. Additionally, the reputation of local food has become stronger, reflecting a worldwide trend (Holt and Amilien, 2007; Stammler and Sidorova, 2014). Finally, Stammler and Sidorova (2014) argue that movement between the city center and summer dachas can be considered to some extent a seasonal mobility reminiscent of transhumant pastoralism.

Hunting and Fishing

Many households may supplement or replace beef and dairy products with fishing and hunting fowl, bear, moose, squirrel and hare. (Crate, 2006: 29; Sorensen, 2003: 252). Fishing mainly takes place during the warmer months, although ice fishing is not uncommon (Takakura, 2015: 74-92). Hunting tends to be more of a year-round leisure sport for men, and the type of animal hunted depends on the season (Takakura, 2015: 74-92).

Acculturation, Modernization, and Lifestyle Heterogeneity

Human biologists have traditionally characterized lifestyle change in circumpolar regions through frameworks of modernization and acculturation (Shephard and Rode, 1996). Acculturation is defined as culture change resulting from first-hand contact between two distinct cultural groups (Redfield et al., 1936). Modernization encompasses a suite of economic, political, demographic and cultural changes that occur with the transition from traditional economies to more complex economic systems (Baker, 1986: 3-18; Dressler, 1999). The original conceptualization of modernization, however, has been extensively criticized for its link to models of social and economic progress (Goodman and Leatherman, 1998: 3-42). Despite these limitations, modernization and acculturation frameworks are often applied to the investigation of the health of indigenous circumpolar populations. Such studies have revealed the following secular trends among circumpolar populations with increasing modernization/acculturation: decreasing energy expenditure; increasing intake of refined carbohydrates and/or alcohol; and decreasing intake of more nutritious food items, especially fruits and vegetables (Shephard and Rode, 1996: 87).

Lifestyle change in the Sakha Republic has been described as “failed modernization”, “de-modernization”, and “incomplete modernization” (Sorensen, 2003; Snodgrass, 2004). While individual lifestyles in the Sakha Republic may vary across a spectrum ranging from “traditional” to “modern”, recent work by Takakura (2015) suggests that the diversity of lifestyles are deeply intertwined through social networks. Lifestyle heterogeneity can be interpreted as evidence of a unique economic system in the Sakha Republic that integrates Yakut notions of kin-based reciprocity, Soviet-style collectivization, and recent privatization initiatives (Takakura 2015).

Climate Change in the Sakha Republic

Climate scientists agree that the accumulation of greenhouse gases in the atmosphere from human activities, such as the combustion of fossil fuels, is causing climate change worldwide (Haines et al., 2006; IPCC 2013). Evidence from marine, terrestrial and atmospheric studies indicates that the climate of the Arctic is warmings (Serreze et al., 2000). According to the IPCC (2013), the smallest climate change scenario predicts that by the end of the 21st century, the near-surface permafrost area will shrink by 37%, while the scenario with the highest confidence predicts shrinkage of 81%.

In the last 100 years, the average temperature in the Sakha Republic has risen by 2-3°C and the average winter temperature has risen by 10°C (Crate, 2006: 145). The local ecological effects of global climate change in Arctic regions include thawing of the permafrost, flooding of rivers and lakes, shifting local plant and animal communities, and increasing annual precipitation, especially snow fall (Hinzman et al., 2005; Nelson et al., 2002). In the Sakha Republic, lakes found in *alaas* are expanding due to hydrological processes within the underlying permafrost in response to greater warming (Ijima et al., 2010; Ulrich et al., 2017).

The current scale and speed of environmental change increasingly challenges the capacity for Yakut people to utilize naturally growing hay fields in *alaas* (Crate et al., 2017). Pastoral land is limited to mature forms of thermokarst which have developed over thousands of years. The initial stages of thermokarst created by current climate trends are too inundated with water to support grassy fields (Takakura, 2017: 166-202). The expansion of lakes results in less area for hay fields. If snow is too deep, grazing horses cannot dig through to reach the grass underneath (Takakura, 2015: 166-202). Spring floods can be beneficial because they bring nutrient rich water to pastures; flooding in the summer, however, can prevent people from cutting hay (Crate et al., 2017).

During a knowledge exchange between local inhabitants and climate scientists in eight rural communities and in Yakutsk, Crate et al. (2017) found that, with respect to ecological changes, the citizens of the Sakha Republic were most concerned about the increase in flooding. In particular, they voiced concern regarding flooding and its impacts on hay production, access to the forest and other resources, houses near lakes needing to be relocated due to damp conditions, and flooding of cellars within the permafrost (Crate et al., 2017). Many Yakut people perceive these environmental patterns as being one component of a wide array of ongoing social and ecological changes (Crate et al., 2017).

Cardiovascular Health in the Sakha Republic

Cardiovascular Disease Mortality

Mortality from cardiovascular disease is the leading cause of death among the Yakut. In 1999, the mortality rate from all cardiovascular diseases was 391 per 100,000 deaths (Sorensen, 2003). This rate is considerably higher than the mortality rate from cardiovascular disease in the United States, which is 204 per 100,000 deaths (Center for Disease Control and Prevention, 2011). The 1999 mortality rate from cardiovascular diseases includes mainly deaths from ischemic heart disease, at a rate of 254 per 100,000 deaths, followed by cerebrovascular disease at 87 per 100,000 deaths (Ministry of Health of the Republic of Sakha, 2000). Unfortunately, more recent cause-of-death data is not available because Russian census data is not disaggregated by ethnicity.

Obesity

Rates of obesity are on the rise in the Sakha Republic, particularly for Yakut women (Snodgrass et al., 2006). An increase in Western food products that are high in refined carbohydrates and fat most likely play an important role in the rising rates of obesity in Siberia. Indigenous Siberians tend to carry their weight primarily on the abdomen, which is highly correlated to cardiovascular disease and diabetes (Leonard et al., 1996). In 2006, an assessment of body composition in Berdygestiakh, Sakha Republic found that only 12% of women and 7% of men were obese. Subsequent studies in 2009 and 2011 found that average BMI and percent body fat for Yakut men and women were in the overweight category (Levy et al., 2016).

Snodgrass et al. (2006) assessed the influence of lifestyle and socioeconomic variables on the development of excess body fat among the Yakut. The results of this study indicated that Yakut men with higher incomes and who owned more luxury goods were more likely to have excess body fat. None of the lifestyle factors were significantly associated with body composition of Yakut women except for dispersed resource subsistence activities. The authors suggest that higher rates of obesity among women may be due to lower levels of physical activity. A study of the physical activity levels in another indigenous Siberian group, the Evenki, found that levels were lower among Evenki women than men (Leonard et al., 1996).

Cholesterol

Despite high rates of mortality from cardiovascular disease, Sorensen et al. (2005) report that mean serum lipid levels among the Yakut are below the cutoffs recommended by the National Cholesterol Education Program (NCEP) (National Institutes of Health, 1999). More recently, Levy et al. (2016) found that average cholesterol levels were within the recommended values; however, the number of individuals exceeding the recommended levels appears to increase from summer to winter. Previous research examining the metabolic health of circumpolar indigenous groups document an increase in serum lipids and body fat following the adoption of modern lifestyles (Shephard and Rode, 1996).

The results of Sorensen et al. (2005) suggest, however, that the relationship between cholesterol levels and Yakut dietary and lifestyle patterns diverge from this trend due to the unique economic system characteristic of the Sakha Republic. The authors found a positive association between a subsistence diet and total cholesterol and LDL, while a modern lifestyle was associated with lower LDL and total cholesterol levels (Sorensen et al., 2005). While these results may be surprising at first glance, it is important to note that high “modern lifestyle” scores were significantly correlated to “market” and “mixed” diets but not “subsistence” diets, while “subsistence lifestyle” scores were correlated to both “mixed” and “subsistence” dietary patterns. The main difference between “mixed” and “subsistence” diets was the presence or absence of vegetables since cow products like meat and milk were strongly associated with all three diet types (Sorensen et al., 2005). These results show that characterizing “modern” as unhealthy and “subsistence” as healthy is overly simplistic and that more sophisticated methodology is needed for assessing the health consequences of post-Soviet transitions.

Finally genetic factors may account for a portion of the population variation in serum lipid levels. Apolipoprotein E forms a major constituent of serum lipids and their components and is essential for the receptor-mediated uptake of serum lipids into the liver and other tissues (Hofker et al., 1998). The apolipoprotein E gene (APOE) has three alleles (known as ε2, ε3 and ε4) and the presence of each allele is associated with varying risk of hyperlipidemia, and thus cardiovascular disease and Alzheimer’s risk. Despite low rates of hyperlipidemia, indigenous circumpolar populations have a high population frequency of the allele, ε4, most associated with high serum lipid levels (Borinskaya et al., 2007). The dissociation between APOE polymorphisms and serum lipid levels among indigenous circumpolar populations, however, appears to be moderated by lifestyle factors, such as physical activity levels, ambient cold exposure, and diet (Jørgensen et al., 2006). As these environmental factors change, so may population averages of serum lipid levels.

Hypertension

The risk of cardiovascular disease is compounded by high rates of hypertension among indigenous Siberians. In a study of a pooled sample of three native Siberian groups (Evenki, Yakut and Buryat), 64.8% of women and 82.7% of men were hypertensive (Snodgrass et al., 2008). Previous research indicates that indigenous circumpolar populations adapt to cold stress through elevations in basal metabolic rate (Roberts, 1952; Leonard et al., 2002, 2005). It has been proposed that a link exists between basal metabolic rate and hypertension (Luke et al., 2004). In support of this hypothesis, Snodgrass et al. (2008) found that basal metabolic rate was the strongest predictor of blood pressure in multiple regression models. Dietary factors and psychosocial stress also likely contribute to blood pressure elevation among indigenous Siberians.

The Metabolic Syndrome among Indigenous Circumpolar Populations

Previous research has shown that the prevalence of various symptoms associated with metabolic syndrome vary greatly across populations (Okosun, 2000). In particular, the dose-dependent effects of obesity on serum lipid and glucose levels appear to be reduced among indigenous circumpolar populations compared to other populations across the globe (Snodgrass et al., 2006; Sorensen et al., 2005; Young, 2007). For example, a study comparing the components of the metabolic syndrome in an Inuit community of the Keewatin region in Canada and the general population of Manitoba found that the two groups exhibited similar rates of obesity and an increasing trend between obesity and blood pressure (Young, 1996). However, the Inuit had significantly lower triglycerides, higher high density lipoprotein (HDL) levels and lower levels of blood glucose. These results have been supported by several other studies examining obesity and the metabolic syndrome in other indigenous circumpolar populations of Canada, Greenland and Siberia (Jorgensen, 2003; Leonard et al., 1994; Levy et al., 2016; Young, 2003; Young et al., 2007).

Historically, researchers have thought that this pattern was due to the protective effects of a traditional diet high in fish and marine mammals, which is associated with higher HDL cholesterol and lower LDL cholesterol levels (Jørgensen et al., 2006). The Yakut, however, are reported to consume high amounts of saturated fats. On average, Yakut men and women consume over twice the daily amount of saturated fats recommended by the American Heart Association; yet, average total cholesterol levels among the Yakut remain below the recommended cutoff (Levy et al., 2016).

Lower cholesterol and blood glucose at a given level of adiposity among indigenous Siberians may reflect greater energy expenditure due to high physical activity levels or metabolic adaptation to cold stress (Leonard et al., 1994, 2002, 2005). An elevated metabolic rate and cellular turnover may place a higher physiological demand for several cellular substrates, including cholesterol and glucose. Studies of cardiovascular disease risk factors among circumpolar groups in North America and Greenland have documented a strong association between processes of acculturation and modernization and the population burden of plasma lipids (de Knijff et al., 1992; Young et al., 1995). These changes in disease risk may be mediated through increased sedentary lifestyles and shifts from traditional to market food sources.

CHAPTER 4

BROWN ADIPOSE TISSUE

Introduction

This chapter presents background information on the function and physiology of brown adipose tissue (BAT) and various methods used to quantify its activity in adult humans. As discussed below, the functional significance of human BAT, its contribution to energy expenditure and the determinants of BAT variation are still widely debated. This background information was used to form the protocols applied in the dissertation research and was critical for interpreting the results.

The Function and Physiology of Brown Adipose Tissue

BAT is the primary source of thermogenesis in infants and is the only human tissue dedicated exclusively to heat production; however, it was previously assumed that as humans develop, BAT levels decrease to vestigial amounts (Ahene and Hull, 1966). More recent research enabled by ^{18}F-FDG positron tomography (PET) and computer tomography (CT) has redacted this assumption. This research indicates that not only is BAT metabolism activity acutely stimulated by exposure to cold temperatures, but also that a large amount of individual variation exists in both human BAT volume and activity (Enerback, 2010).

Brown, White, and Beige Adipose Tissue

Based on recent histological studies, human adipose tissue consists of three types: white, brown and beige. White adipose tissue (WAT) is the most abundant form of fat tissue on the body and it consists of large unilocular cells that contain large fat vacuoles rich in lipids.

In contrast, BAT is made of smaller multilocular cells that contain small fat vacuoles and are rich in mitochondria, which give the tissue its' reddish-brown color (Cannon and Nedergaard, 2004). The mitochondria of brown adipocytes are also unique due to the presence of uncoupling protein 1 (UCP1). UCP1 is integrated within the mitochondrial membrane where it uncouples the proton gradient from the production of ATP so that energy is instead released in the form of heat (Lowell and Spiegelman, 2000). In mice, brown preadipocytes share a common developmental precursor with muscle cells that is not shared by white fat cells (Cannon and Nedergaard, 2008). The presence of the transcription factor PRDM16 will stimulate the precursor cell to develop into a brown adipocyte and in its absence, it will develop into a muscle cell.

Beige fat, also known as brite fat, consists of adipocytes that are similar to brown adipocytes in phenotype but are found interspersed in WAT. The amount of UCP1 found in beige cells is about 10% of that found in BAT (Symonds et al., 2015). Unlike BAT, beige cells can be derived from the same progenitor cells as WAT (Walden et al., 2012), although it may be possible to derive beige cells from muscle progenitors as well (Long et al., 2014).

Recent research calls this classification system into question. In particular, the three tissue types may be interchangeable and may have depot-specific lineages (Symonds et al., 2015). Fat biopsies from the supraclavicular region in humans have identified a mix of classic BAT and beige cell markers (Sharp et al., 2012; Symonds et al., 2015); however, the relative amount of beige versus brown adipocyte phenotypes various human BAT and WAT depots is currently unknown. For the sake of the simplicity, the remainder of this dissertation will refer to all adipose tissue with UCP1-mediated thermogenesis as BAT regardless of the beige or brown distinction.

Human Variation in BAT

In adult humans, BAT is located above the clavicle, and around heart, esophagus, kidneys, pancreas, liver, spleen, and scattered within white fat deposits of the greater omentum and mesocolon (Sacks and Symonds, 2013). The supraclavicular depot is the most common BAT deposit; adults with active BAT in other regions typically exhibit greater BAT mass in the supraclavicular area. As mentioned above, the relative amount of beige and brown adipocyte phenotypes that can be found in various BAT and WAT deposits is currently unknown. Furthermore, it is possible that the different fat deposits may vary in their degree of lipid and carbohydrate metabolism during cold-induced thermogenesis depending on the location of the fat deposit and the relative amount of brown or beige adipocytes.

Currently, population variation in BAT is poorly characterized. Prior to this study, data had been collected in Canada, China, Japan, the Netherlands, Scotland, and the United States (see Table 4.1). Admiraal et al. (2013) and Bakker et al. (2013) compared the BAT mass of men born in the Netherlands of South Asian and European decent. Bakker et al. (2013) documents significantly greater BAT mass in men of European decent than the South Asian sample; however, Admiraal et al. (2013) did not detect significant differences.

Adult BAT mass appears to fluctuate with the seasons. Rates of BAT detection using PET-CT scans under thermoneutral conditions are higher in the winter than the summer (Yeung et al., 2009). This is likely because plasticity in BAT mass is sensitive to the process of acclimatization to cold stress. Van der Lans et al. (2013) exposed subjects to a 10-day cooling regimen and found a significant increase in BAT mass. Thus, it is possible that BAT plays a role in seasonal acclimatization to cold stress.

BAT mass appears to decline with age in humans beginning around 20 years old (Hanssen et al., 2015; Kindred et al., 2016; Matsushita et al., 2014; Saito et al., 2009; Yoneshiro et al., 2011b; Zhang et al., 2013). Aging BAT progenitor cells display cellular aging – a senescence-like phenotype that accounts for their age-dependent failure to differentiate into new brown adipocytes (Berry et al., 2016). PET/CT studies that cluster subjects into BAT positive and BAT negative groups based on the presence of glucose uptake in the supraclavicular area find that BAT positive subjects are younger, have a lower BMI and less body fat (Hanssen et al., 2015; Matsushita et al., 2014; Yoneshiro et al., 2011b; Zhang et al., 2013).

Based on the studies summarized in Table 4.1, a majority of healthy, non-obese adults between 18 and 30 years old living in temperate zones exhibit evidence of BAT metabolism in reaction to acute cold stress. Whether this pattern applies to subtropical, tropical, subarctic and arctic zones remains an open question. Additionally, the relationship between age and BAT mass is currently unexplored in other climatic regions. As the following section describes, future work characterizing population variation in BAT will have important implications for understanding variation in metabolism and cardio-metabolic disease risk.

Table 4.1. Body cooling techniques applied in PET-CT studies of brown adipose tissue.

Cooling Method	Study[a]	Study Location	Sample Size *Male*	*Female*	Mean Age	BMI	% BAT Detection
Cold Room							
19°C room, 12 hrs	Lee et al. (2012)	Bathesda, USA	14	10	28	22.5	25.0
18.3°C room, 3 hrs	Kindred et al. (2016)	Fort Collins, USA	2	0	23.5	28.3	100.0
17°C room, 2 hrs	Yoneshiro et al. (2013)	Sapporo, Japan	51	0	24.4	22	52.9
17°C room, 2 hrs	Admiraal et al. (2013)	Amsterdam, Netherlands	20	0	22.8	22.2	80.0
17°C room, 2 hrs	Schopman et al. (2014)	Amsterdam, Netherlands	9	0	22	22.4	100.0
17°C room, 2 hrs	Ramage et al. (2016)	Edinburgh, Scotland	6	0	22.1	22	100.0
16-18°C room, 2 hrs	Vrieze et al. (2012)	Amsterdam, Netherlands	10	0	27.5	22.2	60.0
16-18°C room, 2 hrs	Bahler et al. (2016)	Amsterdam, Netherlands	64	0	25.4	22.9	76.6
16-17°C room, 2 hrs	Bahler et al. (2015)	Amsterdam, Netherlands	14	0	25.5	22	92.9
15°C room, 90 minutes	Muzik et al. (2013)	Detroit, United States	10	15	30	23.8	36.0
Cold Room and Ice Block							
19°C room, 2 hrs, feet on ice	Saito et al. (2009)	Changzhou, China	31	25	37.1	22.6	32.1
19°C room, 2 hrs, feet on ice	Yoneshiro et al. (2011)	Sapporo, Japan	13	0	22.8	20.8	50.0
19°C room, 2 hrs, feet on ice	Yoneshiro et al. (2012)	Sapporo, Japan	18	0	22.8	21.3	55.6
19°C room, 2 hrs, feet on ice	Matsushita et al. (2013)	Sapporo, Japan	184	76	26	21.6	67.9
19°C room, 2 hrs, feet on ice	Yoneshiro et al. (2016)	Sapporo, Japan	45	0	23.4	21.9	73.3
Cooling Vest							
15°C cooling pack vest, 2 hrs	Hwang et al. (2015)	New Haven, USA	10	0	24.6	21.6	80.0
14°C water-perfused vest, 2 hrs	Cypess et al. (2015)	Boston, USA	15	0	22.2	22.7	80.0
Individualized Protocol							
Water-perfused suit, 90 min	van der Lans et al. (2013)	Maastricht, Netherlands	8	9	23	21.6	94.1
Water-perfused suit, 90 min	Hanssen et al. (2014)	Maastricht, Netherlands	8	8	21.9	21.3	93.8
Water-perfused mattress, 2 hrs	Bakker et al. (2013)	Leiderdorp, Netherlands	12	0	24.6	22	91.7
Water-perfused mattress, 2 hrs	Bakker et al. (2013)	Leiderdorp, Netherlands	12	0	23.6	21.5	100.0
Air temp. above shivering, 2 hrs	Vosselman et al. (2013)	Maastricht, Netherlands	10	0	22.5	21.6	100.0

[a] Study inclusion criteria: participants were healthy, mean age of sample was between 18 and 40 years old, mean BMI of sample was under 25

BAT Metabolism

Recent research suggests that human BAT may play a role in non-shivering thermogenesis. Adults with greater BAT metabolism exhibit a larger increase in energy expenditure during cooling (Blondin et al., 2015; van der Lans et al., 2015; van Marken Lichtenbelt et al., 2015). The primary molecular substrates for brown adipocyte function include lipids, such as triglycerides and chylomicrons, and glucose (Cannon and Nedergaard, 2004). When brown adipocytes are stimulated by norepinephrine in response to low temperatures, the cell produces the enzyme lipoprotein lipase and releases it into the capillaries where it acts on circulating chylomicrons and lipoprotiens. This leads to the uptake of free fatty acids from the blood stream, which are either combusted within the mitochondria or stored as triglyceride droplets. In addition, BAT has a high uptake of glucose per gram of tissue (Cannon and Nedergaard, 2004). This is mediated through a high level of GLUT4 expression, which is an insulin-regulated glucose transporter. The removal of free fatty acids and glucose from the blood stream through the action of brown adipose tissue may have important implications for the prevalence of markers of cardiovascular risk among cold-acclimatized populations.

Preliminary estimations of the tissue-specific metabolic rate of BAT in humans varies widely between studies. Rothwell and Stock (1983) used metabolic data collected from mice and calculated that the heat-producing capacity of BAT is 300 W/kg or 4.3 kcal//kg/min. Using this rate, the authors calculated that just 40-50g of adult human BAT could account for 20% of daily energy expenditure. While this estimate is often reported, it is unrealistically high. At 4.3 kcal/kg/min (258 kcal/kg/hour, this estimate is about 20 times the rate of energy expenditure for adult brain tissue (12-14 kcal/kg/hour), and about 12 times the rate of peak energy expenditure of the brain during childhood (18-20 kcal/kg/hr) (Holliday, 1986; Kuzawa et al., 2014).

More recent calculations based on the metabolic rate of oxygen (MRO_2) of human BAT suggest that the tissue-specific metabolic rate of adult human BAT may be lower than previously thought. Muzik et al. (2013) quantified the MRO_2 of human BAT using dynamic PET-CT scans with triple oxygen ($H_2{}^{15}O$, $C^{15}O$, and $^{15}O_2$) and ^{18}F-FDG tracer. That is, along with the glucose tracer commonly used in PET-CT studies of BAT, subjects inhaled oxygen with a ^{15}O tracer, carbon dioxide with ^{15}O tracer, and received an injected of water with a ^{15}O tracer. The triple oxygen tracer data were used to calculate the MRO_2. The authors found that, when activated by cold, BAT contributed less than 20 kcal/day to total energy expenditure. Interestingly, whole-body energy expenditure increased by 17.4% in the BAT positive group and only 0.4% in the BAT negative group. Similar estimates were found by Din et al. (2016). Both authors report a significant correlation between whole-body energy expenditure and BAT mass.

The significant relationship between whole-body energy expenditure during non-shivering thermogenesis and supraclavicular BAT mass seems paradoxical given the low tissue-specific metabolic rate of this BAT depot. There are several possible explanations for this pattern. First, it is possible that supraclavicular BAT mass may act as a biomarker for BAT metabolism in other parts of the body, which may have a higher tissue-specific metabolic rate. As discussed above, various BAT deposits, such as BAT around the heart, kidneys, or spine, may differ in their metabolic activity depending on the concentration of brown vs. beige phenotype adipocytes. They may also differ in the degree to which they metabolism lipids vs. carbohydrates. Additionally, it is possible that adults with greater supraclavicular BAT mass have a higher concentration of beige adipocytes scattered in WAT deposits. Virtanen et al. (2009) found that subjects with supraclavicular BAT exhibit a larger increase in WAT metabolism during cooling compared to subjects without supraclavicular BAT – perhaps due to a higher concentration of beige adipocytes in WAT. Thus, while supraclavicular BAT may not be entirely responsible for an increase in energy expenditure during non-shivering thermogenesis, it may act as a biomarker for metabolism in other BAT depots.

Alternatively, BAT metabolism during acute cold stress may trigger an increase in metabolism within other tissues or act as an indirect biomarker of an increase in metabolism in other tissues. It is possible that, like in mice, human BAT may contribute to whole-body energy expenditure through its interface with thyroid hormone dynamics (Cannon and Nedergaard, 2004). When brown adipocytes are stimulated by norepinephrine, they express type II deiodinase (DIO2), which converts free thyroxine (fT4) into free triiodothyronine (fT3). The absence of DIO2 inhibits BAT function. In addition, fT3 directly stimulates transcription of the UCP1 gene and promotes UCP1 activity (Silva, 1995).

Depending on the concentration of DIO2 within human brown adipocytes, the fT3 generated within BAT may be released into circulation and lead to an elevation in metabolism within other tissues, such as skeletal muscle (Fernandez et al., 1987). Human skeletal muscle is unique in that it also expresses DIO2; thus, BAT metabolism may be an indirect biomarker of DIO2 expression and fT3-mediated metabolism in other tissues including skeletal muscle. Most muscles do not display a significant increase in glucose uptake during cooling; however, if non-shivering thermogenesis in skeletal muscle is primarily fueled by lipids, it would go overlooked by dynamic PET-CT scans.

Methods for Quantifying Brown Adipose Tissue Thermogenesis

The Gold Standard: PET-CT Scans

The current gold standard for quantifying BAT volume and metabolism is a form of positron emission tomography (PET) that utilizes images that are taken at various angles in order to generate a three-dimensional image using computed tomography (CT). PET-CT scans of BAT typically use the radiopharmaceutical ^{18}F-flourodeoxyglucose (FDG), which is a glucose analog in which a hydroxyl group has been replaced with a positron-emitting radionuclide-18. When BAT thermogenesis is activated by norepinephrine in response to cold stimulation, glucose is taken out of the bloodstream into brown adipocytes and used to fuel BAT thermogenesis. Thus, ^{18}F-FDG PET-CT quantifies a tissue's glucose metabolism by reporting the amount of ^{18}F-FDG in a tissue in standard uptake value (SUV) units. Some studies argue that an SUV threshold of 2.0 units or greater in the supraclavicular area and other common BAT depots signifies the presence of active brown adipocytes (Yoneshiro et al. 2016), while others use an SUV cutoff of 1.5 units and greater (Chondronikola et al. 2016). SUV values can be converted into BAT volume using an auto-contouring function. Biopsies of fat tissue from the supraclavicular area reveal that subjects with greater ^{18}F-FDG uptake in this area exhibit greater expression of genes related to BAT metabolism, including uncoupling protein 1 (UCP1), β_3-adrenoceptor (ADRB3), NADH dehydrogenase (ubiquinone) iron-sulfur protein 3 (NDUFS3), and PR domain containing 16 (PRDM16) (Lee et al. 2011; Rockstroh et al. 2015).

While PET-CT allows researchers to accurately quantify BAT volume and glucose metabolism, there are several limitations to this method. For example, PET-CT scans are expensive, invasive and they exposure participants to radioactive tracers. Furthermore, ^{18}F-FDG PET-CT only detects glucose uptake by BAT; however, fatty acids are a major substrate for BAT thermogenesis and are considered to be the primary substrate for BAT metabolism in mice. While Ouellet et al. (2012) confirmed that there is increased fatty acid oxidation in the supraclavicular area in humans during cold exposure using the PET-CT tracer fluoro-thiaheptadecanoic acid, the relative contribution of fatty acids vs. glucose to BAT thermogenesis in humans is currently unknown. Thus, it is possible that individuals that exhibit low or undetectable BAT using ^{18}F-FDG PET-CT may have active brown adipocytes that rely primarily on fatty acid oxidation. Finally, in order to detect and quantify BAT glucose uptake, PET-CT scans require that the participant is exposed to cold temperatures. Additionally, it appears that the amount of BAT detected for each individual depends on the time length and intensity of the cold condition (see Table 4.1) for a list of commonly used cooling techniques). Currently, many of the PET-CT studies of human BAT use a range of cooling techniques, thus making comparisons across studies difficult.

Cooling Protocols

In the early 2000s, physicians using PET-CT scans for diagnostic purposes began to notice that some patients exhibited ^{18}FDG-uptake in the supraclavicular area. The majority of these diagnostic scans were performed under thermoneutral conditions; thus, the rates of BAT detection in healthy young adults ranged between 2% to 24% of scans (Choi et al. 2014; Shao et al. 2016; Lapa et al. 2015; Lee et al. 2013; Zhang et al. 2013). Interestingly, rates of BAT detection under thermoneutral conditions are higher in the winter, thus many of these studies may be detecting seasonal variation in BAT recruitment and metabolism (Yeung et al. 2009).

Table 4.1 provides a list of published PET-CT studies that measure BAT activity using body cooling protocols. Studies were included in the table if they recruited healthy adults with a sample mean age between 18 and 40 years old and a sample mean BMI under 25.0. One body cooling technique is to cool the subject in an air-conditioned room at a temperature that is below the thermoneutral zone. While there is variation across individuals, the thermoneutral zone for humans is typically 25-30°C/77-86°F. Thus, previous studies have exposed subjects to room temperatures ranging from 19°C (66.2°F) to 15°C (59.0°F) for anywhere from 2 to 12 hours (Lee et al. 2012; Kindred et al. 2016; Yoneshiro et al. 2011; Admiraal et al. 2013; Schopman et al. 2014; Ramage et al. 2016; Vrieze et al. 2012; Bahler et al. 2015, 2016; Muzik et al. 2013). PET-CT scans are typically performed during the final hour of the cooling protocol. This cooling technique increases the rate of BAT detection in a sample. For instance, the weighted mean percentage of participants with detected BAT using this cooling technique is 63.6%.

Another common cooling technique is to lower the room temperature using air conditioning and intermittently place the participant's feet on an ice block for several minutes. While fewer studies have used this method, the weighted average detection percentage of studies using this method is 62.3%. Thus, the added cold challenge does not appear to produce a large increase in the number of participants that experience stimulation of BAT thermogenesis.

In the last few years, researchers have begun to use cooling garments. For example, Hwang et al. (2015) utilized a vest that contains cold packs in order to cool subjects. Alternatively, researchers have used "water-perfused" clothing items that are lined with tubing

(Blondin et al., 2014). Cold water is then pumped through the tubing of the clothing item in order to cool the subject. Cooling garments can be utilized in one of two ways. The first is to hold the temperature of the cooling garment constant across participants. Past studies have used cooling vests that are 14-16°C (57.2-50.9°F) and on average they detected BAT in 80.0% of young, healthy adult participants.

The second method for utilizing cooling garments is to implement an individualized cooling protocol. This technique is commonly applied in studies that simultaneously quantify energy expenditure from non-shivering thermogenesis. The goal is to expose the subject to a temperature that is low enough to ensure activation of any brown adipocytes present in the subject while avoiding shivering. In addition to using cooling garments, some studies utilized a water-perfused mattress or an air-conditioned room to induce body cooling. During this protocol, the external temperature is decreased until the subject begins to shiver. The subject is then rewarmed in order to halt shivering and the external temperature is maintained a few degrees above the point at which the subject began shivering. The average rate of BAT detection using this method is 95.5%. Based on the studies summarized in Table 4.1, it appears that a majority of healthy, non-obese adults around 25 years old have brown adipocytes capable of cold-induced glucose metabolism.

Measuring Skin Temperature: iButtons and Infrared Thermography

Detecting changes in skin temperature of the supraclavicular area when the body is exposed to cool temperatures may act as an indirect measure of BAT thermogenesis and a non-invasive alternative to PET-CT scans of BAT ^{18}FDG-uptake (Symonds et al., 2012). In this region, brown adipocytes are located between the anterior neck muscles in the supraclavicular fossa posterior to the brachial plexus, under the clavicles, and around the common carotid arteries (Sacks and Symonds, 2013). Supraclavicular BAT is located toward the surface of the body, and therefore is more likely to influence skin temperature.

SCV temperature is commonly quantified using either Thermochron iButtons (Maxim Integrated) (Boon et al., 2014; Chondronikola et al., 2016; van der Lans et al., 2015; Yoneshiro et al., 2016) or infrared thermography (Jang et al., 2014; Salem et al., 2015). The Thermochron iButton is a small (17.35mm diameter) metal canister that contains a semiconductor temperature sensor, a computer chip with a real-time clock and memory, and a 3V Lithium battery. The iButton is taped to the area above the clavicle with the sensor side flush against the skin. The manufacturer advertises that the iButton DS1291H has an accuracy of ±1°C and a thermal sensitivity of ±0.5°C. Thermal sensitivity is the smallest target temperature change that instrument can detect (Kaplan 1999).

Van Marken Lichtenbelt et al. (2006) performed a validation study investigating the utility of iButtons for measuring changes in skin temperature by comparing iButton and thermocouple measurements and found that the mean accuracy was ± 0.09°C under constant thermoneutral conditions. When the room temperature was increased to 34.9°C (94.8°F), however, the iButton measurements were significantly below those of the thermocouple for the first 15 minutes of warming. This is likely because the iButton's temperature sensor is insulated by the metal casing. When the room temperature was decreased to 15°C (60°F), measurements taken from the iButton were significantly warmer than the thermocouple measurements for the entire 30-minute cooling period. Thus, when ambient temperature changes quickly and dramatically, iButton skin temperature errors are likely to be greater than 1°C due to thermal inertia (van Marken Lichtenbelt et al., 2006).

Infrared thermography is a non-invasive technique that measures mid to long wave infrared radiation emanating from objects. Infrared data is converted to temperature and used to create a digitized image or a high speed video rendering of a thermal map in false color (Tattersall, 2016). One advantage of this technique is that it does not require that the measurement device come into direct contact with the skin surface, thus avoid potential error introduced by thermal inertia. Additionally, infrared thermal imaging cameras are significantly less expensive that PET-CT scans.

There are, however, several limitations to infrared thermography, many of which can be minimized by applying a standardized protocol (Moriera et al. 2017). Manufactures such as FLIR advertise that many of their infrared cameras, such as the E60bx, have an absolute accuracy of 2% or ±2.0°C. In fact, depending on the conditions in which the image is captured, measurements have at most 2°C margin of error (FLIR 2016). With proper calibration and attention to measurement parameters such as ambient temperature, emissivity and spot size, the possible margin of error can be less than 1°C. In order to maximize the accuracy of skin temperature measurements, the correct thermography parameters must be entered into the camera before the image is captured, including ambient temperature and humidity and the emissivity of the target object. Emissivity is a measure of a material's effectiveness at emitting energy as thermal radiation. Dry skin, for example, has an emissivity of value 0.98. Additionally, objects from the surrounding environment can emit or reflect infrared light and introduce error. Thus, images should be captured away from objects that may emit or reflect potentially interfering infrared light such as windows, walls, or a radiator (Moriera et al., 2017).

An advantage of infrared thermal imaging is that many cameras have a high degree of thermal sensitivity and therefore can detect small changes in temperature of the target object. For example, the FLIR E60bx has an advertised thermal sensitivity of <0.045°C. Given that changes in BAT thermogenesis might result in subtle shifts in SCV skin temperature, a high degree of thermal sensitivity of infrared thermography is advantageous in this context.

Potential Skin Temperature Biomarkers of BAT Thermogenesis

Past work has compared a range of SCV skin temperature variables with BAT ^{18}FDG uptake via PET-CT scans in order to test whether SCV skin temperature is a valid indirect measure of BAT thermogenesis. Table 4.2 provides a list of potential skin temperature variables that may act as a potential marker of BAT thermogenesis. For example, Boon et al. (2014) and Yoneshiro et al (2016) found that SCV skin temperature after a two hour cooling condition is significantly correlated with BAT SUV. The temperature of the clavicle, below the clavicle and the core after cooling, however, were not correlated with BAT SUV (Boon et al., 2014). Additionally, when Yoneshiro et al. (2016) grouped participants by whether they had active BAT determined by an SUV threshold of 2.0 units, BAT positive subjects had significantly warmer SCV skin temperatures after the cooling condition than BAT negative subjects. Jang et al. (2014) did not find a significant relationship between SCV skin temperature after cooling and SUV. This may be due to the small sample size, or a lower rate of BAT detection using PET-CT in the sample due to a milder cooling treatment.

Table 4.2. Studies that compare PET-CT scans with SCV skin temperature in adults.

Study	**Sample Size**		**Mean**	**Equipment**	**Skin Temp.**	**Correlated w/**	**R**[b]	**Differnce between**
	Men	***Women***	**Age**		**Variable**	**BAT SUV?**[a]		**BAT+ and BAT-**[c]
Boon et al. (2014)	24	0	24.1	iButtons	SCV, TN	no		
					SCV, cold	yes	0.27	
					Δ SCV	no		
					SBCV, cold	no		
					Δ SBCV	no		
					CV, cold	no		
					Δ CV	no		
					Core, cold	no		
Jang et al. (2014)	12	5	36	Infrared	SCV, TN	no		no
					SCV, cold	no		no
					Chest, cold			yes
					SCV - chest, TN			yes
					SCV - chest, cold	yes	0.75	yes
Salem et al. (2015)	10	0	26	Infrared	Δ SCV			yes
van der Lans (2015)	36	0	23.4	iButtons	Δ SCV	yes	0.48	
Yoneshiro et al. (2016)	45	0	23.4	iButtons	SCV, TN	no		no
					SCV, cold	yes, positive	0.33	yes
					Δ SCV in summer			no
					Δ SCV in winter			yes
					Δ SBCV in winter			no
					Δ hand in winter			no
Chondronikola et al. (2016)	18	0	46.9	iButtons	Δ SCV	yes	0.58	yes
					Δ trunk	no		

[a]Reports whether there's a significant correlation between the skin temperature variable and BAT SUV ($p<0.05$); [b]Pearson correlation coefficient between skin temperature variable and BAT SUV; [c]Reports whether there is significant difference in skin temperature between BAT + and BAT - groups; Abbreviations: TN - thermoneutral condition; cold - cold condition; SCV - supraclavicular temperature; SBCV - subclavicular temperature; CV - clavicular temperature

Jang and colleagues (2014) argue that the difference between the SCV skin temperature and the temperature of a point on the chest may be a biomarker of BAT thermogenesis. While BAT positive and BAT negative subjects had similar SCV temperatures before and after cooling, the temperature of the chest was significantly cooler in the BAT positive group. Thus, they found that the difference between SCV temperature and chest temperature after cooling was significantly correlated with SUV. Interestingly, Boon et al. (2014) and Chondronikola et al. (2016) did not find significant differences in core temperature between BAT positive and BAT negative subjects, nor did they detect a significant relationship between SUV and core temperature. These conflicting results may be due to differences in the anatomical locations used to calculate core temperature or differences in the type of cooling treatment.

An alternative potential biomarker of BAT thermogenesis is change in SCV skin temperature between the thermoneutral and cooling conditions. Van der Lans et al. (2015) and Chondronikola et al. (2016) found that change in SCV temperature was significantly correlated with BAT SUV units. Additionally, change in SCV temperature was significantly correlated with percent change in energy expenditure (van der Lans et al., 2015). Furthermore, comparisons of BAT positive (SUV > 1.5 units) and BAT negative subjects indicate that BAT positive participants have smaller declines in SCV temperature (Chondronikola et al., 2016) and even significant increases in SCV temperature (Salem et al., 2015). Interestingly, Yoneshiro and colleagues (2016) found significantly smaller declines in SCV temperature among BAT positive subjects in the winter but not in the summer. This may be due to the fact that PET-CT scans were only performed during the winter; therefore, the study lacks data on seasonal changes in BAT positive/negative status as attributed by SUV. Boon et al. (2014) did not find a significant relationship between change in SCV temperature and BAT SUV. It is possible that the changes in SCV skin temperature in this study were too small to be detected by iButtons, which have a thermal sensitivity of 0.5°C. Differences in change in SCV temperature between BAT positive and BAT negative adults can be as small as 0.3°C depending on the type of cooling treatment and the age of the participants.

Description of Chosen Protocol

Based on the conclusions presented above, this study quantified BAT thermogenesis by measuring change in SCV skin temperature using an infrared thermal imaging camera. A range of standardized protocols are necessary to ensure that BAT thermogenesis is quantified and to minimize potential errors (Symonds and Budge, 2012). Skin temperature and metabolism exhibit a diurnal rhythm; therefore, the time of day should be standardized or controlled for in analyses. Time since food and drink consumption and ambient temperature must be standardized across participants. Skin temperature is sensitive to changes in anxiety; therefore, measures must be taken to ensure that subjects are calm. Changes in blood flow due to vasoconstriction or vasodilation will alter skin temperature independent of BAT thermogenesis. In this study, statistical analyses controlled for skin temperature of the sternum below the suprasternal notch in order minimize the effect of vasoconstriction/vasodilation of the core. Additionally, SCV skin temperature may be sensitive to changes in blood temperature due to shifts in metabolism of other tissues in the body. Some studies document a relationship between change in SCV skin temperature, internal temperature, and skin temperature of the trunk while others do not (Chondronikola et al., 2016). Finally, participants with greater white adipose tissue in this area will have lower skin temperatures, thus potentially masking the effect of BAT thermogenesis. Studies using SCV skin temperature as a marker of BAT thermogenesis should therefore control for percent body fat or skinfold thickness of the clavicle. Despite these limitations, preliminary studies of BAT metabolism using PET-CT scans suggests that SCV skin temperature may be a useful indirect measure of BAT thermogenesis.

Summary

This chapter reviews the function and physiology of BAT, as well as methods used to quantify its thermogenesis. BAT differs from white adipose tissue in that it has a high concentration of mitochondria that contain a unique protein specialized for thermogenesis. BAT deposits can contain adipocytes that are derived from muscle progenitors, also known as classical brown adipocytes, or from white adipocyte progenitors, also known as beige adipocytes. Future research should investigate how these various adipocyte phenotypes vary across different fat deposits of the body and how they vary across individuals and populations. Little is currently known about the determinants of population variation in BAT; however, acclimatization to repeated cold stress is likely to shape population variation in BAT.

Investigating the biological and social determinants of population variation in BAT requires new methods. The gold standard – dynamic PET-CT scans combined with a cooling protocol – is highly invasive and expensive. Change in SCV skin temperature represents an effective indirect biomarker of BAT thermogenesis. Quantifying change in SCV after a cooling condition using an infrared thermal imaging camera is a promising method for measuring BAT thermogenesis and studying its variation across individuals and populations.

CHAPTER 5

RESEARCH METHODS

This chapter outlines the sample and methods used to assess brown adipose tissue (BAT) thermogenesis among indigenous populations of Siberia. Data were collected in the Sakha Republic, Russia in the rural village of Berdygestiakh and in the city Yakutsk. Data collection took place during three phases – summer of 2009, summer of 2011, and fall of 2015. The chapter provides a brief description of the locations in which data were collected, the study personnel, and the participant recruitment process. Additionally, data collection protocols such as anthropometric measurements, indirect calorimetry, infrared thermography, and questionnaires are described. Finally, a brief summary of the statistical analyses applied in this study is provided.

Field Locations

Berdygestiakh, Sakha Republic

Data collection took place in Berdygestiakh, Sakha Republic, Russia at the Gorny Regional Medical Center during three separate phases. The first phase was from July 29, 2009 through August 7, 2009. The second phase began on January 16, 2011 and ended on January 21, 2011. The third and final phase was data collection in Berdygestiakh was from September 5-11, 2015. Berdygestiakh is a rural village located in the subarctic zone (62°N, 127°E) and is 180 km (111 miles) west of the capital city, Yakutsk. As of 2010 (Russian Census, 2010) the village of Berdygestiakh has a population of 6,462 people. The majority of the population is Yakut, an ethnic minority population within the Russian Federation that is indigenous to northeastern Siberia.

The Gorny Regional Medical Center – a modern and well-equipped hospital – graciously provided climate-controlled lab space, access to freezers and other critical equipment for data collection. A longstanding, positive relationship exists between the visiting human biologists, the staff at the Gorny Regional Medical Center and the surrounding community. Northwestern University researchers have collected data at this site since 2001; therefore, this work builds on a growing longitudinal dataset.

Data was collected in Berdygestiakh during three separate collection phases. The first phase was in July and August of 2009. The average high temperature during this time period was 75°F (24°C) and the average low was 55°F (13°F). Data was then collected in January of 2011, during which the average high was -22°F (-30°C) and the average low temperature was -37°F (-38°C). The final data collection phase in Berdygestiakh was in early September 2015. During this data collection phase, the average daily high temperature was 67°F (19°C) and the average low was 32°F (0°C).

Yakutsk, Sakha Republic 2015

During the third data collection phase, research was also conducted in Yakutsk from September 11-23, 2015. Yakutsk has a population of 269,601 people, and a majority of the residents of are of Yakut ethnicity; however, there are also many people of other indigenous minorities, such as Buryat, Evenki, Even and Ket, as well as people from western Russia and migrants from China, Mongolia, Uzbekistan and elsewhere (Russian Census, 2010). During data collection in Yakutsk, the average high temperature was 51°F (11°C) and the average low was 32°F (0°C).

The first three days of data collection in Yakutsk was conducted at the Institute of Health at M.K. Ammosov North-Eastern Federal University (NEFU). The Institute of Health was first established in 1995 and became part of the university in 2011. The Institute is committed to investigating population health in Russia's North and it functions as both as a research center with labs for analyzing biological samples and a teaching facility with classrooms and faculty offices. A small classroom was aside for data collection and space heaters were used to raise the temperature of the classroom in order to match the room temperature of the Gorny Regional Medical Center. Along with classroom space, the Institute of Health graciously provided access to their freezers and other critical equipment.

The following ten days of data collection took place at the NEFU Medical Clinic. The Medical Clinic is a modern, well-equipped facility that serves as a teaching hospital for NEFU's medical school. Data collection was set up in an available doctor's office/examination room. Again, the Medical Clinic graciously allowed us to use their freezer and other necessary equipment.

Study Personnel

2009 and 2011 Study Personnel

The study personnel for the 2009 and 2011 data collection phases included William R. Leonard (W.R.L.) in the Department of Anthropology at Northwestern University, J. Joshua Snodgrass (J.J.S.) in the Department of Anthropology at University of Oregon, Tatiana M.

Klimova (T.M.K.), Valentina I. Fedorova (V.I.F.), and Marina E. Baltakhinova (M.E.B.) at the Institute of Health at NEFU, and Larissa A. Tarskaia (L.A.T.) in the Department of Anthropology at University of Kansas. This work was performed with the assistance of several staff members at the Gorny Regional Medical Center. Additionally, this research was conducted under the direction of Vadim Krivoshapakin, the former director of the Institute of Health and in collaboration with Elizaveta Popova (E.P.) in the Yakutsk Medical Center Department of Endocrinology.

2015 Study Personnel

The 2015 study personnel included W.R.L. and S.B.L. in the Department of Anthropology at Northwestern University, and T.M.K., V.I.F., M.E.B., and Zakharova Raisa Nicolaevna (Z.R.N.) in the Institute of Health at NEFU. Additionally, this work was conducted in collaboration with J.J.S. in the Department of Anthropology at University of Oregon and with the assistance of staff members at the Gorny Regional Medical Center.

Participants

Recruitment

2009 and 2011 Recruitment – Berdygestiakh, Sakha Republic

Table 5.1 presents a summary of the sample sizes and the data generated in each phase of the study. Participants were recruited from the rural community of Berdygestiakh on a voluntary basis based on word of mouth and advertisements for the study that were posted around the village and broadcasted on the local radio station and in the local newspaper. Recruitment was coordinated by T.M.K and individuals interested in participating were told to arrive at the Gorny Regional Medical Center in the morning having fasted and refrained from smoking for 12 hours prior to their arrival. Conditions in this remote part of Siberia prevent the recruitment of a truly random sample. Therefore, the study sample may be biased toward individuals who are open to health and physiological research and have the resources and time available to visit the health clinic. All participants were healthy at the time of data collection (no known acute conditions) and pregnant and lactating women were excluded. During the 2009 data collection phase, a total of 293 participants were recruited (147 women, 146 men), and during the 2011 phase, 296 participants were recruited (183 women, 113 men) (see Table 5.1). The participants ranged in age from 18 to 81 years old.

2015 Recruitment – Berdygestiakh, Sakha Republic

Participants were recruited from the community of Berdygestiakh in manner similar to the 2009 and 2011 study phases. Again, recruitment was coordinated by T.M.K. and the study was advertised in the local newspaper and on the local radio station. Potential participants were told to arrive at the Gorny Regional Medical Center in the morning having fasted and refrained from smoking for 12 hours prior to arrival. Many of the participants were staff at the Gorny Regional Medical Center or the family members of patients at the clinic. Pregnant and lactating women were excluded and all participants were healthy at the time of data collection and had no known acute conditions. In Berdygestiakh, a total of 171 participants were recruited (127 women, 44 men) and they spanned from age 18 to 81 years old.

Table 5.1 Sample Sizes for Yakut data by year, study location and type of data collected.

			Sample Size		
Data Collected	**Year**	**Location**	***Female***	***Male***	***Total***
Anthropometry	2009	Berdygestiakh	147	146	293
	2011	Berdygestiakh	183	113	296
	2015	Berdygestiakh	127	44	171
	2015	Yakutsk	30	27	57
Thyroid Hormones	2009	Berdygestiakh	136	129	265
	2011	Berdygestiakh	179	108	287
	2015	Berdygestiakh	129	46	175
	2015	Yakutsk	29	25	54
Blood Glucose and Lipid Levels	2009	Berdygestiakh	148	142	290
	2011	Berdygestiakh	183	112	295
	2015	Berdygestiakh	127	45	172
	2015	Yakutsk	30	26	56
Resting Metabolic Rate (RMR)	2009	Berdygestiakh	102	101	103
	2011	Berdygestiakh	155	96	251
	2015	Berdygestiakh	6	18	24
	2015	Yakutsk	27	29	56
Brown Adipose Tissue Thermogenesis	2015	Berdygestiakh	6	19	25
	2015	Yakutsk	31	29	60
Style of Life (SOL) Score	2009	Berdygestiakh	137	134	271
Childhood and Adult Outdoor Activities	2015	Berdygestiakh	11	4	15
	2015	Yakutsk	29	23	52

2015 Recruitment – Yakutsk, Sakha Republic

In Yakutsk, participant recruitment was coordinated by Z.R.N. The study was advertised via word of mouth and advertisements around the NEFU campus. Again, the study setting and timeline prevented a truly random sample and many of the participants were undergraduate students, graduate students, and university employees. Pregnant and lactating women and individuals with acute health conditions were excluded from the study. Potential participants were told to arrive at the Institute of Health (September 11 – 14) or the NEFU Medical Clinic (September 15 – 24) having refrained from eating, drinking or smoking for 12 hours prior to their arrival. There was a total of 57 participants (30 women 27 men) and their age range was 18 years old to 46 years old.

Informed Consent

2009 and 2011 Informed Consent

Permission to conduct this study was granted by the University of Oregon Institutional Review Board. The project goals and methods were explained to potential participants in either Yakut or Russian by T.M.K depending on the potential participant’s preference and then verbal consent was provided.

2015 Informed Consent

The Northwestern University Institutional Review Board granted permission to conduct this study (IRB 00200092). In both Berdygestiakh and Yakutsk, the goals and methods of the study were explained by T.M.K in either Yakut or Russian based on individual preference. Verbal consent was provided for participation.

Remuneration

2009, 2011 and 2015 Remuneration – Berdygestiakh, Sakha Republic

As remuneration, the participants in Berdygestiakh were offered a cardio-metabolic disease risk assessment and consultation with a physician. The assessment included anthropometric measurements, such as body weight, BMI, and percent body fat, blood pressure, fasted lipid measurements including total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride levels, and fasted glucose levels. Cholesterol, triglyceride and glucose levels were measured using a Cardiochek PA Analyzer and Lipid Panel and Glucose test strips. The health assessment and consultations were performed by T.M.K and V.I.F.

2015 Remuneration – Yakutsk, Sakha Republic

In Yakutsk, participants received a gift certificate that could be redeemed at a café on the NEFU campus. Additionally, participants received a cardio-metabolic disease risk assessment and consultation with T.M.K or V.I.F. Again, the health assessment included anthropometric measurements, such as body weight, BMI, and percent body fat, blood pressure, fasted lipid measurements including total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride levels, and fasted glucose levels. Cholesterol, triglyceride and glucose levels were measured using a Cardiochek PA Analyzer and Lipid Panel and Glucose test strips.

Data Collection Protocol

Timeline

Upon arrival at either the Gorny Regional Medical Center, the Institute of Health, or the Medical Clinic, participants were first met with TMK for the consent and enrollment process, and then moved through a series of stations for data collection. First, anthropometric measurements were collected and this information was used for the indirect calorimetry and thermal imaging portion of the study. Participants then had their blood drawn and filled out several surveys regarding their education, socioeconomic status, lifestyle, and health habits. Next anthropometric dimensions were collected, followed by indirect calorimetry and thermal imaging.

Anthropometry

Anthropometric dimensions were taken using standardized techniques (Frisancho, 2008; Lohman et al., 1988). Stature was measured to the nearest millimeter using a portable field anthropometer. Tricep, bicep, subscapular, and suprailiac skinfold thicknesses was measured to the nearest 0.5 millimeter using calipers. Body mass, percent body fat and FFM was measured using a Tanita digital bioimpedence analysis (BIA) scale. Percent body fat was also calculated using from the sum of four skinfolds (triceps, biceps, subscapular, and suprailiac skinfolds) using the equations of Durnin and Womersley (1974).

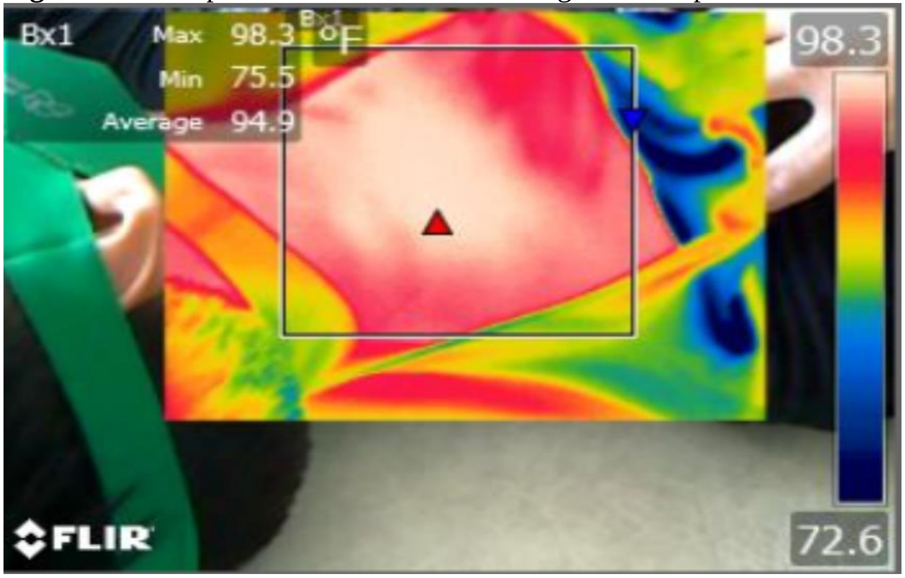
Indirect Calorimetry and Thermal Imaging

Resting metabolic rate (RMR) and BAT activity data collection occurred during two temperature conditions – a thermoneutral condition during which measurements were taken at room temperature (20-28°C), and a cooling condition during which the participant wore a cooling suit with an internal temperature of 15°C. RMR was measured using open circuit indirect calorimetry following a standard protocol outlined by Leonard (2012) and BAT heat production was quantified by infrared thermal imaging using a technique modified from Symonds et al. (2012b). Participants wore wear a water-perfused suit (Allen-Vanguard, Ottawa, ON) for temperature manipulation. The suit consists of a jacket and pants that are lined with tubing. Cold water (~10°C) is pumped through the suit's tubing in order to cool the participant. Prior to metabolic measurement, participants were shown the indirect calorimetry equipment and were given a chance to adjust to breathing in the face mask. Heart rate was simultaneously measured using a Polar S610 heart rate monitor in order to track anxiety during metabolic measurements.

Thermoneutral Condition

Participants rested quietly in a supine position. Measurements of oxygen consumption (VO2, L/min.) and carbon dioxide production (VCO2, L/min.) were recorded using MedGraphics VO2000 open-circuit metabolic analyzers (Medical Graphics UK Ltd., Gloucester, UK) interfaced with MedGraphics Breeze Lite software. RMR was calculated by converting VO2 to kcal/day based on the respiratory quotient using the modified Weir (1949) formula (McArdle et al., 2001). During the thermoneutral condition, RMR was measured for a total of 20 minutes. The first 10 minutes of data were discarded because during this time the participant is adjusting to breathing in the mask. Heart rate was monitored to track anxiety and all participants exhibited a stable heart rate by the 10-minute mark. Beginning at the 10 minute-mark, thermal images were captured of the left and right sides of the neck (see Figure 5.1) every five minutes using an infrared thermal imaging camera (E60bx, FLIR).

Figure 5.1 Example of an infrared thermal image of the supraclavicular area.



Cooling Condition

The cooling condition protocol was modified from Blondin et al. (2014) and Bakker et al. (2014). Cold water (mean temperature = 10.3°C +/- 2.9°C) was pumped through the tubing of the water-perfused suit for 30 minutes. If the participant began to shiver, the skin temperature of the sternum was recorded and the pumps were shut off so that the subject would rewarm in order to stop shivering. If the skin temperature of the sternum increased 2°C above the temperature at which shivering began, the pumps were turned back on. The goal of this protocol was to maximize non-shivering thermogenesis and minimize shivering. A total of six participants shivered. The energy expenditure for the cooling condition was calculated from the average values taken over the course of the cooling protocol during the time points when the subject was not shivering. Thermal images of the left and right sides of the neck were captured every five minutes during the cooling condition.

Analysis of Thermographs

Using FLIR Tools Software (FLIR), the maximum SCV temperature and the temperature of a point on the sternum were determined for each image. From these data, the thermoneutral SCV temperature was calculated by averaging the maximum temperatures from the images of the left and right sides taken at the 10 and 15-minute mark. Next, the cooling condition SCV temperature was calculated by averaging the maximum SCV temperature of left and right side after 30 minutes of cooling. BAT thermogenesis was calculated by subtracting the thermoneutral SCV temperature from the cooling condition SCV temperature. Change in SCV temperature was chosen as a biomarker of BAT activity because, when using infrared thermography, within-subject changes in skin temperature are more accurate than estimates of absolute temperature (see Chapter 2, Measuring Skin Temperature: iButtons and Infrared Thermography).

Survey Data

Socioeconomic Status, Education, and Health Habits

Surveys administered by TMV or VIF were used to collect data on socioeconomic status and education. In particular, participants reported their occupation, income, and highest level of education attained. Information on whether subjects smoke, how often, and alcohol consumption frequency was collected.

Lifestyle, Diet and Subsistence Participation

Participants were asked whether they consumed items from a list of common foods, if so, how often, and whether the item was purchased from a market, produced at home, traded for other goods, or received from family members. In order to assess material style of life, participants were asked about their ownership of 20 items: car, motorcycle, bicycle, television, stereo, video player, video camera, camera, computer, telephone, washing machine, bath house, ice cellar, barn, tractor, house, cows, horses, pig, and chickens. For each item, subjects reported whether they owned it and, if so, how many, and how important the item is in daily life (1 – not important; 3 – very important). Other questions were asked about participation in various daily activities, such as watching TV, and participating in various subsistence activities (i.e. tending animals, cutting hay, gardening, fishing, hunting, foraging).

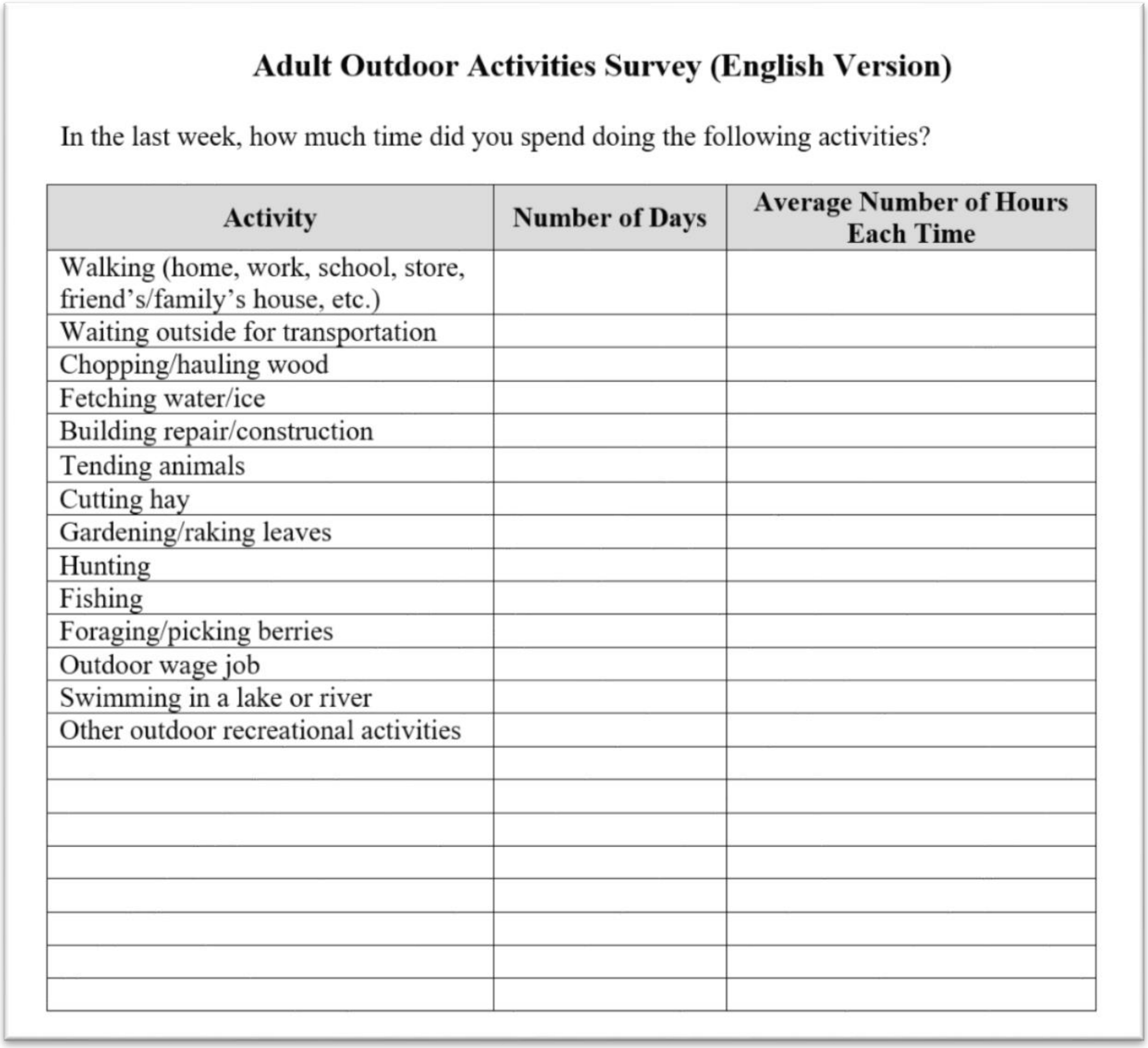
A style of life (SOL) scale was created based on that of Bindon et al. (1997) to consider participation in subsistence activities, diet, and ownership of common consumer goods and livestock. Other questions were asked about participation in various daily activities, such as watching TV, and participating in various subsistence activities (i.e. tending animals, cutting hay, gardening, fishing, hunting, foraging). Low SOL scores indicate more traditional ways of life (e.g., participation in more subsistence activities, less market food consumption, less formal education, and fewer consumer goods), whereas a high SOL suggests greater integration to the market. The individual components if the SOL score are presented and discussed in more detail in Cepon et al. (2011:161).

Quantification of Cold Exposure

Current Adult Cold Exposure

Participants were given a list of outdoor activities (see Figure 5.2) and asked to report whether they participated in each of the activities in the last week and, if so, how often. These data were used to calculate an estimate of the number of hours spent outside in the past week.

Figure 5.2 English version of the adult outdoor activities survey.



Adult Outdoor Activities Survey (English Version)

In the last week, how much time did you spend doing the following activities?

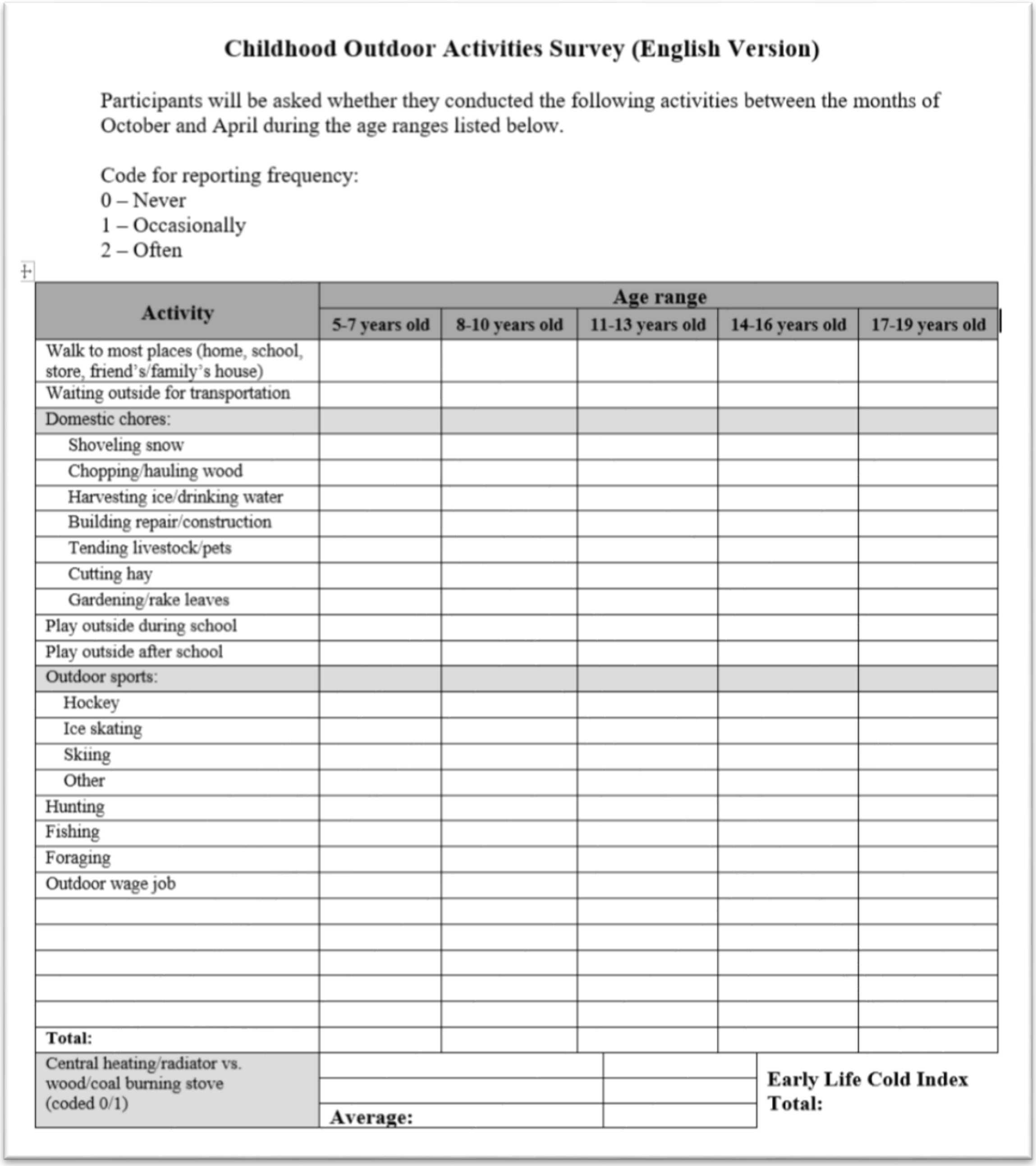
Activity	Number of Days	Average Number of Hours Each Time
Walking (home, work, school, store, friend's/family's house, etc.)		
Waiting outside for transportation		
Chopping/hauling wood		
Fetching water/ice		
Building repair/construction		
Tending animals		
Cutting hay		
Gardening/raking leaves		
Hunting		
Fishing		
Foraging/picking berries		
Outdoor wage job		
Swimming in a lake or river		
Other outdoor recreational activities		

Early Life Cold Exposure

Early-life cold exposure was quantified two ways. First, an early life cold exposure index (ELCI) survey was administered. The survey is based on a previous study assessing how children spend their time (Wiley, 1991; Silvers et al., 1994) and is modified to be suitable for the Siberian cultural context (see Figure 5.3). The survey involves reporting whether they participated in a list of winter outdoor activities and how often they were performed between ages 5-7, 8-10, 11-13, and 14-18 years old. The frequency of each activity is coded 0 through 4 according to how often the activity was performed (0: less than once a month; 1: 1-3 days/month; 2: 1-3 days/week; 3: 4-5 days/week, 4: 6-7 days/week) and added together. The participants will also report whether the home(s) in which they lived were heated by a radiator (coded as 0) or a wood burning stove (*pechka*) (coded as 1) and the average value will be calculated. The early-life cold index is the sum of the coded values.

The second approach to quantifying early life cold exposure involved downloading historical weather data collected at the Yakutsk meteorological station between 1950 to 2015. These data were downloaded from the NOAA Climate Data Online (CDO) (NOAA National Centers for Environmental Information). The mean temperature of the first, second, third, etc. year of life was calculated for each participant ending with the seventeenth year.

Figure 5.3 English version of the childhood outdoor activities survey.



Childhood Outdoor Activities Survey (English Version)

Participants will be asked whether they conducted the following activities between the months of October and April during the age ranges listed below.

Code for reporting frequency:
0 – Never
1 – Occasionally
2 – Often

Activity	**Age range**				
	5-7 years old	**8-10 years old**	**11-13 years old**	**14-16 years old**	**17-19 years old**
Walk to most places (home, school, store, friend's/family's house)					
Waiting outside for transportation					
Domestic chores:					
Shoveling snow					
Chopping/hauling wood					
Harvesting ice/drinking water					
Building repair/construction					
Tending livestock/pets					
Cutting hay					
Gardening/rake leaves					
Play outside during school					
Play outside after school					
Outdoor sports:					
Hockey					
Ice skating					
Skiing					
Other					
Hunting					
Fishing					
Foraging					
Outdoor wage job					
Total:					

Central heating/radiator vs. wood/coal burning stove (coded 0/1)			**Early Life Cold Index Total:**
	Average:		

Analysis of Blood Biomarkers

Serum Thyroid Hormones

Whole blood samples were obtained by a trained nurse using venipuncture. Glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were measured from whole blood samples using a CardioChek PA analyzer and Glucose and Lipid Panel test strips (Polymer Technology Systems, Indianapolis, IN). Low density lipoprotein (LDL) levels were calculated from total cholesterol, HDL, and triglycerides using the Friedwald et al. (1972) equation. The CardioChek PA professional lipid and glucose testing system meets clinical guidelines for accuracy and precision.

Blood samples were then immediately centrifuged so that the plasma fraction can be separated and stored at -20°C until laboratory analysis. Free triiodothyronine (fT_3), free thyroxine (fT_4), and thyroid stimulating hormone (TSH) levels (pmol/l) were determined using enzyme-linked immunosorbent assay (ELISA) kits. All laboratory analyses were conducted at the Institute of Medicine at NEFU in Yakutsk.

Statistical Analyses

All variables were examined for outliers, which were removed as appropriate. Additionally, all regressions were checked for heteroscedasticity and run with robust standard errors as needed. Statistical tests were run using StataIC 13.0 (Statacorp LLC) and considered statistically significant at p-value ≤ 0.05.

Chapter 4: Seasonal Change in Thyroid Hormones

Paired Student’s t-tests were used to examine seasonal changes in thyroid hormone measures, body mass, and body composition. Unpaired Student’s t-tests were used to compare selected socioeconomic variables between Yakut men and women. Pair-wise correlations were used to examine relationships between seasonal change in thyroid hormones, body composition, and lifestyle measures.

Chapter 5: Brown Adipose Tissue, Energy Expenditure and Biomarkers of Cardio-Metabolic Health

As mentioned above, change in SCV temperature was calculated as a biomarker of BAT thermogenesis. Percent change in energy expenditure (%ΔEE) was calculated by subtracting the energy expenditure of the thermoneutral (EE_{TN}) condition from the energy expenditure of the cold condition (EE_C) and dividing by the energy expenditure of the thermoneutral condition $\left[\% \Delta EE = \left(\frac{EE_C - EE_{TN}}{EE_{TN}}\right) * 100\right]$. A combination of unpaired Student's t-tests and two-sample Wilcoxon rank-sum tests were used to compare the age, anthropometric dimensions, BAT thermogenesis, and vasoconstriction of the core, %ΔEE, and change in respiratory quotient (RQ) of men and women.

Multiple regression analyses were used to examine the relationship between BAT thermogenesis, age, anthropometric dimensions and trial start time, and vasoconstriction of the core in order to identify potential confounding variables. Six variables were identified as potential confounders. Due to the large number of potential confounding variables and the small sample size, multiple regression analyses examining the relationship between BAT thermogenesis and %ΔEE and change in RQ utilized a propensity score to account for the relationship between confounding variables and change in SCV. Covariate adjustments using a propensity score is particularly useful when running a multiple regression with many confounding variables because it reduces the likelihood of having an over-inflated adjusted R^2 value due to the large number of variables in the model (Austin, 2011). First, the confounding variables were regressed on change in SCV. Then the propensity score was calculated using the “predict varname, xb” code in Stata 13.0. Subsequent regressions included the propensity score rather than the list of confounding variables.

Next, Student’s t-tests and Wilcoxon rank-sum tests were used to compare biomarkers of cardio-metabolic health between Yakut men and women. Additionally, multiple regression analyses that incorporated a propensity score were used to examine the relationship between BAT thermogenesis and blood biomarkers of health.

Chapter 6: Developmental Plasticity and Brown Adipose Tissue

This chapter analyzed data for a subsample of 58 adults. Student’s t-tests and Wilcoxon rank-sum tests were used to compare the age, anthropometric dimensions, and BAT thermogenesis of the subsample and the group of participants that were excluded. Wilcoxon rank-sum tests were also used to compare the ELCI scores of men and women. Multiple regression analyses were used to examine the relationship between BAT thermogenesis and ELCI score and the annual temperature during development after controlling for age, sex, body composition, trial start time and vasoconstriction of the core.

CHAPTER 6

BROWN ADIPOSE TISSUE, ENERGY EXPENDITURE AND BIOMARKERS OF CARDIO-METABOLIC HEALTH

Introduction

Dating back to D.F. Roberts' seminal research of the 1950s, biological anthropologists have noted that humans utilize metabolic adaptations to increase thermogenesis in response to cold stress. These metabolic adaptations include elevations in resting metabolic rate (RMR) under thermoneutral conditions, shivering, and non-shivering thermogenesis (NST) during acute cold stress. For instance, a growing body of research documents that high-latitude populations exhibit RMR values that are higher than predicted based on body mass and composition (Froehle, 2008; Galloway et al., 2000; Itoh, 1980; Leonard et al. 1999, 2002; Roberts, 1952, 1978; Rode and Shephard, 1995; Snodgrass et al., 2005). The mechanisms that control adaptive elevations in RMR are likely controlled by shifts in thyroid hormone dynamics, which can trigger an increase in metabolism in skeletal muscle and other tissues via changes in calcium cycling, protein turnover, and mitochondrial uncoupling (Reed 1986, 1990a, b; Leonard et al., 2014; Levy et al., 2013). Shivering is the first line of defense during acute cold exposure; however, the energetic costs of shivering are high and adults that are acclimatized to chronic cold stress exhibit a lower shivering threshold and greater increases in metabolism via NST.

Variation in NST among indigenous circumpolar populations, surprisingly, has yet to be described. Furthermore, the physiological mechanisms underlying NST, however, are widely debated. Initially, the internal organs were considered to be the main source of NST, particularly the liver, due to increases in vascularization of the internal organs during cooling (Jansky, 1973; Kosaka 1930). Skeletal muscle may also contribute to NST by increasing mitochondrial uncoupling through the expression of uncoupling protein 3 (UCP3) (van der Berg et al., 2011; Wijers et al., 2008).

More recently, in response to the discovery that BAT is present and active in adult humans, brown adipose tissue (BAT) has been hypothesized to play a role in NST (Enerback 2010). Fast activation of brown adipocytes by the sympathetic nervous system causes these cells to produce uncoupling protein 1 (UCP1), which facilitates mitochondrial uncoupling through a process called BAT thermogenesis (Lowell and Spiegelman, 2000). BAT is highly vascularized in order to facilitate the transport of oxygen to the BAT cells and heat away from BAT deposits. Individuals with active BAT depots exhibit significantly greater increases in energy expenditure during NST than adults without BAT, suggesting that this tissue plays a mechanistic role in NST (Blondin et al., 2015; van der Lans et al., 2015; van Marken Lichtenbelt et al., 2015; Yoneshiro et al., 2011a). If BAT plays a role in metabolic adaptation to cold stress via NST, then it is likely to be present and active among indigenous circumpolar populations, such as the Yakut of northeastern Siberia. The present study is the first investigation of functional and health significance of BAT in an indigenous circumpolar group.

In adult humans, BAT is primarily found above the clavicle and occasionally around heart, esophagus, kidneys, pancreas, liver, spleen, and scattered within white fat deposits of the greater omentum and mesocolon (Sacks and Symonds, 2013). While some adults completely lack BAT, others exhibit over 100 g of this tissue. It is currently unknown whether the various BAT deposits vary in their degree of lipid and carbohydrate metabolism during cold-induced thermogenesis. Adult BAT mass appears to fluctuate with the seasons. Rates of BAT detection using PET-CT scans under thermoneutral conditions are higher in the winter than the summer (Yeung et al., 2009). This is likely because plasticity in BAT mass is sensitive to the process of acclimatization to cold stress. Van der Lans et al. (2013) exposed subjects to a 10-day cooling regimen and found a significant increase in BAT mass in parallel to increases in non-shivering thermogenesis. Thus, it is possible that BAT plays a role in seasonal acclimatization to cold stress.

Currently, population variation in BAT is poorly characterized and this study represents the first investigation of BAT thermogenesis in an indigenous circumpolar population. Prior to this study, data had been collected in Canada, China, Japan, the Netherlands, Scotland, and the United States (see Table 3.1). Admiraal et al. (2013) and Bakker et al. (2013) compared the BAT mass of men born in the Netherlands of South Asian and European decent. Bakker et al. (2013) documents significantly greater BAT mass in men of European decent than the South Asian sample; however, Admiraal et al. (2013) did not detect significant differences.

The primary molecular substrates for brown adipocyte function include lipids, such as triglycerides and chylomicrons, and glucose (Cannon and Nedergaard, 2004). Bartlet et al. (2011) found that in mice, activation of BAT by cold exposure led to a significant decrease in serum lipids. Thus, the removal of free fatty acids and glucose from the blood stream through BAT’s role in NST may have important implications for levels of biomarkers of metabolic health across populations. Furthermore, exposure to low temperatures was found to increase fat oxidation by 63% and carbohydrate oxidation by 588% (Vallerand and Jacobs, 1989). Thus, NST may lead to preferential utilization of carbohydrates as a fuel for metabolism.

Historically, indigenous circumpolar populations have exhibited a low prevalence of cardiovascular disease mortality and diabetes, as well as low levels of serum lipids and glucose (Bang and Dyerberg, 1980; Chateu-Degat, 2011; Kozlov et al., 2007; Rode et al., 1995; Young et al., 1993, 1995). However, a number of studies of cardiovascular disease risk factors among circumpolar groups in North America and Greenland have documented a strong association between processes of acculturation and modernization and the population burden of plasma lipids (de Kniff et al., 1992; Kozlov et al., 2007; Young et al., 1995). Among the Yakut, however, higher cholesterol levels have been documented in individuals with less access to market foods such as vegetables and chicken (Sorensen et al., 2005). Fasting glucose levels are relatively low in this population with very few cases of diabetes. However, average levels of fasting glucose, as well as obesity prevalence, appear to be increasing (Snodgrass et al., 2009).

In circumpolar regions, the relationship between health lifestyle is not only structured by differences in diet and physical activity, but also exposure to cold stress (Mäkinen et al., 2006). Like diet and exercise, variation in exposure to cold stress has important implications for physiology and cardio-metabolic disease risk. For example, in response to cold stress, an increased metabolic rate and cellular turnover may place a higher physiological demand for several cellular substrates, including cholesterol and glucose. Thus, underlying biological variation shaped by adaptive factors may interact with ongoing changes in lifestyle and nutrition to produce differences in cardio-metabolic disease risk.

Recent research reports that change in supraclavicular skin temperature (ΔSCV) can be applied as an indirect biomarker of BAT thermogenesis (Chondronikola et al., 2016; Salem et al., 2015; van der Lans et al., 2015; Yoneshiro et al., 2016). ΔSCV is typically measured using infrared thermal imaging. It reflects the change in heat produced by BAT within the supraclavicular area after the body is exposed to low temperatures, such as from a cooling suit. Past research comparing ΔSCV from infrared thermal imaging to BAT metabolism quantified by ^{18}FDG PET-CT scans (the gold standard method for quantifying BAT) documents that adults with greater BAT metabolism experience a smaller decline in supraclavicular skin temperature after cooling (Chondronikola et al., 2016; Salem et al., 2015; van der Lans et al., 2015; Yoneshiro et al., 2016). Many subjects with active BAT mass experience a decline in ΔSCV due to conduction between the skin and the cooling suit and vasoconstriction of the core; however, the greater the BAT metabolism, the smaller the decline in ΔSCV. In contrast, change in skin temperature of the sternum (Δ sternum) after cooling declines several degrees because BAT is absent from this region (Boon et al., 2014; Chondronikola et al., 2016; Yoneshiro et al., 2016). The decline in Δ sternum is due to conduction from the cooling suit and vasoconstriction of the core is larger than ΔSCV because of a lack of BAT in this location. There is no relationship between Δ sternum and BAT mass (Boon et al., 2014; Chondronikola et al., 2016; Yoneshiro et al., 2016); therefore, this measure can be used a control for vasoconstriction of the core and conduction between the cooling suit and the skin.

Adults with greater BAT thermogenesis and a smaller decline in ΔSCV after cooling also exhibit a larger increase in energy expenditure via NST (Blondin et al., 2015; van der Lans et al., 2015; van Marken Lichtenbelt et al., 2015). As mentioned above, NST is highly variable across adults. Some individuals produce a large increase in energy expenditure during NST while others experience a decline (Blondin et al., 2017; Celi et al., 2010; van Marken Lichtenbelt et al., 2002, 2015; Yoneshiro et al., 2013). Whole-body energy expenditure declines during mild cooling when vasoconstriction of the periphery leads to cooling of the appendages, a reduction in the rate of reactions within the peripheral tissues (i.e. the Q10 effect), and a resultant decline in the rate of oxygen consumption in the area (Barany, 1967; Bennet, 1985; Wakabayashi et al., 2017). If the decline in the metabolic rate of the periphery is larger than the increase in metabolism at the core, then the resulting whole-body energy expenditure will decline during cooling (Wakabayashi et al. 2017). Adults with greater BAT thermogenesis are less likely to experience an overall decline in energy expenditure (Blondin et al., 2015; van der Lans et al., 2015; van Marken Lichtenbelt et al., 2015).

This chapter explores the functional and health significance of BAT thermogenesis in the Yakut, an indigenous circumpolar population, by testing whether individuals with greater BAT also exhibit greater whole-body energy expenditure and healthier biomarkers of cardiometabolic disease risk. This chapter investigates three hypotheses. First, BAT thermogenesis is hypothesized to be inversely associated with body fatness. Many researchers have proposed that adults with greater energy expenditure due to larger BAT deposits and greater BAT thermogenesis may be protected against obesity and exhibit less white fat mass (Iyengar and Scherer, 2016; Loh et al., 2017; van Marken Lichtenbelt et al., 2014). Alternatively, BAT thermogenesis may be positively associated body fatness because larger fat stores may signal that there is greater energy available for thermogenesis.

Second, I hypothesize that Yakut adults with greater BAT thermogenesis will expend more energy during a cooling condition. Overall, ΔSCV is likely to be relatively constant or decline slightly due to vasoconstriction and conduction between the cooling suit and the skin. A small decline in ΔSCV on average would be consistent with past studies (Chondronikola et al.

2016; Salem et al., 2015; van der Lans et al. 2015; Yoneshiro et al., 2016). Δ Sternum, however, is predicted to decline significantly due to the absence of BAT in this area. Additionally, similar to past studies, percent change in energy expenditure (%ΔEE) is predicted to be highly variable across individuals with some participants experiencing an increase in %ΔEE and others experiencing a decline due to the Q10 effect. Yakut participants with a smaller decline in ΔSCV are predicted to exhibit a larger increase in %ΔEE after controlling for vasoconstriction and conduction using the Δ sternum measure. This would suggest that BAT thermogenesis plays a role in NST among indigenous Siberian adults.

Finally, adults with greater BAT activity are hypothesized to exhibit lower blood lipid and glucose levels. This would suggest that BAT metabolism may facilitate greater clearance of circulating lipids and glucose. Alternatively, BAT thermogenesis may be positively associated with blood lipid and glucose levels if circulating lipids and glucose signal there is more energy available for BAT metabolism. Examining possible changes in respiratory quotient (RQ) during cooling may shed light on this hypothesis. RQ can act as a proxy for whether the body is primarily metabolizing carbohydrates or fats.

Results

Descriptive Statistics

Anthropometric dimensions, change in maximum supraclavicular temperature (SCV), RMR and RQ were collected for 43 women and 31 men. Table 6.1 displays the mean age, anthropometric dimensions and change in maximum supraclavicular temperature (SCV) for the sample of Yakut men and women. The study sample was relatively young; the mean age was 29 years for men and 27 years for women. As expected, Yakut men were significantly taller, heavier and had greater fat-free mass than Yakut women. While the body mass index (BMI) did not differ between men and women, Yakut women had significantly greater percent body fat as calculated using the sum of four skinfolds (triceps, biceps, subscapular, and suprailiac skinfolds) using the equations of Durnin and Womersley (1974) and using a bioelectric impedance analysis (BIA) scale. Estimates of percent body fat from the BIA scale were significantly lower than the estimates based on sum of skinfolds for both sexes. Since indigenous Siberian groups typically carry their weight on the core and have a high muscle mass, subsequent analyses used percent body fat estimates based on the sum of skinfolds (Leonard et al., 1996).

Table 6.1 T-tests of sex differences in age, anthropometric dimensions and change in maximum supraclavicular temperature.

Measure	Men (n=31) Mean ± SD	Women (n=43) Mean ± SD	p-value
Age (years)[a]	28.8 ± 8.0	27.4 ± 8.7	0.185
Height (cm)	171.7 ± 5.4	158.5 ± 5.3	0.000
Weight (kg)	66.2 ± 11.1	54.4 ± 8.9	0.000
BMI[a]	22.4 ± 3.6	21.6 ± 3.5	0.300
Percent body fat	21.4 ± 5.5	33.2 ± 4.6	0.000
Fat free mass (kg)[a]	55.8 ± 5.8	41.0 ± 5.4	0.000
Change in SCV (°C)	0.03 ± 0.3	0.05 ± 0.3	0.764

[a] The variable is not normally distributed; therefore, p-value is derived from a two-sample Wilcoxon rank-sum (Mann-Whitney) test.

Percent change in energy expenditure (% ΔEE) was calculated by subtracting the energy expenditure of the thermoneutral condition (EE_{TN}) from the energy expenditure of the cold condition (EE_C) and dividing by the energy expenditure of the thermoneutral condition $\left[\% \Delta EE = \left(\frac{EE_C - EE_{TN}}{EE_{TN}}\right) * 100\right]$. Additionally, change in RQ, change in the maximum supraclavicular skin temperature (SCV), and change in skin temperature of a point on the sternum were calculated by subtracting the thermoneutral value from the cold condition value.

Figure 6.1 includes histograms of the SCV and sternum temperatures from the thermoneutral and cold conditions and the change in SCV and sternum temperatures across conditions. Additionally, Tables 6.2 and 6.3 show the mean SCV temperature, sternum temperature, RMR, and RQ across the thermoneutral and cold conditions for men and women, respectively. These results demonstrate that, on average, SCV did not change significantly while the temperature of a point on the sternum decreased. The decrease in sternum temperature likely reflects vasoconstriction of the skin in this area and conduction between the cooling suit and the skin. The lack of change in SCV on average is likely a result of the warming effects of BAT thermogenesis in this region counteracting the decline in temperature from conduction between the skin and the suit and vasoconstriction in the area. As demonstrated in Table 6.2 and 6.3, men experienced a small but significant decline in RMR after cooling while women did not experience a significant change on average. The decline RMR among men is likely linked to a concomitant decline in temperature and metabolic rate of the appendages due to the Q10 effect. The RQ of women increased significantly during cooling while men did not exhibit a significant change in RQ. An increase in RQ is a proxy for increased carbohydrate metabolism during cooling.

Figure 6.2 displays the % ΔEE after cooling for Yakut men and women. The % ΔEE was not significantly different between the sexes. Similarly, Figure 6.3 displays the change in RQ after cooling and the amount of change was not significantly different between men and women. The ΔSCV temperature and change in sternum temperature were not significantly different between men and women either (see Figure 6.3).

Figure 6.1 Histograms of the maximum supraclavicular skin temperature (A) and sternum skin temperature (B) of the thermoneutral condition, the maximum supraclavicular skin temperature (C) and the sternum skin temperature of the cold condition (D) and the change in supraclavicular (E) and sternum temperature (F) (n = 74).

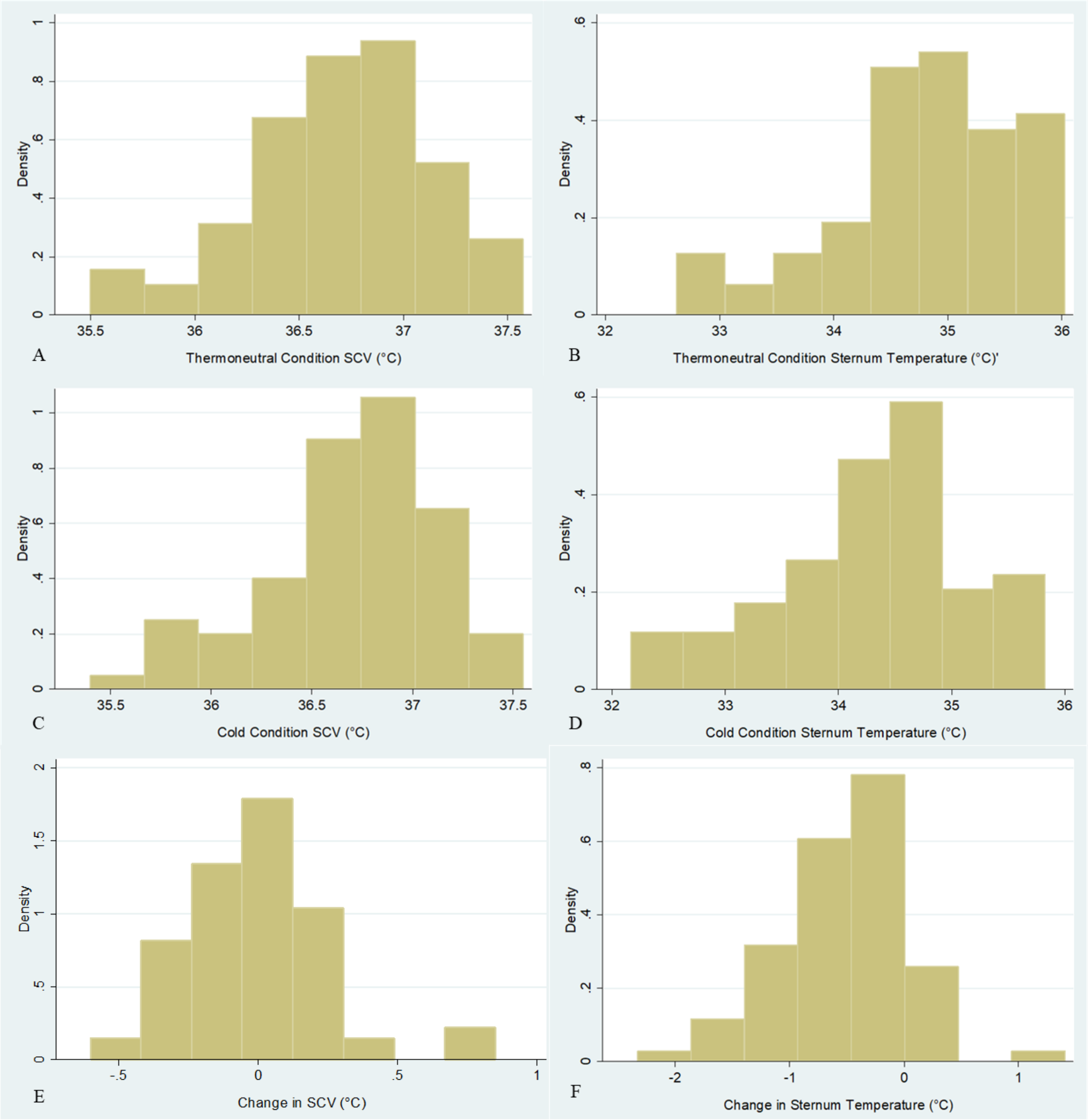


Table 6.2 Mean resting metabolic rate, respiratory quotient, supraclavicular temperature, and sternum temperature for the thermoneutral and cold conditions for men (n=31).

Measure	Thermoneutral Mean ± SD	Cold Mean ± SD	p-value
SCV (°C)	36.793 ± 0.068	36.782 ± 0.061	0.400
Sternum (°C)	34.773 ± 0.136	34.315 ± 0.126	0.000***
RMR (kcal/day)	1575 ± 48	1528 ± 49	0.038*
RQ	0.846 ± 0.015	0.86 ± 0.019	0.230

Paired t-tests of within-subject change significant at: *p≤0.05; **p≤0.01; ***p≤0.001

Table 6.3 Mean resting metabolic rate, respiratory quotient, supraclavicular temperature, and sternum temperature for the thermoneutral and cold conditions for women (n=43).

Measure	Thermoneutral Mean ± SD	Cold Mean ± SD	p-value
SCV (°C)	36.629 ± 0.066	36.622 ± 0.074	0.434
Sternum (°C)	34.812 ± 0.129	34.239 ± 0.138	0.000***
RMR (kcal/day)	1129 ± 31	1094 ± 43	0.144
RQ	0.8 ± 0.010	0.84 ± 0.015	0.000***

Paired t-tests of within-subject change significant at: *p≤0.05; **p≤0.01; ***p≤0.001

Figure 6.2 Percent change in energy expenditure after cooling for men and women. The error bars denote standard error values.

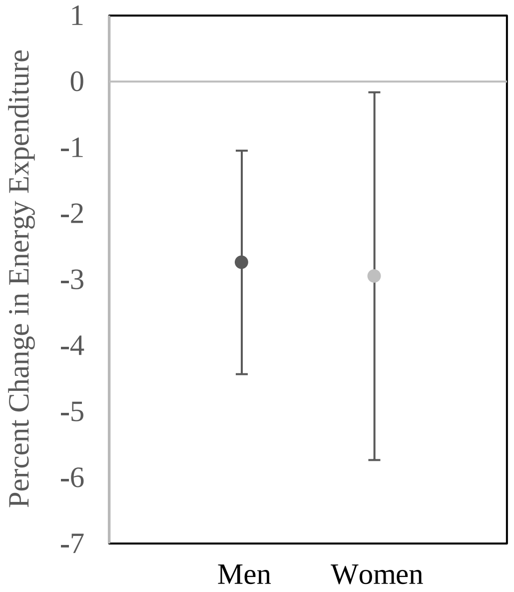


Figure 6.3 Change in RQ between the thermoneutral and cooling condition for men and women. The error bars denote standard error values.

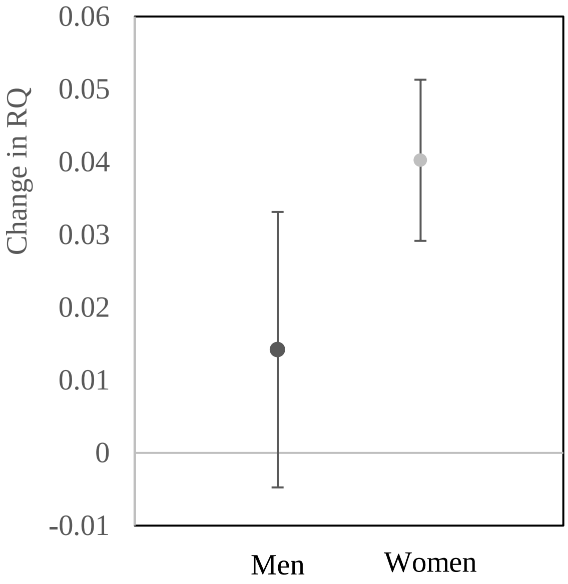
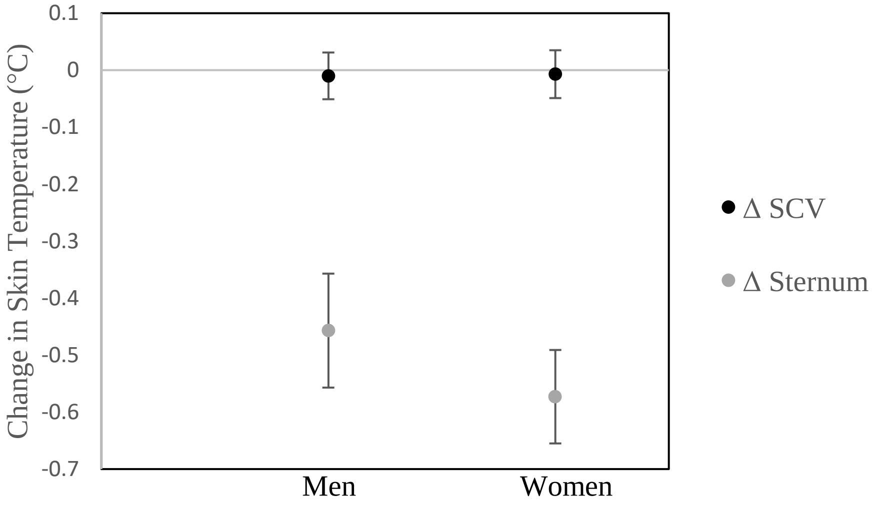


Figure 6.4 Change in supraclavicular and sternum skin temperature after cooling for Yakut men and women. The error bars denote standard error values.



Hypothesis 1: BAT Thermogenesis and Body Composition

Table 5.4 displays multiple regression analyses assessing body composition and other variables as predictors of BAT thermogenesis (ΔSCV). In model 1, ΔSCV is regressed on age and body composition measures. Model 2 adjusts for the time at which the trial began in order to account for the diurnal rhythm of skin temperature and whole-body energy expenditure. Model 3 additionally tests for a relationship between ΔSCV and shifts in vasoconstriction of the trunk by including change in temperature of a point on the sternum. There is a trend in model 1 and 2 indicating that with increasing age, BAT thermogenesis decreases. Percent body fat, on the other hand, is positively correlated with ΔSCV in model 1. The positive association between percent body fat and ΔSCV suggests that participants with greater fat stores may have more energy available for thermogenesis. Change in skin temperature of a point on the sternum tends to be positively related to ΔSCV temperature. This is expected given that the degree of vasoconstriction and the effects of conduction between the cooling suit and the skin should be similar for both points on the body.

Table 6.4 Multiple regression analyses of possible correlates of change in supraclavicular skin temperature after 30 minutes of a cooling condition.

	Model 1		**Model 2**		**Model 3**	
	Adj. R2 = 0.013		**Adj. R2 = 0.048**		**Adj. R2 = 0.075**	
Measure	***β Coef.***	***p-value***	***β Coef.***	***p-value***	***β Coef.***	***p-value***
Age (years)	-0.008	0.09^{+}	-0.009	0.084^{+}	-0.008	0.141
Sex	-0.164	0.291	-0.159	0.291	-0.136	0.343
FFM (kg)	-0.000	0.991	0.001	0.929	0.001	0.881
% Body fat	0.016	0.047*	0.016	0.11	0.016	0.127
Start time	---	---	-0.659	0.104	-0.658	0.104
ΔSternum (°C)	---	---	---	---	0.092	0.06^{+}

Multiple regression analyses: relationship with ΔSCV is significant at: *p≤.05; **p≤0.01; ***p≤0.001
Relationship with ΔSCV indicates a trend at: $^{+}p<0.1$

Hypothesis 2: BAT Thermogenesis and Energy Expenditure

Next, the relationship between ΔSCV temperature and % ΔEE was examined. Figure 6.5 provides a scatter plot of the positive relationship between ΔSCV after 30 minutes of cooling and % ΔEE. This suggests that, as expected, individuals with a greater increase in BAT thermogenesis also exhibit a greater increase in energy expenditure after cooling. In contrast, Figure 6.6 shows a scatter plot of percent change in energy expenditure vs. change in sternum skin temperature. Based on this graph, there appears to be a weak negative relationship between Δ sternum temperature and % ΔEE. It is possible that participants that expend greater energy during NST exhibit more pronounced vasoconstriction of the core, which would lead to an inverse association between temperature change of the sternum and energy expenditure during cooling. Furthermore, it is possible that vasoconstriction of the core has a masking effect on the relationship between ΔSCV and % ΔEE.

Figure 6.5 Percent change in energy expenditure vs. change in supraclavicular temperature after 30 minutes of cooling. Under cold exposure, increases in skin temperature at the site of BAT are associated with significantly greater increases in energy expenditure relative to baseline thermoneutral conditions.

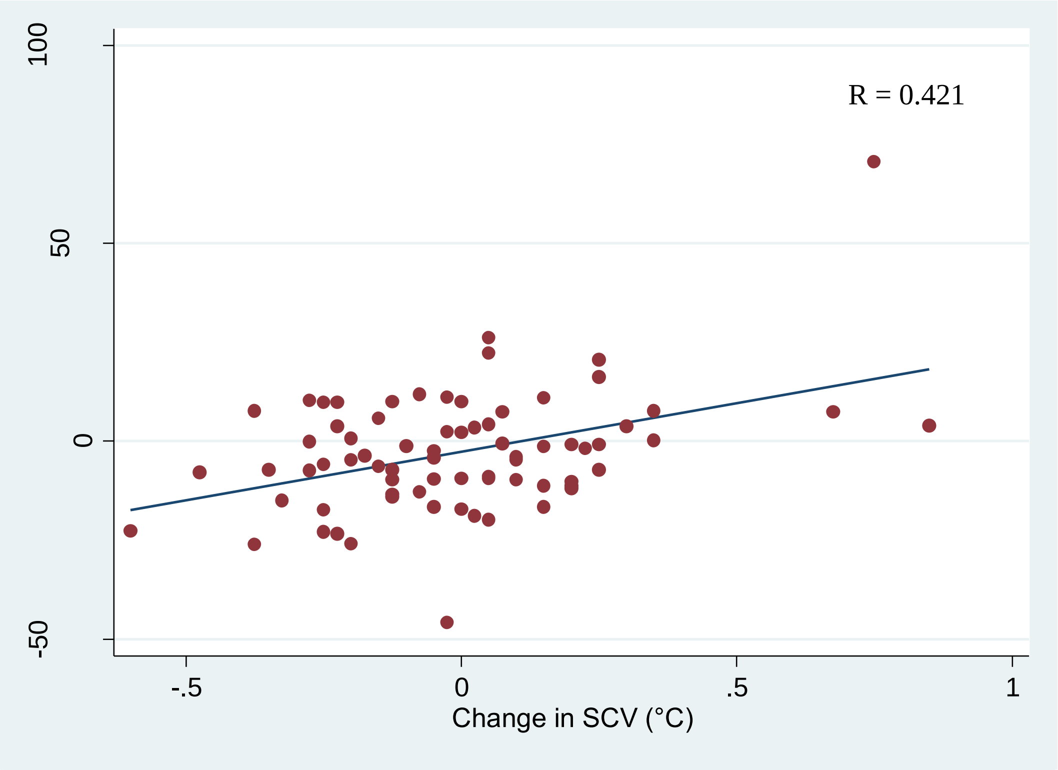
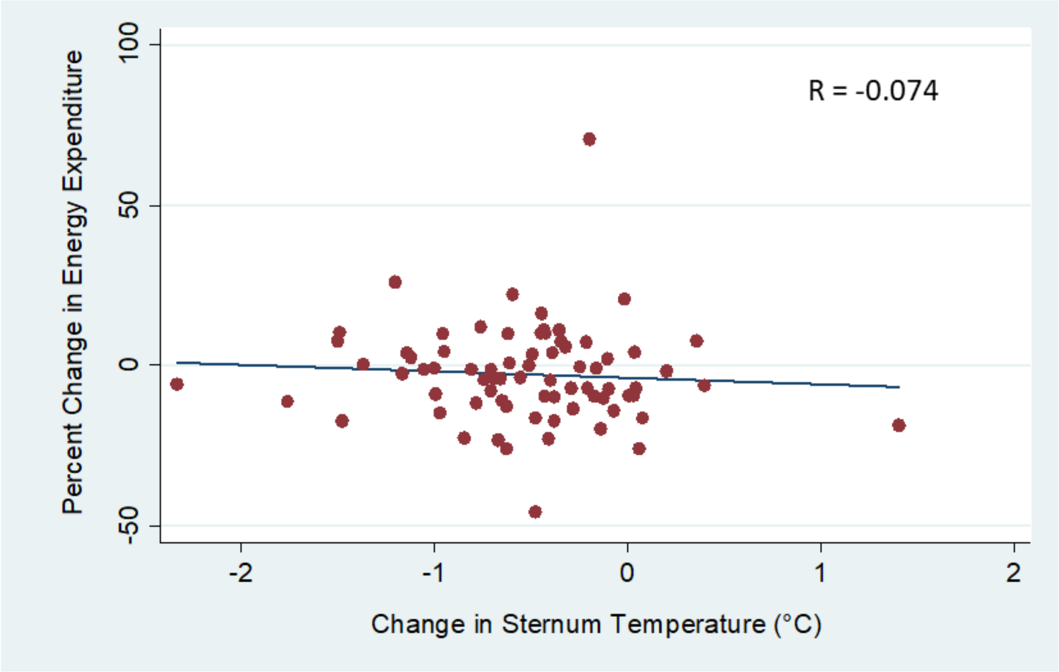


Figure 6.6 Percent change in energy expenditure vs. change in sternum temperature after 30 minutes of cooling.



The variables included in Model 3 of Table 6.4 (age, sex, time of data collection and change in sternum temperature) were all potential confounding variables and may obscure the relationship between SCV and % ΔEE. Table 6.5, therefore, explores the relationship between ΔSCV and % ΔEE after controlling for these variables. Comparing Model 1, which displays the results of a multivariate regression of ΔSCV on % ΔEE controlling for age, sex, fat-free mass, percent body fat and trial start time, and Model 2, which adds Δ sternum to the list of confounding variables, reveals that the relationship between ΔSCV and % ΔEE is likely masked by the confounding effects of Δ sternum and including this variable may account for some of the variation in ΔSCV that is due to vasoconstriction or conduction between the cooling suit and the skin.

Due to the large number of potential confounding variables, Model 3 of Table 6.5 use a propensity score to account for the relationship between confounding variables and ΔSCV.

Covariate adjustments using a propensity score are particularly useful when running a multivariate regression with many confounding variables on a small sample size by reducing the number of variables in the regression while still accounting for the effects of confounding variables (Austin, 2011). The predicted values of a propensity score represent the variation in the independent variable (ΔSCV) that is due to variation in the confounders. In other words, the propensity score is the expected value of ΔSCV for each individual, based on their age, sex, etc. First, ΔSCV was regressed on the confounding variables. Propensity scores were calculated as the predicted ΔSCVs from this model. Model 3 in Table 6.5 reveals a significant positive association between ΔSCV and % ΔEE independent of the propensity score. Subsequent regressions included the propensity score rather than the list of confounding variables.

Table 6.5 Multivariate regression analysis of change in supraclavicular temperature on percent change in energy expenditure controlling for various confounding variables (n=74).

	Model 1		**Model 2**		**Model 3**	
	Adjusted R^2 = 0.11		**Adjusted R^2 = 0.13**		**Adjusted R^2 = 0.15**	
Measure	**β Coefficient**	**p-value**	**β Coefficient**	**p-value**	**β Coefficient**	**p-value**
ΔSCV (°C)	22.14	0.028	24.46	0.015	24.45	0.012
Age (years)	-0.23	0.238	-0.28	0.145	-	-
Sex (M-1; F-2)	-0.43	0.956	-1.33	0.867	-	-
Fat-free Mass (kg)	0.16	0.498	0.14	0.548	-	-
% Body Fat	0.27	0.454	0.28	0.417	-	-
Trial Start Time	-12.59	0.54	-11.16	0.587	-	-
ΔSternum (°C)	-	-	-5.1	0.043	-	-
Propensity Score[a]	-	-	-	-	0.293	0.983

[a] Propensity score controlling for age, sex, fat-free mass, percent body fat, trial start time, and change in sternum temperature.

Table 6.6 displays the relationship between ΔSCV and % ΔEE at 15, 20, 25, and 30 minutes of cooling after controlling for possible confounding variables. As the cooling condition progresses from 15 to 25 minutes, the relationship between ΔSCV and % ΔEE becomes more significant. Additionally, the proportion of variation in % ΔEE that is explained by the model (adjusted R^2) increases from 15 to 25 minutes of cooling. There is a small drop in the adjusted R^2 and an increase in the p-value from 25 to 30 minutes; however, the data suggest that participants with greater BAT thermogenesis exhibit greater energy expenditure during cooling.

Table 6.6 Relationships between percent change in energy expenditure and change in the supraclavicular skin temperature and possible confounding variables after 15, 20, 25, and 30 minutes of cooling.

	Model 1: 15 min.		**Model 2: 20 min.**		**Model 3: 25 min.**		**Model 4: 30 min.**	
	Adj. R^2 = 0.01		**Adj. R^2= 0.16**		**Adj. R^2 = 0.18**		**Adj. R^2 = 0.15**	
Measure	***β Coef.***	***p-value***	***β Coef.***	***p-value***	***β Coef.***	***p-value***	***β Coef.***	***p-value***
Δ SCV (°C)	10.34	0.422	28.61	0.013*	26.24	0.005**	24.455	0.012*
Propensity score[a]	6.75	0.615	-14.494	0.097	-7.824	0.422	0.293	0.983

Multiple regression analyses: relationship with percent change in energy expenditure were significant at: *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$

[a] Propensity score controlling for age, sex, fat-free mass, percent body fat, trial start time, and change in sternum temperature.

Figure 6.7 displays the relationship between ΔSCV and change in RQ. Additionally, Table 6.7 displays the results of multiple regression analyses between change in RQ and ΔSCV at 15, 20, 25 and 30 minutes of cooling after controlling for confounding variables. Interestingly, similar to the pattern with % ΔEE, the positive relationship between ΔSCV and change in RQ becomes significant after 20 minutes of the cooling condition and remains significant for the remainder of the trial. These data suggest that individuals with greater BAT thermogenesis may preferentially utilize carbohydrates as a metabolic substrate during non-shivering thermogenesis.

Hypothesis 3: BAT Thermogenesis and Blood Biomarkers of Cardio-metabolic Health

Fasting cholesterol, triglyceride and glucose levels were measured for a sub-sample of 62 participants (24 males; 38 females). Table 6.8 compares the age, anthropometric dimensions, ΔSCV and % ΔEE of the subjects for which blood biomarker data were collected against those that were excluded. The subsample with blood biomarker data is significantly older and has a higher percent body fat than the subjects that were excluded from the blood tests. The following analyses were conducted using Sample A.

Figure 6.7 Change in respiratory quotient vs. change in supraclavicular skin temperature after a 30-minute cooling condition.

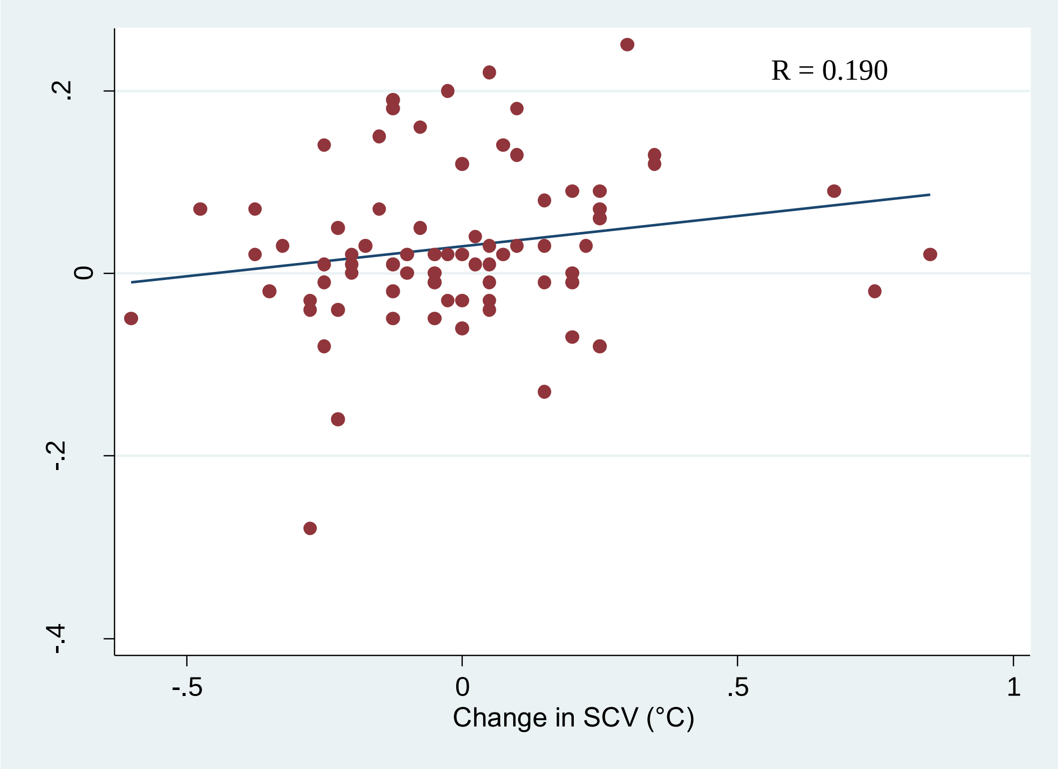


Table 6.7 Relationships between change in respiratory quotient and change in supraclavicular skin temperature and possible confounding variables after 15, 20, 25 and 30 minutes of cooling.

	Model 1: 15 min.		**Model 2: 20 min.**		**Model 3: 25 min.**		**Model 4: 30 min.**	
	Adj. R^2 = 0.01		**Adj. R^2= 0.04**		**Adj. R^2 = 0.05**		**Adj. R^2 = 0.03**	
Measure	***β Coef.***	***p-value***	***β Coef.***	***p-value***	***β Coef.***	***p-value***	***β Coef.***	***p-value***
Δ SCV (°C)	0.07	0.106	0.10	0.034*	0.099	0.022*	0.086	0.05*
[a]Propensity score	-0.066	0.511	-0.077	0.383	-0.066	0.433	-0.137	0.223

Multiple regression analyses: relationships with change in RQ were significant at: *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$

[a] Propensity score controlling for age, sex, fat-free mass, percent body fat, trial start time and change in sternum temperature.

Table 6.8 T-tests comparing descriptive measures of Sample A and Sample B.

Measure	Sample A: Blood Biomarker Particicipants n = 62 Mean ± SD	Sample B: Non-Participants n = 12 Mean ± SD	p-value
Sex Ratio (M/F)	(24/38)	(7/5)	0.213
Age[a] (years)	27.0 ± 8.4	23.1 ± 8.0	0.034*
Fat-free mass[a] (kg)	47.0 ± 9.6	48.3 ± 7.6	0.598
BMI[a]	22.2 ± 3.5	20.8 ± 3.7	0.14
Weight (kg)	59.6 ± 11.7	58.1 ± 10.6	0.669
Height (cm	163.5 ± 8.4	167.0 ± 8.6	0.188
Percent Body fat (%)	29.1 ± 7.2	23.7 ± 8.7	0.026*
Change in SCV (°C)	-0.02 + 0.24	0.04 ± 0.31	0.44
Change in sternum (°C)	-0.5 + 0.6	-0.4 + 0.3	0.38
Percent Change in EE	-4.3 + 12.3	4.8 ± 24.5	0.056
Change in RQ	0.03 ± 0.09	0.02 ± 0.08	0.799

[a] The variable is not normally distributed; therefore, a two-sample Wilcoxon rank-sum (Mann-Whitney) test was run.

Table 6.9 presents the mean lipid and glucose levels for Yakut men and women in Sample A. Yakut women have significantly higher total cholesterol and high-density lipoprotein (HDL) cholesterol levels. On average, the blood glucose and lipid levels were within the ranges recommended by the American Heart Association (AHA) (Lichtenstein et al., 2009).

Table 6.9 T-tests of sex differences of biomarkers of cardio-metabolic health.

Measure	Males n=24 Mean ± SD	Females n=38 Mean ± SD	p-value
Total Cholesterol[a] (mg/dL)	132.1 ± 30.7	151.4 ± 32.6	0.014
HDL Cholesterol (mg/dL)	51.3 ± 10.8	73.3 ± 14.6	0.000
LDL Cholesterol (mg/dL)	63.9 ± 26.3	64.0 ± 26.4	0.986
Triglycerides[a] (mg/dL)	84.3 ± 23.6	76.9 ± 16.8	0.326
Glucose (mg/dL)	86.7 ± 8.4	88.2 ± 12.2	0.230

[a] The variable is not normally distributed; therefore, Two-sample Wilcoxon rank-sum (Mann-Whitney) test was run.

Multiple regression analyses of blood biomarkers of cardio-metabolic health on ΔSCV are presented in Table 6.10. After controlling for age, sex, fat-free mass, percent body fat, trial start time and change in sternum temperature using a propensity score, relationships between ΔSCV and blood lipid levels were not significant. ΔSCV, however, was positively associated with fasted blood glucose levels. Change in RQ and percent change in energy expenditure were not significant predictors of blood glucose levels (data not shown).

Table 6.10 Multiple regression analyses of biomarkers of cardio-metabolic disease risk on change in supraclavicular skin temperature.

Dependent Variable: Total Cholesterol (mg/dL)		
	β Coef.	**p-value**
Δ SCV	14.08	0.44
Propensity Score[a]	-110	0.031
Adjusted R^2 = 0.045		
Dependent Variable: HDL Cholesterol (mg/dL)		
	β Coef.	**p-value**
Δ SCV	3.01	0.748
Propensity Score[a]	-56.55	0.032
Adjusted R^2 = 0.048		
Dependent Variable: LDL Cholesterol (mg/dL)		
	β Coef.	**p-value**
Δ SCV	11.03	0.416
Propensity Score[a]	-50.5	0.223
Adjusted R^2 = -0.006		
Dependent Variable: Triglycerides (mg/dL)		
	β Coef.	**p-value**
Δ SCV	9.96	0.379
Propensity Score[a]	9.18	0.768
Adjusted R^2 = -0.013		
Dependent Variable: Glucose (mg/dL)		
	β Coef.	**p-value**
Δ SCV	14.97	0.009
Propensity Score[a]	25.15	0.103
Adjusted R^2 = 0.181		

[a] Propensity score controlling for age, sex, fat-free mass, percent body fat, trial start time and change in sternum temperature.

Discussion

This chapter investigates the relationships between BAT thermogenesis, whole-body energy expenditure and biomarkers of cardio-metabolic health, such as body composition and blood lipid and glucose levels. Since the discovery that humans retain active BAT stores into adulthood, there has been renewed interest in the metabolic costs of this tissue and its significance to overall cardio-metabolic health. Indigenous circumpolar populations appear to adapt to cold climates via elevations in metabolic rate; however, the adaptive significance of NST and BAT activity in native high-latitude populations was previously unexplored. Understanding the determinants of population variation in energy expenditure will shed light on the biological and social pathways that underlie cardio-metabolic disease risk.

The descriptive statistics for this sample summarized in Table 6.1 reveal that, on average, the participants were relatively short and lean. As shown in Figure 6.1 and Table 6.2, the present study detected no significant change in SCV temperature (men: -0.01°C±0.041°C; women: -0.007°C±0.042°C) after cooling and a small but significant decrease in sternum temperature (men: -0.457°C±0.1°C; women: -0.573°C±0.082°C). Comparing changes in SCV temperature and sternum temperature across studies is fraught with limitations because investigations of cold induced thermogenesis employ a wide variety of cooling protocols. Each protocol will vary in the type of metabolic and vasoconstriction response depending on the intensity and time duration of cold exposure. Nevertheless, Table 6.11 summarizes several studies that document change in skin temperature of the supraclavicular area and change in temperature of a point on the chest after cooling. Interestingly, the decline in ΔSCV and Δ sternum is smallest in the Yakut sample. Small, non-significant decreases in ΔSCV may be indicative of greater BAT thermogenesis while smaller declines in sternum temperature may suggest differences in vasoconstriction or muscular thermogenesis. Alternatively, the smaller change in SCV and sternum skin temperature may be due to the fact that the cooling condition is shorter than many of the other studies. Data collected in Evanston, IL using the same cooling protocol indicates that the Evanston sample experienced a slightly larger decrease in ΔSCV. Additionally, the average decrease in sternum temperature was similar to past studies that utilized longer cooling protocols, suggesting that just 30 minutes of cooling was sufficient for stimulating a ~2°C decrease in sternum temperature like the other cooling protocols. These data suggest that there may be population differences in BAT thermogenesis, NST, and vasoconstriction.

Table 6.2 also displays that, on average, Yakut men experienced a small but significant decline in RMR, while Yakut women did not experience a significant change. Table 6.12 compares the average percent change in energy expenditure for this study to past work. Percent change in energy expenditure for the Yakut sample was highly variable (minimum: -45.9%; maximum: +70.6%; standard deviation: 15.12%). In addition to the present study, past work reports both increases and declines in RMR during mild cooling (Chen et al., 2013; Hanssen et al., 2015; Muzik et al. 2017). As discussed above, whole-body energy expenditure declines during mild cooling when the decline in metabolic rate of the appendages due to the Q_{10} effect is greater than the increase in metabolism at the core (Barany, 1967; Bennet, 1985; Wakabayashi et al., 2017). An alternative explanation is that the mild cooling condition elicits a habituation response in some individuals, characterized by blunted vasoconstriction and a blunted metabolic response (Young et al., 1996).

Table 6.11 Studies that quantify change in supraclavicular skin temperature and change in skin temperature of the chest after cooling.

	Sample Size			**Δ SCV**		**Δ Chest**	
Study	**Men**	**Women**	**Cooling Method**	**Mean**	**SD**	**Mean**	**SD**
Present study	31	43	30 min. of cooling from cooling suit	-0.01	0.25	-0.52	0.54
Levy et al. (2017) (data from Evanston, IL)	19	40	30 min. of cooling from cooling suit	-0.1	0.38	-2.29	2.73
van der Lans (2015)	36	0	90 min. of cooling from air-conditioning	-0.9	0.6	-2.2	1
Yoneshiro et al. (2016)	45	0	120 min of cooling from air-conditioning				
Summer sample				~-0.9	n/a	~-2.2	n/a
Winter sample				~-0.55	n/a	~-1.6	n/a
Chondronikola et al. (2016)	18	0	6 hour of cooling from cooling suit				
BAT negative sample				~-1.75	~0.6	n/a	n/a
BAT positive sample				~-.4	0.3	n/a	n/a

Table 6.12 Studies reporting percent change in energy expenditure after a cooling protocol.

Study	Cooling Protocol	%ΔEE Mean	%ΔEE SD
Present study	30 min. of cooling suit	-2.9	15.12
van Marken Lichtenbelt et al. (2002)	60 hours at 16°C	6.0	n/a
Celi et al. (2010)	12 hours at 19°C	5.9	n/a
Muzik et al. (2017)	1.5 hours of cooling suit	10.5	21.3
Hadi et al. (2016)	20 min of hand in 5°C in water	11.0	n/a
Chen et al. (2013)	12 hours at 19°C	5.3	5.9
van der Lans et al. (2013)	6 hours at 16°C	10.8	7.5
Hanssen et al. (2015)	30 min. from cooling suit	9.7	9.1

Figures 6.2 – 6.4 compare changes in SCV temperature, sternum temperature and percent change in energy expenditure of Yakut men and women. It appears that both men and women exhibit similar changes in skin temperature and energy expenditure. A significant increase in RQ after cooling was detected in women but not men. A similar pattern was detected by Hadi et al. (2016) after immersing subjects' hands in 5°C water for 20 minutes; however, most investigations of NST report no change in RQ (Din et al., 2016; Celi et al., 2010; Hanssen et al., 2015; Muzik et al., 2017; Peterson et al., 2015; Stelly, 2015). An increase in RQ among women may represent a shift toward utilizing carbohydrates as a metabolic substrate for thermogenesis. Previous work has detected improvements in insulin sensitivity after 12 hours of mild cold exposure (19°C) (Celi et al., 2010) and 10 days of cold acclimatization (van Marken Lichtenbelt et al., 2015), thus suggesting changes in glucose metabolism during thermogenesis. Alternatively, an increase in breathing rate and pressure of the breath can lead to an erroneous increase in RQ.

The present study hypothesized that BAT thermogenesis would be inversely associated with measures of body fatness since adults with greater BAT metabolism may have a higher total daily energy expenditure, less likely to be in positive energy balance, and thus less likely to deposit excess energy as white fat. Alternatively, BAT thermogenesis may be positively associated with percent body fat if larger white fat stores indicate that there is more energy available for thermogenesis. The multivariate regression of ΔSCV on age, sex, fat-free mass, and percent body fat displayed in Model 1 of Table 6.4 detected a significant positive relationship between ΔSCV and percent body fat. These results suggest that greater white fat stores may signal that the body has more energy available for thermogenesis.

Past work investigating the relationship between BAT metabolism and body fatness has produced mixed results. Saito et al. (2009), Matsushita et al. (2014); Hanssen et al. (2015) document that participants with greater BAT activity have lower body fatness; however, Lee et al. (2012) documented a positive association between BAT mass and fat mass. Many studies do not detect significant relationships between BAT metabolism and body composition, (Bahler et al., 2015; Franssens et al., 2017; Yoneshiro et al., 2011a, 2012). For instance, Bahler et al. (2015) compared 10 young obese men with healthy blood biomarkers of cardio-metabolic disease risk with 11 young lean men and did not find significant differences in BAT volume or activity. These mixed results point to the limitations tied to parsing out causality between BAT metabolism, energy balance and body fatness using observational studies. Past experimental studies document that 10 days of cold acclimation triggers a significant increase in BAT metabolism and NST (Blondin et al. 2014; van der Lans et al. 2013); however, these studies do not report data on body composition after cold acclimation.

The aging process may alter the relationship between BAT and adiposity. The present study documents a trend suggesting a negative relationship between BAT thermogenesis and age in Models 1 and 2 of Table 6.4. The prevalence of BAT declines with age (Hanssen et al., 2015;

Kindred et al., 2016; Matsushita et al., 2014; Saito et al., 2009; Yoneshiro et al., 2011b; Zhang et al., 2013). Aging BAT progenitor cells display cellular aging – a senescence-like phenotype that accounts for their age-dependent failure to differentiate into new brown adipocytes (Berry et al., 2016). PET/CT studies that cluster subjects into BAT positive and BAT negative groups based on the presence of glucose uptake in the supraclavicular area find that BAT positive subjects are younger, have a lower BMI and less body fat (Hanssen et al., 2015; Matsushita et al., 2014; Yoneshiro et al., 2011b; Zhang et al., 2013). Thus, issues of causality regarding the aging process, BAT metabolism and adiposity remain unclear.

The second hypothesis was that Yakut adults with greater BAT thermogenesis will expend more energy during a cooling condition. The present study reports in Table 6.5 a significant positive relationship between ΔSCV and % ΔEE after controlling for age, sex, fat-free mass, percent body fat, trial start time and change in sternum temperature. These results suggest that BAT thermogenesis is linked to NST among Yakut adults. The change in skin temperature of a point on the sternum, which lacks BAT deposits, was not associated with change in energy expenditure.

The positive relationship between BAT activity and energy expenditure during cold exposure is consistent with past investigations (Chen et al., 2013; Muzik et al., 2017; van der Lans et al., 2013; van Marken Lichtenbelt et al., 2015; Yoneshiro et al., 2016). Interestingly, participants that experienced an increase in SCV temperature had a mean percent change in energy expenditure of +1.41%, while participants that experienced a decrease in SCV temperature had a mean percent change in energy expenditure of -6.49%.

The physiological mechanisms that control NST are widely debated and the degree to which BAT metabolism directly contributes to whole-body energy expenditure during NST remains unclear. Muzik et al. (2013) measured the oxygen extraction fraction using dynamic PET-CT scans with triple oxygen ($[^{15}O]H_2O$, $[^{15}O]CO_2$, and $[^{15}O]O_2$) and $[^{18}F]$FDG tracer in order to estimate BAT's tissue-specific metabolic rate. The authors found that, when activated by cold, BAT contributed less than 20 kcal/day to total energy expenditure (Muzik et al., 2013). Similar estimates were found by Din et al. (2016) using the radiotracers $[^{15}O]O_2$, $[^{15}O]H_2O$, and $[^{18}F]$FTHA.

Data estimating the degree to which skeletal muscle metabolism contributes to NST varies greatly depending on the muscle location. A majority of studies in which biopsies were taken from muscles in the periphery, such as the vatus lateralis (Blondin et al., 2017; Hanssen et al. 2015; van der Lans et al. 2015), trapezius, and deltoid (Ouellet et al. 2012) found that there was no change in mitochondrial uncoupling and metabolic rate of these tissues during NST, although Wijers et al. (2008) does report an increase in mitochondrial uncoupling in vatus lateralis after cooling. Deep muscles, such as the levator scapulae (Din et al. 2016) and lungus colli (Ouellet et al. 2012), which co-locate with BAT, do exhibit an increase in metabolism during NST. Din et al. (2016) estimated that muscle of the cervico-thoracic region contributes about 86 kcal/day during cold exposure. The tissue-specific of other deep muscle tissues, such as the lungus colli, has yet to be estimated during cooling. Additionally, few recent studies have attempted to quantify possible changes in metabolic rate during NST of the internal organs.

There are several possible explanations for this pattern. In particular, BAT thermogenesis may act as a biomarker of systemic changes within the core related to cold-induced thermogenesis. Norepinephrine and thyroid hormones both trigger BAT thermogenesis, the generation of new brown adipocytes, and stimulate metabolism in other tissues such as skeletal muscle, the heart and liver; thus, BAT may be a biomarker for the metabolic action of these hormones.

BAT may also directly influence the action of thyroid hormone through its possible role as an endocrine or paracrine organ. For instance, fibroblast growth factor 21 (FGF21) produced by BAT can induce the conversion of white adipocytes to beige adipocytes and can stimulate metabolic processes associated with thermogenesis (Villarroya et al., 2016). FGF21 along with IL-6 produced in BAT can improve insulin secretion and beta-cell function in the pancreas and increase cardiac substrate oxidation (Villarroya et al. 2016). Brown adipocytes convert free thyroxine (fT4) into free triiodothyronine (fT3), the metabolically active form of thyroid hormone, through the expression and action of the enzyme type II deiodinase (DIO2). The absence of DIO2 inhibits BAT function. In mice, fT3 generated in BAT is released into circulation (Fernandez et al., 1987). While around 80% of fT3 in humans is generated in the periphery rather than by the thyroid gland, the exact pathways for fT3 production are still unknown (Bianco and Kim, 2013; Schimmel and Utiger, 1977). Finally, the supraclavicular BAT depot may be correlated with the presence of BAT deposits in other regions of the body, such as around the spine and heart, or brown adipocytes found scattered within white adipose tissue. The contribution of these additional BAT stores to energy expenditure during cold stress remains unclear.

In addition to BAT's contribution to total energy expenditure and energy balance, BAT thermogenesis may influence cardio-metabolic health by altering the levels of circulating glucose and lipids. Alternatively, BAT thermogenesis may be positively associated with blood lipid and glucose levels if circulating lipids and glucose signal there is more energy available for BAT metabolism. The results displayed in Table 6.10 revealed that serum lipids were not correlated with BAT activity, however, blood glucose levels were positively associated with BAT thermogenesis independent of age, sex, body composition, trial start time and vasoconstriction of the core. Additionally, this is the first study to document a significant positive correlation between BAT thermogenesis and change in RQ, thus suggesting that participants with greater BAT activity preferentially metabolize carbohydrates during cold exposure. These results suggest that circulating glucose may act as an important fuel source for BAT thermogenesis, and higher blood glucose levels may connote that there is more energy available for BAT metabolism.

Vallerand and Jacobs (1989) report that acute cold exposure triggers an increase in lipid oxidation of 63% and an increase in carbohydrate oxidation of 588%. Previous studies that recruited more elderly subjects found that participants with greater BAT volume exhibit greater insulin sensitivity, lower fasting insulin (Zhang et al., 2013) and lower HB1ac levels (Matsushita et al., 2014).

In order to explore the relationship between BAT metabolism and blood biomarkers of cardio-metabolic disease risk, future studies should measure baseline blood glucose and lipid levels and then sample again after the cooling condition. This would facilitate direct linkages between BAT activation and changes in circulating lipid and glucose levels. Vasoconstriction of the hands post-cooling limited our ability to collect bloodspots after the cold condition.

Yakut lifestyles that include more frequent cold exposure, such as greater participation in winter-time subsistence activities, may structure cardio-metabolic disease risk via BAT thermogenesis. Yakut men that spend more time participating in subsistence activities exhibit greater elevations in metabolic rate, and higher HDL and total cholesterol levels (Leonard et al., 2014; Levy et al. 2016). Future research should examine whether lifestyle shapes seasonal fluctuations in BAT metabolism and explore possible connections to seasonal shifts in cardio-metabolic health.

In order to better estimate BAT's contribution to overall energy balance, additional research must attempt to quantify metabolic responses to low temperatures in a setting outside of the lab. Ocobock (2016) quantified RMR, physical activity, thermoregulation and the thermic effect of food in 59 highly active adults participating in National Outdoor Leadership School in hot, temperate and cold climates. Total energy expenditure in the hot and temperature climates were statistically similar; however, while in the cold climate, subjects burned an extra 1550 kcal/day on average. Additionally, thermoregulation accounted for 16% of total energy expenditure in the cold climate (Ocobock, 2016). Thus, discovering the underlying determinants of variation in NST has important implications for understanding energy balance.

There are several other important limitations to this study. First, BAT thermogenesis was quantified indirectly by measuring change in the SCV temperature using infrared thermal imaging. This technique has been verified using PET-CT scans (see Chapter 2); however, skin temperature of this region is influenced by adiposity and vasoconstriction as well as BAT thermogenesis. Additionally, the sample size is small, thus limiting the possibility of sex-specific statistical analyses.

Summary

This chapter explores the adaptive and health significance of BAT among a sample of Yakut adults. First, the present study examines the relationship between BAT thermogenesis and body composition. BAT was positively correlated with percent body fat. It is possible that among relatively young and healthy adults, greater fat stores may signal that there is more energy available for BAT metabolism. Second, we tested the relationship between BAT thermogenesis and whole body energy expenditure. The results provide evidence for a link between BAT heat production and energy expenditure during NST. Thus, BAT activity may play a role in adaptation to acute cold stress among Yakut adults. Future research should explore the relationship between BAT activity and hormones that regulate metabolism, such as norepinephrine and thyroid hormone, in order to clarify the mechanistic pathways between BAT and energy balance. Finally, the results present a significant positive association between BAT thermogenesis, and RQ and fasted blood glucose levels. These results suggest greater BAT activity may lead to preferential utilization of carbohydrates as a fuel source for oxidative phosphorylation and could alter blood biomarkers of cardio-metabolic health.

CHAPTER 7

SEASONAL CHANGE IN THYROID HORMONES

Introduction

Circumpolar populations are exposed to marked seasonality in environmental conditions that strongly shape their metabolism (Snodgrass et al., 2007). Elevated basal metabolic rates (BMRs) are a central adaptation to cold temperature stress and alter health patterns among indigenous subarctic groups (Leonard et al., 2002, 2005; Snodgrass et al., 2005, 2008). Increased rates of production and clearance of thyroid hormones appear to be one mechanism responsible for high BMRs among circumpolar populations (Leonard et al., 1999).

Previous research has shown substantial seasonal changes in thyroid hormone activity among residents and sojourners to high latitudes. In particular, increased rates of production and clearance of thyroid hormones may be a mechanism responsible for high basal metabolic rates among circumpolar populations (Leonard et al., 1999). The secretion of thyroid hormone from the thyroid gland is regulated by thyroid-stimulating hormone (thyrotropin or TSH) from the pituitary. TSH, in turn, is regulated by thyrotropin-releasing hormone (TRH) from the hypothalamus. Circulating thyroid hormone levels negatively feed back to the pituitary and hypothalamus, thus regulating TSH secretion. In humans, production of triiodothyronine (T3), the active form of thyroid hormone, occurs in both the thyroid gland and in peripheral tissues, such as skeletal muscle, the heart and brown adipose tissue (BAT), via conversion of thyroxine (T4) into T3. T3 is thought to modify BMR by increasing oxygen consumption and heat production at the cellular level via calcium cycling and sodium-potassium ATPase activity (Ulijaszek, 1996).

In a series of studies among sojourners to Antarctica, Reed and colleagues (1986, 1990a, b) identified a constellation of physiological changes in response to severe cold exposure and reduced photoperiod. This cluster of responses is often referred to as the "polar T3 syndrome", has three main characteristics: 1) a significant increase in the TSH response to TRH; 2) unchanged or small decreases in free T4; and 3) greatly increased T3 production rate and total volume of distribution and small, variable changes in serum T3 levels (Reed et al., 1990b). Thus "polar T3 syndrome" is associated with increased rates of production and clearance of T3, the active form of thyroid hormone, and thyroxine T4, generally leading to reduced circulating levels of free (i.e., unbound and biologically active) T3 and T4 (fT3 and fT4) (Reed et al., 1990a, b; Harford et al., 1993).

Overall, previously available evidence does not provide a consistent picture of how extreme seasonality shapes thyroid function. Research conducted in northern Europe documents greater variability in seasonal changes in thyroid function, demonstrating both winter increases and decreases in fT3 and fT4 (Hassi et al., 2001; Maes et al., 1997; Plasqui et al., 2003). Furthermore, previous work on this topic is limited by small sample sizes of sojourners or recent migrants to severe climates, often including only men. As such, we still know relatively little about seasonality in thyroid function among populations native to Arctic and subarctic climes. Additionally, previous work documents interactions between biological adaptation to cold stress and negative health outcomes, such as elevated blood pressure and high rates of autoimmune thyroid disorders in women (Snodgrass et al., 2008; Cepon et al., 2011). Finally, interactions between biological adaptation and health may be altered by changing lifestyle contexts. The purpose of this study is to examine seasonal variation in thyroid hormone levels among an indigenous population of Siberia, the Yakut (Sakha). We predict that the Yakut will show evidence of the polar T3 responses – having reduced levels of fT3 and fT4 during the winter. Further, we expect that these responses will be modified by lifestyle factors such that individuals with greater subsistence activity participation will show more pronounced seasonal variation in thyroid hormone levels.

Results

Seasonal Changes in Body Composition and Thyroid Function

Table 7.1 presents descriptive statistics of seasonal changes in anthropometric and thyroid hormone measures for men and women. Both men and women exhibit significant increases in TSH levels and significant declines in fT3 and fT4 from summer to winter. Women show significant increases in weight, BMI, percent body fat and fat mass during the winter, whereas the changes in men are smaller and not statistically significant.

Figures 7.1 and 7.2 display the percent seasonal changes in body mass, body composition and thyroid hormone levels. In both sexes, seasonal changes in body mass are modest (< 2%), with most of the winter increase presenting as fat mass (+3% in men, and +5% in women), while FFM remains stable. For the thyroid measures, TSH increases by ~17-18% in the winter, while fT4 levels decline by 12-16% and fT3 decline by 25-26%.

Summer and winter anthropometric dimensions are strongly correlated with one another. The correlations range from 0.87 (percent body fat) to 0.98 (weight) in Yakut men and from 0.91

(percent body fat) to 0.97 (weight) in women ($p < 0.001$ for each pair-wise correlation). Thyroid measures are more variable across the seasons. The correlations between summer and winter measures range from 0.34 (fT3) to 0.76 (TSH) in men, and from 0.32 (fT3) to 0.69 (TSH) in women ($p < 0.01$ for each pair-wise correlation).

Table 7.1 Seasonal changes in anthropometric dimensions and thyroid hormone levels in Yakut men (n=51) and women (n=83).

	Summer	**Winter**		**Inter-season**
Measure	**Mean±SD**	**Mean±SD**	**t-statistic[a]**	**r[b]**
		Men (n=51)		
Anthropometric:				
Weight (kg)	69.2±12.1	69.5±12.1	0.95	0.98***
BMI (kg/m^2)	25.1±4.2	25.3±4.3	1.57	0.97***
Percent Body Fat (%)[c]	23.6±7.1	24.0±8.0	0.71	0.87***
Fat mass (kg)	16.9±7.6	17.3±8.4	0.89	0.91***
Fat-free mass (kg)	52.3±6.0	52.2±6.0	0.19	0.93***
Thyroid:				
TSH (mlU/l)	1.2±0.8	1.4±0.8	2.29*	0.76***
Free T4 (pmol/l)	16.0±2.8	13.6±2.1	6.65***	0.47***
Free T3 (pmol/l)	4.9±1.7	3.7±0.9	4.90***	0.34*
		Women (n=83)		
Anthropometric:				
Weight (kg)	62.0±11.3	62.8±11.5	2.52*	0.97***
BMI (kg/m^2)	25.9±4.3	26.2±4.3	2.45*	0.96***
Percent Body Fat (%)[c]	33.6±7.4	34.4±7.2	2.16*	0.91***
Fat mass (kg)	21.6±8.1	22.3±8.4	2.55*	0.95***
Fat-free mass (kg)	40.4±3.8	40.5±3.7	0.48	0.93***
Thyroid:				
TSH (mlU/l)	1.5±1.2	1.8±1.6	2.07*	0.69***
Free T4 (pmol/l)	15.5±3.5	13.7±2.7	4.31***	0.58**
Free T3 (pmol/l)	4.7±1.1	3.7±1.5	6.90***	0.32**

[a] Paired t-tests: seasonal differences are significant at: $^{*}p \le 0.05$; $^{**}p \le 0.01$; $^{**}p \le 0.001$

[b] Pair-wise correlations between summer and winter measures; significant at: *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001

[c] Percent body fatness from bioelectrical impedance analysis (BIA).

Figure 7.1 Percent seasonal changes in body weight and body composition among Yakut men and women.

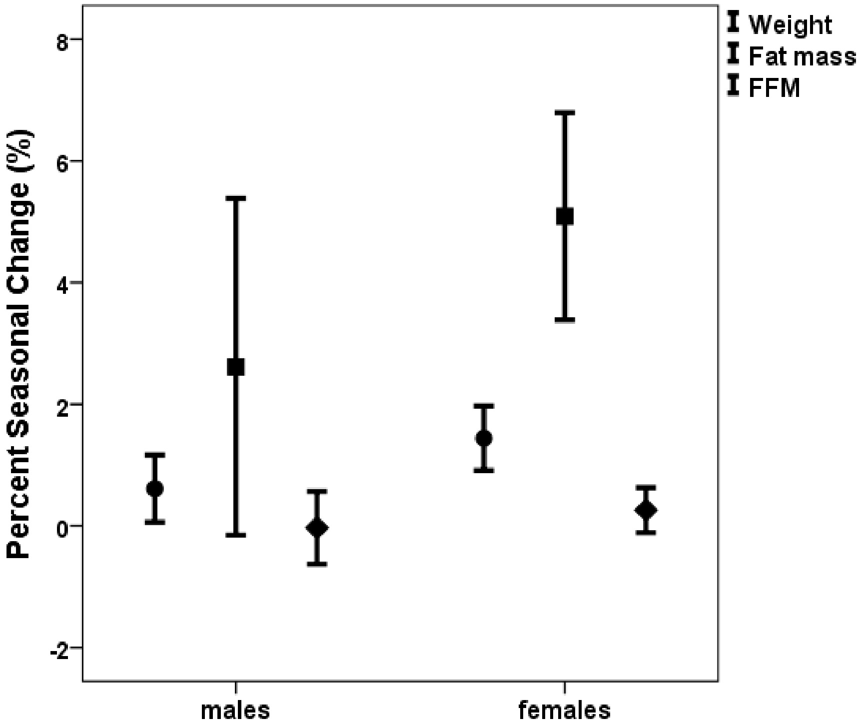
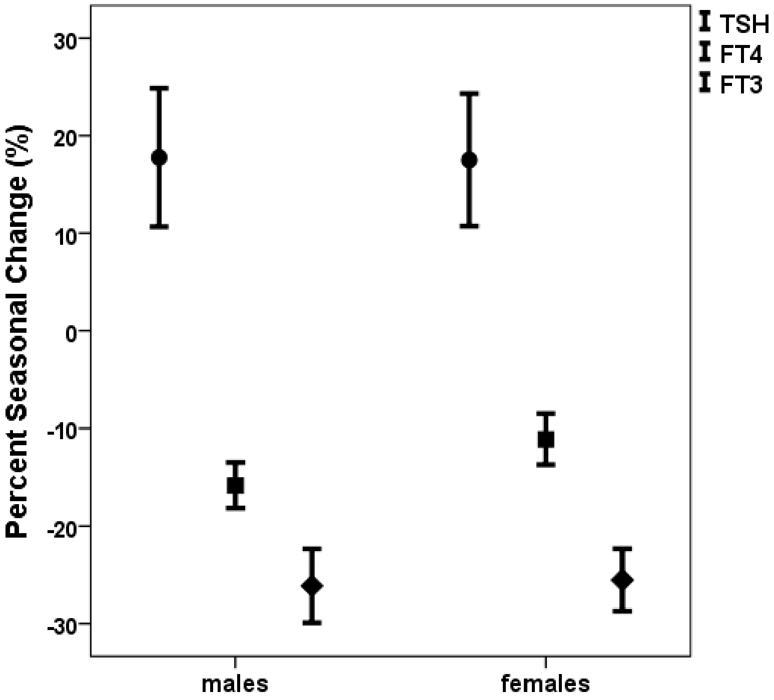


Figure 7.2 Percent seasonal changes in thyroid hormone measures (TSH, fT4, fT3) among Yakut men and women.



Seasonal changes are significant at: *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$

Table 7.2 shows correlations between seasonal changes in body composition and thyroid function for Yakut men and women. Among men, changes in fT3 are positively associated with changes in percent body fat ($r = 0.30$; $p < 0.05$), and negatively associated with FFM ($r = -0.40$; $p < 0.01$). Seasonal changes in TSH are positively associated with FFM ($r = 0.38$; $p < 0.01$) and negatively associated with percent fatness ($r = -0.24$; $p < 0.05$). Among women, seasonal changes in fT4 are positively correlated with changes in percent body fat ($r = 0.25$; $p < 0.05$).

Table 7.2 Correlations[a] between seasonal changes in thyroid hormone levels and age and seasonal changes in anthropometric dimensions in Yakut men and women.

Measure	ΔTSH	ΔFT4	ΔFT3
Men:			
Age (years)	0.01	0.05	0.06
ΔBMI (kg/m^2)	0.08	-0.19	-0.01
ΔPercent body fat (%)	-0.24*	-0.13	0.30*
ΔFat-Free mass (kg)	0.38**	-0.02	-0.40**
Women:			
Age (years)	0.18	-0.09	0.04
ΔBMI (kg/m^2)	0.05	0.16	-0.01
ΔPercent body fat (%)	-0.03	0.25*	-0.09
ΔFat-Free mass (kg)	0.07	-0.10	0.03

[a] Significance: $^{*}p \leq 0.05$; $^{**}p \leq 0.01$

Socioeconomic and Lifestyle Influences on Seasonal Changes

Table 7.3 presents the descriptive statistics for selected socioeconomic and lifestyle factors based on data collected during the summer of 2009. Men and women of this sample have similar levels of income, use of store-bought food, and hours of TV watching per week. In contrast, men report significantly more time devoted to hay cutting (14.2 vs. 4.1 days/year; $p < 0.001$), a major subsistence task, and have significantly lower style of life (SOL) scores than women (10.6 vs. 14.4; $P < 0.001$).

Table 7.3 Selected socioeconomic measures in Yakut men and women.

Measure	**Males (n=46)** **Mean±SD**	**Females (n=74)** **Mean±SD**	**t-statistic**[a]
Monthly Income (rubles)	29,711±13,091	27,461±13,812	0.89
Hay cutting (days)	14.2±13.7	4.1±10.8	4.48***
Percent Store food (%)	74.9±19.5	79.1±20.3	1.13
TV watching (hr/wk)	18.1±9.8	17.2±19.3	0.31
SOL Score	10.6±3.6	14.4±2.7	6.51***

[a] Sex differences are significant at: $^{*}p \le 0.05$; $^{**}p \le 0.01$; $^{***}p \le 0.001$

Table 7.4 presents the pair-wise correlations of the lifestyle variables with seasonal changes in thyroid and body composition measures for men and women. Among men, changes in fT4 levels are positively correlated with consumption of store-bought foods ($r = 0.43$; $p < 0.01$) and SOL ($r = 0.25$; $P < 0.05$), and show an inverse trend with days of hay cutting ($r = -0.24$; $p = 0.058$). Changes in TSH levels are inversely related to hours of TV viewing ($r = -0.29$; $p < 0.05$) and show positive trends with consumption of store-bought food ($r = 0.24$; $p = 0.056$) and the SOL index ($r = 0.24$; $p = 0.052$). As for changes in body composition, changes in BMI are positively associated with days of hay cutting ($r = 0.28$; $p < 0.05$) and changes in percent fatness are inversely related to SOL ($r = -0.27$; $p < 0.05$). Among women, changes in TSH levels are positively correlated with monthly income levels ($r = 0.34$; $p < 0.01$). None of the lifestyle variables are significantly correlated with the changes in body composition.

Table 7.4 Correlations[a] of seasonal changes in thyroid hormone levels and anthropometric dimensions with socioeconomic measures in Yakut men and women.

Measure	ΔTSH	ΔFT4	ΔFT3	ΔBMI	ΔPctFat	ΔFFM
Men:						
Income	0.01	-0.18	-0.10	-0.16	-0.18	0.07
Hay cutting	-0.18	-0.24†	0.05	0.28*	0.23†	-0.07
%Store Food	0.24†	0.43**	-0.11	-0.15	-0.11	-0.03
TV hours	-0.29*	-0.02	0.11	-0.08	-0.01	-0.14
SOL	0.24†	0.25*	-0.07	-0.21†	-0.27*	0.16
Women:						
Income	0.34**	-0.05	-0.02	-0.17†	-0.11	-0.07
Hay cutting	0.05	-0.05	-0.07	-0.11	-0.16	0.08
%Store Food	-0.13	-0.12	0.01	-0.02	-0.05	0.02
TV hours	0.01	-0.07	0.02	-0.05	-0.06	-0.01
SOL	0.16	-0.01	0.08	0.15	0.11	0.07

[a] Significance (1-tailed): †$p \le 0.10$; $^{*}p \le 0.05$; $^{**}p \le 0.01$

Comparative Analyses of Seasonality in Thyroid Function

Table 7.5 compares seasonal variation in thyroid measures in the Yakut to those of other circumpolar populations. The comparative data were restricted to those studies that presented comparable thyroid measures to the present study (i.e., TSH, fT3, and/or fT4) for two seasons on the same individuals. The three studies by Reed and colleagues (1986, 1990a, b) all examined changes in thyroid function among male naval officers at McMurdo Station in Antarctica. Similarly, Levine et al. (1995) examined seasonal changes in fT4 levels in U.S. soldiers stationed in Alaska. The other three studies were all conducted on European populations in their home countries – among men in Northern Finland (Hassi et al., 2001), and among men and women from Belgium (Maes et al., 1997) and the Netherlands (Plaqui et al., 2003).

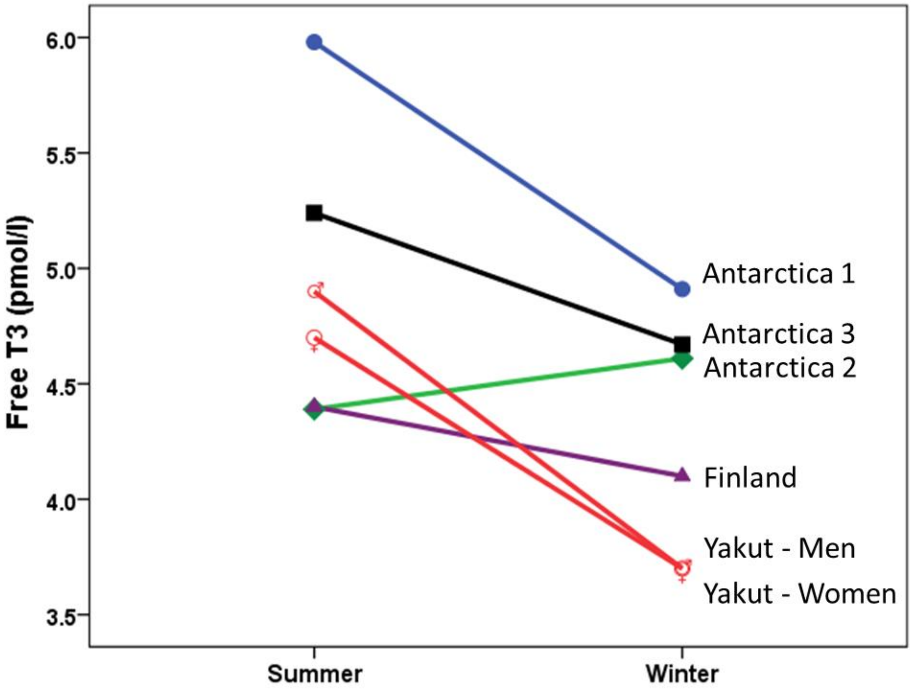
Table 7.5 Comparative data on seasonal changes in TSH, FT4 and FT3 levels in circumpolar environments.

			TSH (mlU/l)		**Free T4 (pmol/l)**		**Free T3 (pmol/l)**	
Location/Reference	**Sex**	**n**	**Summer**	**Winter**	**Summer**	**Winter**	**Summer**	**Winter**
Antarctica1 (Reed et al. 1986)	M	17	2.17	2.02	32.18	29.60	5.98	4.91*
Antarctica2 (Reed et al. 1990a)	M	13	2.62	2.59	25.80	26.40	4.39	4.61
Antarctica3 (Reed et al. 1990b)	M	15	2.79	2.83	25.40	24.70	5.24	4.67*
Alaska (Levine et al. 1995)	M	19	----	----	13.90	17.76*	----	----
Belgium (Maes et al., 1997)	M	13	1.38	1.38	13.40	13.40	----	----
	F	13	2.11	2.15	15.10	15.00	----	----
Finland (Hassi et al. 2001)	M	20	1.70	2.10*	15.06	15.06	4.40	4.10*
Netherlands (Plasqui et al. 2003)	M	10	1.70	1.20	14.00	13.10*	----	----
	F	15	2.00	1.70	12.10	12.60	----	----
Yakutia (present study)	M	51	1.20	1.40*	16.00	13.60*	4.90	3.70*
	F	83	1.50	1.80*	15.50	13.70*	4.70	3.70*

*Significant seasonal changes

Relative to the other circumpolar samples, seasonal changes in thyroid hormone levels among the Yakut are pronounced. Similar to the sample from Finland, Yakut men and women experienced a significant increase in TSH. As seen in Figure 7.3, the Yakut sample experienced a steep decline in fT3 and had the lowest winter values.

Figure 7.3 Seasonal changes in fT3 levels among selected circumpolar groups.



Discussion

The present study examined seasonal changes in thyroid hormone function among an indigenous circumpolar population, the Yakut, and explored the influence of body composition and lifestyle factors on shaping these patterns of seasonal change. We found that both Yakut men and women experienced significant decreases in serum concentration of fT3 and fT4 and significant increases in TSH levels from summer to winter. These results are consistent with “polar T3 syndrome,” first described by Reed and colleagues (1986, 1990b).

While seasonal changes in thyroid measures are quite marked among the Yakut, changes in body mass and composition were relatively modest (Figure 7.1). Yakut men showed small changes in weight and body composition that were not statistically significant. Yakut women showed significant increases in body weight during the winter, with most of the gain presenting as fat mass.

Among men, it appears that gains or preservation of lean mass may play an important role in regulating thyroid function. For example, changes in fT3 levels in men are inversely related to changes in FFM and positively correlated with body fatness. Changes in TSH levels are positively correlated with FFM. These findings suggest that greater lean mass is associated with higher uptake/clearance of fT3 during the winter among Yakut men. The patterns are less clear among Yakut women. None of the thyroid changes are associated with changes in FFM. In contrast, fT4 levels are positively correlated with change in percent fatness. The differences between men and women may highlight underlying differences in metabolic responses to seasonal change that are shaped by differences in body composition.

In comparison to samples of other circumpolar residents, the Yakut show relatively large seasonal changes in thyroid function, and have relatively low free thyroid hormone levels (both fT3 and fT4) during the winter (see Table 7.5). The substantially larger sample size of the present study compared to past circumpolar work strengthens our confidence in these results. The comparative data were restricted to studies that presented comparable thyroid measures to the present study (i.e., TSH, fT3, and/or fT4) for two seasons on the same individuals. The studies by Reed and colleagues (1986, 1990a, b) examined changes in thyroid function among male naval officers in Antarctica. Similarly, Levine et al. (1995) examined seasonality in fT4 levels in U.S. soldiers stationed in Alaska. The other three studies involved European populations in their home countries – including men in Northern Finland (Hassi et al., 2001), and both men and women from Belgium (Maes et al., 1997) and the Netherlands (Plasqui et al., 2003).

Analyses of socioeconomic data suggest that lifestyle factors may play a role in mediating seasonal thyroid responses, particularly among men. The correlational analyses suggest that that men pursuing a more traditional lifestyle experience greater reductions in fT4 and larger increases in TSH during the winter. Changes in fT4 levels were positively correlated with the consumption of store-bought food and the SOL index, and inversely correlated with days of hay cutting. Changes in TSH levels were inversely related to hours of TV viewing, and positively associated with days of hay cutting and SOL.

While highly speculative, it is possible that measures of seasonal change in FFM may be influenced by seasonal changes in brown adipose tissue (BAT). BAT contains abundant amounts of type II 5'-iodothyronine deiodinase (DIO2), a protein that converts T4 to T3; therefore, seasonal BAT recruitment may regulate adaptive changes in thyroid hormone function in response to cold temperature stress (Silva and Larsen, 1985).

As shown in Figure 7.3, the most consistent pattern of seasonal thyroid changes observed across circumpolar groups is the reduction in fT3 levels during the winter. This is the key characteristic of the polar T3 syndrome described by Reed et al. (1990b), and appears to reflect increases in both the rate of T3 production and the rate of fT3 uptake into tissues to elevate metabolic rate as an adaptation to cold temperature stress. Yakut men and women show the largest percent reduction in fT3 levels during the winter, approximately 24% for men and 21% for women, as compared to ~7-17% in other circumpolar groups that have been studied.

Additional evidence of the “polar T3 syndrome” is provided by Andersen et al. (2012). The authors measured serum thyroid hormones levels during the fall among Inuit groups of Greenland living in the capital, in a major town in a rural district, and in four settlements that lack modern housing facilities and roads. Individuals living in the settlements had significantly lower serum fT3 levels than those living in the town and the city. Assuming that the settlement-dwellers and Inuit hunters are exposed to greater cold stress, these results provide further evidence that decreases in serum T3 levels among acclimatized populations are indicative of higher rates of T3 clearance and metabolic adaptation to low temperatures. Andersen et al. (2012) also compared thyroid hormone function among Inuit male hunters, Inuit men who did not hunt, and non-indigenous Greenlanders. These results exemplify the possible relationship between lifestyle and socioeconomic factors and thyroid hormone function. Men adopting a hunting lifestyle and residing in the settlement displayed a significantly different thyroid hormone profile than non-hunters and individuals living in the town and city.

Cross-cultural comparisons of seasonal change in free T4 provide only mixed support for adaptive seasonal decreases in serum T4 levels (see Table 7.5). As with the Yakut, Plasqui et al. (2003) reported significant winter declines in fT4 levels in the men of their Dutch sample, but not the women. Levine et al. (1995) reported significant increases in fT4 during the winter among U.S. soldiers stationed in Alaska. None of the other studies shown in Table 7.5 found significant seasonal changes in fT4 levels.

Evidence of seasonal change in serum TSH concentration is also mixed across groups studied in circumpolar environments. Besides the Yakut, the only other group to show significant seasonal change in TSH levels was the Finnish men studied by Hassi et al. (2001). As with the Yakut, the Finnish men had higher TSH levels during the winter. Indeed, of all the comparative groups considered here, the Finnish sample exhibits a seasonal pattern in thyroid function most similar to the Yakut – showing significant winter increases in TSH and declines in fT3 levels. There are several limitations to this study. First, the winter and summer data were not collected within the same year, but rather 1.5 years apart. The time lapse in data collection and analysis may be an important source of error due to between-assay variation. Additionally, the modest seasonal differences in fat mass among women may be linked to gradual increases over time. Snodgrass et al. (2006) found that obesity has emerged as an important health issue among indigenous Siberians, particularly for women. Although our data suggest a positive correlation between change in fT4 and change in percent body fat among Yakut women, previous work suggests that fT4 levels are comparable between normal BMI and obese humans (Kozlowska et al., 2003; Reinehr, 2010) and that short term fasting and overfeeding does not alter serum fT4 concentrations (Reinehr et al., 2006).

Second, this study does not control for dietary iodine intake, which is an essential constituent of thyroid hormone. Previous work documents high fish and dairy consumption among the Yakut, which are two food groups known to be rich in iodine and are available yearlong (Crate, 2004; Haldimann et al., 2005; Sorensen et al., 2005). In addition, since our analysis required performing multiple correlations, our results are susceptible to type I error. Finally, this study does not directly examine rates of thyroid hormone uptake from the bloodstream into tissues; however, the cross-population pattern consisting of a drop in serum fT3 from summer to winter depicted in Figure 7.3 supports the interpretation that a decline in serum fT3 is reflective of higher tissue uptake as an adaptation to cold temperature stress.

Summary

In sum, this study has shown that the indigenous Yakut of northeastern Siberia experience marked seasonal changes in thyroid function. Consistent with previous work on circumpolar residents, the Yakut showed significant winter declines in fT3 levels. This polar T3 syndrome appears to result from the tissue-level uptake of T3 increasing at a faster rate than production or conversion. The marked declines in both fT3 and fT4 in Yakut men and women suggest an enhanced capacity to increase metabolic heat production during the severe winter cold. Our work also suggests that lifestyle factors help to mediate seasonal changes in thyroid function. Among men, those with more traditional lifestyle measures (e.g., less store-bought food, more time spent in subsistence tasks) showed exaggerated seasonal responses (declines in fT4, increases in TSH). Given the ongoing economic and lifestyle changes that are occurring in Siberia and in circumpolar regions around the world, additional research is needed to disentangle the pathways through which social and economic factors interact with underlying metabolic adaptations to shape variation in health status and disease risk.

CHAPTER 8

DEVELOPMENTAL PLASTICITY AND BROWN ADIPOSE TISSUE

Introduction

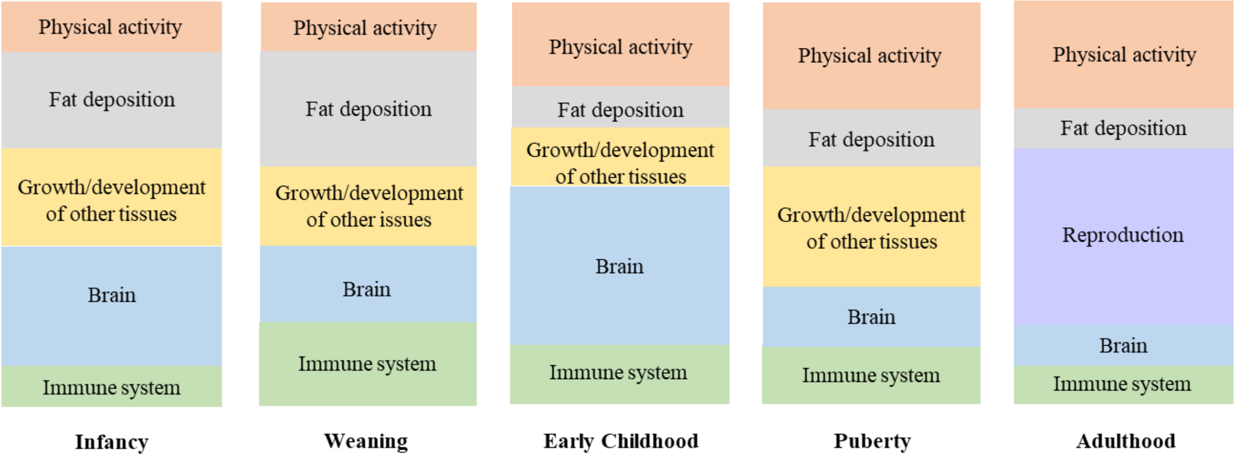
Traditionally, the modern synthesis presented plasticity as decoupling genotypes from their specific phenotypes, thus reducing the strength of selection on underlying genetic variants (Ghalambor et al., 2007). Developmental plasticity, or the ability to tailor development to local conditions, has historically been dismissed as unimportant in adaptive evolution (Simpson, 1953; Williams, 1966; Wright, 1931) and its role has been widely debated by more recent evolutionary thinking (Beaman et al. 2016; Pigliucci and Murren, 2003; Schlichting, 2004). When developmental changes incur a fitness benefit, this process is termed developmental adaptation (Frisancho, 1993). In theory, developmental adaptation will optimize energy allocation toward competing biological processes; however, the degree to which early-life cues can predict future conditions and effectively calibrate energy allocation across the life course is widely debated (Ellison, 2005; Kuzawa, 2005; Kuzawa and Quinn, 2009). Cue fidelity, however, may not necessarily need to be high for predictive signals to be useful (Fischer et al., 2014; Frankenhuis and Panchanathan, 2011; Gluckman et al., 2005).

Integral to this issue is a debate concerning the length and timing of critical periods, or a time period when developing systems permanently modify their settings in response to environmental experience (Bornstein, 1989; Kuzawa and Quinn, 2009). An organism’s biology may respond to external or internal cues during a critical period via changes in cell number, selection-driven changes in cell type, and epigenetic changes in gene expression (Kuzawa and

Quinn, 2009). Evidence generated from studies of growth and nutrition suggests that critical periods exist early in development – particularly during pregnancy and infancy – due to constraints on an individual's ability to adjust its phenotype later in life (Duffy et al., 2002; Wells, 2014). Wells (2014) goes so far as to propose that offspring plasticity is only viable within the niche of maternal care; thus, the length of pregnancy and lactation will determine the length of the critical period.

Alternatively, it is theoretically possible that critical periods may extend past infancy or close and reopen later in development. The relative amount of energy allocated toward competing biological processes is not constant across human development (see Figure 8.1). During infancy, energy is primarily directed toward growth in body size and white adipose tissue deposition (Kuzawa, 1998). An extended period of slow childhood and juvenile growth is a defining feature of human life histories (Bogin, 1999; Kaplan et al., 2000; Kuzawa et al., 2014; Schultz, 1969). In early childhood, increases in the metabolic costs of brain metabolism lead to trade-offs in energy allocation with growth (Kuzawa et al., 2014). The energetic demands of the developing immune system are also thought to lead to trade-offs with growth, particularly under conditions of high disease load and low caloric availability (Blackwell et al., 2010; Lunn, 2000; McDade, 2005a, b). With the onset of puberty and adolescence, energy is allocated toward linear growth and maturation. In adulthood, energy that was once directed toward growth is thought to be redirected toward reproduction (Ellison, 1990). While energy allocation across human life histories exhibits this general pattern, metabolism is sensitive to stochastic and seasonal environmental stressors, such as illness, psychosocial stress, and thermal stress, which will lead to shifts in energy allocation (Belsky et al., 2007; Ellis and Garber, 2000; Katzmarzyk and Leonard, 1998; Leonard et al., 2005, 2014; McDade, 2005a, b).

Figure 8.1 Model of energy allocation toward competing biological processes across the life course.



Thus, each life stage involves a transition in energy allocation and different biological systems develop and mature at different rates. The slow rate of development in humans facilitates the integration of information about energy allocation across the life course and may result in critical periods extending into childhood and adolescence. For example, the tempo of childhood growth and adolescent maturation in human females may act as a signal of energy availability and appears to be coupled to levels of adult ovarian function (Ellison, 1990).

Furthermore, each domain of physiology and morphology must be integrated into a functional whole. Evidence of biological adaptation to hypobaric hypoxia suggests that the various components of the oxygen transport system are sensitive to environmental inputs at different life stages (Greska, 1990). Vital lung capacity appears to be sensitive to hypoxia between birth and nine years old. Maximum oxygen consumption (VO_2max), however, is sensitive to hypoxia in adolescence, and adaptive elevations are not achieved until after puberty.

Thus, adolescence is the period during which all the integrated responses which are required for complete adaptation to hypobaric hypoxia have been fully developed (Greska, 1990).

One way to better calibrate energy allocation for the upcoming life stage is to integrate information gathered across development rather than relying on inputs obtained solely from gestation and infancy. Based on mathematical modeling of adaptive evolution, critical periods will close quickly when cues are highly predictive of the environment. When signals are less predictive, however, perhaps due to environmental fluctuations, the critical period may be extended (Panchananthan and Frankenhuis, 2016). A greater time depth of information about the environment across an individual's life course may help set energy allocation strategies for the future and reduce the chance of mismatch between adaptive strategies and future environmental conditions. Alternatively, environmental sensitivity may extend across adolescence due to biological constraints rooted in the slow rate at which humans develop.

Developmental plasticity in metabolic adaptation to cold stress has not been widely explored; yet, there are compelling reasons to expect that it occurs. Previous work indicates that populations indigenous to cold climates exhibit developmental adaptation with respect to changes in vasoconstriction/vasodilation in response to cold (Frisancho, 1993; Little and Hochner, 1973; Miller and Irving, 1962; So, 1980; Williams et al., 1969). For example, studies of populations native to Alaska and Canada found that adults maintained warmer skin temperatures than children after cooling (Miller and Irving, 1962; Williams et al., 1969; So, 1980). Similarly, in research among the Quechua of the Peruvian Andes, Little and Hochner (1973) reported that after exposure to cold temperatures, adults exhibited significantly warmer hand and foot temperatures than children (mean age = 14 years). Additionally, skin temperatures were not significantly different between males and females. While the larger surface area-to-mass ratio of the children's hands may lead to greater heat loss, the lack of significant sex differences suggests that these results may reflect developmental adaptation.

Human infants are at a substantial thermoregulatory disadvantage compared to adults because of their inability to shiver, their low body masses, and their high surface area-to-weight ratios (Leonard et al., 2009). BAT deposits first develop during the 20th gestational week (Velickovic et al., 2014); however, the thermal environment of the fetus appears to be tightly regulated by the mother's metabolism and variation in gestational BAT development is likely influenced by maternal nutrition rather than cold stress (Symonds et al., 2012a). At birth, the neonate experiences their first significant cold stress, and in response BAT stores grow significantly during the first few weeks of life. Infant BAT deposits are found primarily in the spinal, supraclavicular, axillary and perirenal regions (Rasmussen et al., 2013; Symonds and Lomax, 1992). Then, over the first few months of life, the infant will shift from relying on non-shivering thermogenesis (NST) toward shivering as the primary response to cold stress, and BAT is gradually replaced by white adipose tissue (Naeye, 1974). Interestingly, a comparison of BAT volume of infants at birth and at six months old found that infants that gain more paraspinous musculature experience smaller declines in BAT with age (Ponrartana et al., 2016).

Comparative data suggest that early life environments shape variation in the persistence or loss of BAT. In young ruminants, the rate at which BAT is depleted and the onset of shivering thermogenesis can be delayed by rearing young in cold environments (Casteilla et al., 1989; Darby et al., 1992; Symonds and Lomax, 1992). Additionally, rats reared at 18°C exhibit greater BAT deposits as adults compared to rats reared at 30°C (Young and Shimano, 1998). Human infants that were exposed to cooler environments during the first few days of life were better able to maintain their internal temperature during cooling several days later (Glass et al., 1968; Perlstein et al., 1974); however, it has yet to be investigated whether these adaptations persist later in life. Furthermore, the relationship between early fluctuations in BAT mass and energy expenditure later in life remains an open question (Symonds et al., 2012a).

Rates of BAT detection in retrospective studies of PET/CT scans tend to be higher in studies of children compared to adults (Bar-Sever et al., 2007; Gelfand et al., 2005; Gilsanz et al., 2011, 2016; Zukotynski et al., 2010). This may be due to a higher prevalence of BAT in children or due to the fact that children have a higher surface area to mass ratio and, therefore, are at a thermoregulatory disadvantage. While there are very few studies examining BAT volume of humans between six months and six years old, it appears that BAT stores continue to decline until around age 10 (Robinson et al., 2013; Rockstroh et al., 2015; Symonds et al., 2012b).

Surprisingly, BAT appears to increase with the onset of puberty (Deng et al., 2015; Drubach et al., 2011; Gilsanz et al., 2016). Gilsanz et al. (2016) conducted a retrospective study of PET/CT scans from participants ages four to 20 years old and grouped subjects by Tanner stage. The authors found that subjects in the final two stages of puberty had significantly greater BAT volume compared to Tanner stages 1-3 (Gilsanz et al., 2016). Similarly, Drubach et al. (2011) examined PET/CT scans from subjects between five to 21 years old and found that the 13-14.99 year-old age group had the highest percentage of participants with detectable BAT. Increases in BAT volume during puberty may be linked to changes in muscle mass. Studies of children and adolescents report significant relationships between BAT mass and neck and gluteus musculature (Gilsanz et al., 2011) as well as abdominal musculature (Gilsanz et al., 2016). Additionally, Ponrartana et al. (2012) found that children and adolescents with greater BAT volume had larger bone cross-sectional area and cortical bone area after accounting for height, weight, and sex.

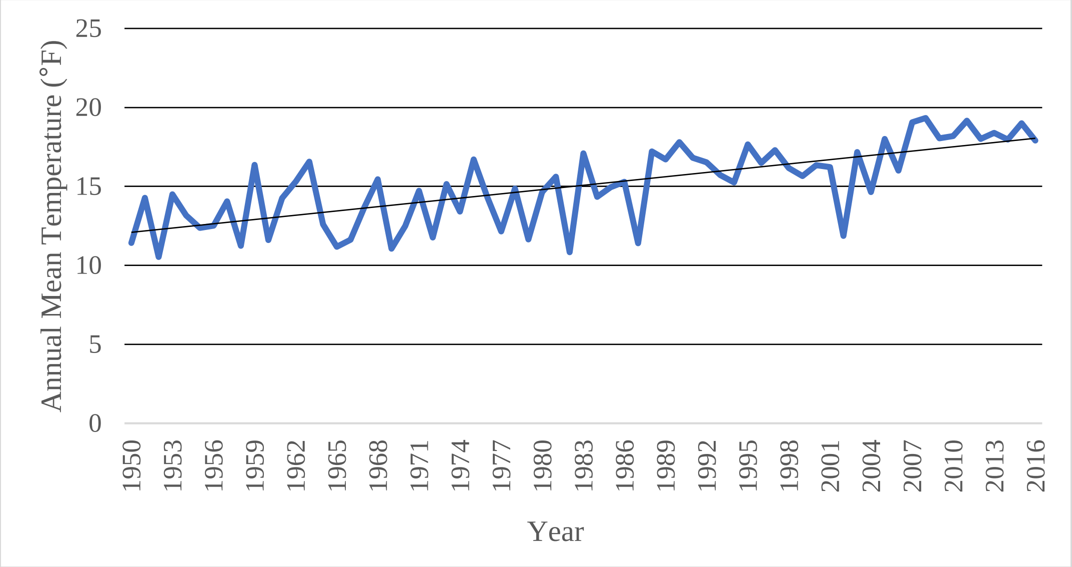
Family lifestyle differences are likely to shape how much time infants, children, and adolescents spend outside and their degree of cold exposure. In addition to unstructured playtime and organized winter-time sports, Yakut children and teenagers help with many outdoor winter chores, depending on the subsistence practices and style of life of their family (Crate, 2006). For example, children may help tend cattle and horses, cut hay for livestock, hunt, fish, and forage with their families (Crate, 2006). The family's location, economic status and subsistence characteristics will determine how the home is heated and how children get from place to place – all of which will influence cold exposure. Thus, developmental plasticity in metabolism is likely sensitive to the surrounding social and economic contexts in addition to the weather conditions. Furthermore, by structuring the daily activities of a child, the social and economic context of one generation is likely to influence the biology of the next through reinforcing biological and social mechanisms (Hoke and McDade, 2015).

The present study explores developmental plasticity in BAT by examining the relationship between adult BAT thermogenesis and cold exposure during infancy, childhood and adolescence. This study examined two main research questions. First, is there evidence of developmental plasticity in adult BAT thermogenesis? Evidence of a significant relationship between early-life cold exposure and adult BAT thermogenesis would suggest that developmental plasticity exists in this tissue. Second, does plasticity in BAT thermogenesis decline with age or is there evidence of multiple critical periods? If critical windows close after infancy, we would expect that temperature exposure during the first few years of life would account for more of the variation in BAT thermogenesis than conditions later in development. Alternatively, if critical periods extend into childhood or adolescence, then exposure during these later time periods would explain more of the variation in BAT.

Methods

Based on the findings presented in Chapter Five, change in skin temperature of the supraclavicular area (SCV) after a 30-minute cooling condition is used as an indirect biomarker of BAT thermogenesis. Additionally, early-life cold exposure is quantified using two approaches. First, data on the average daily temperature of Yakutsk from 1950-2015 was downloaded from the NOAA Climate Data Online (NOAA National Center for Environmental Information). Figure 8.2 presents the mean temperature in Yakutsk, Russia from 1950 to 2016. While the weather in Yakutsk fluctuates widely from year to year, there is a clear trend suggesting that the climate of Yakutsk is warming.

Figure 8.2 Annual mean temperature in Yakutsk, Russia from 1950-2016.



The weather data was used to calculate for each participant the mean temperature of each year of life ranging from the first year to the seventeenth year. Table 8.1 displays descriptive statistics for these variables. Subsequent analyses examining the relationship between ΔSCV and annual temperature exposure for each year of life included all 17 of these variables; therefore, a power analysis was run to ensure that the analysis would not be under powered using the "powerreg" function in Stata. The full regression has an R^2 of 0.5698 and the regression without the variables of interest (i.e. mean temperature of the 1^{st}-17^{th} year of life) has an R^2 of 0.2111. Given that there are 23 total variables in the regression and 17 variables of interest, the power analysis showed that, at a power level of 0.9, the sample would need 48 subjects. Thus, the analysis is not underpowered. The variance inflation factor for the mean temperature variables were all under 10.0; therefore, possible collinearity between across the weather variables is not problematic.

Table 8.1 Descriptive statistics for variables describing the mean temperature of the first through seventeenth year of life (n = 58).

Measure	Mean	SD	Min	Max
1st Year Mean Temp. (°F)	16.59	1.83	12.3	19.85
2nd Year Mean Temp. (°F)	15.94	1.77	11.57	19.26
3rd Year Mean Temp. (°F)	16.16	1.83	11.6	19.26
4th Year Mean Temp. (°F)	16.25	1.5	13.12	19.96
5th Year Mean Temp. (°F)	16.28	1.49	13.16	19.01
6th Year Mean Temp. (°F)	16.6	1.77	11.49	19.58
7th Year Mean Temp. (°F)	16.27	1.49	11.81	19.35
8th Year Mean Temp. (°F)	16.23	1.5	12.38	18.99
9th Year Mean Temp. (°F)	16.67	1.43	12.43	19.42
10th Year Mean Temp. (°F)	16.93	1.36	11.46	19.64
11th Year Mean Temp. (°F)	17.03	1.83	11.49	20.4
12th Year Mean Temp. (°F)	17.51	1.5	13.66	20.5
13th Year Mean Temp. (°F)	17.09	1.85	11.41	20.47
14th Year Mean Temp. (°F)	17.78	1.57	12.25	20.43
15th Year Mean Temp. (°F)	17.79	1.68	14.13	20.54
16th Year Mean Temp. (°F)	17.57	1.49	12.19	20.34
17th Year Mean Temp. (°F)	17.93	1.25	14.55	19.99

As children age, individual variation in lifestyle is likely to structure the amount of time spent outside exposed to low temperatures. Thus, for the second approach to quantifying early-life cold exposure, a Childhood Outdoor Activities Survey was used to generate an Early Life Cold Index (ELCI) score for ages five to seven, eight to 10, 11 to 13, 14 to 16, and 17 to 19 years old (see Chapter 5, Figure 5.4). The Childhood Outdoor Activities Survey was administered to 58 of the 74 adults on whom metabolic data were collected. Table 8.2 compares the sex ratio, age, anthropometric dimensions, BAT thermogenesis, vasoconstriction of the core, and metabolic changes of the subjects that participated in the survey (sample C) and those that did not. Those who participated in the survey are significantly younger, and have greater BAT thermogenesis and larger increases in respiratory quotient after cooling.

Table 8.2 T-tests comparing demographic, anthropometric and metabolic parameters for subjects participating vs. not participating in the Childhood Outdoor Activities Survey.

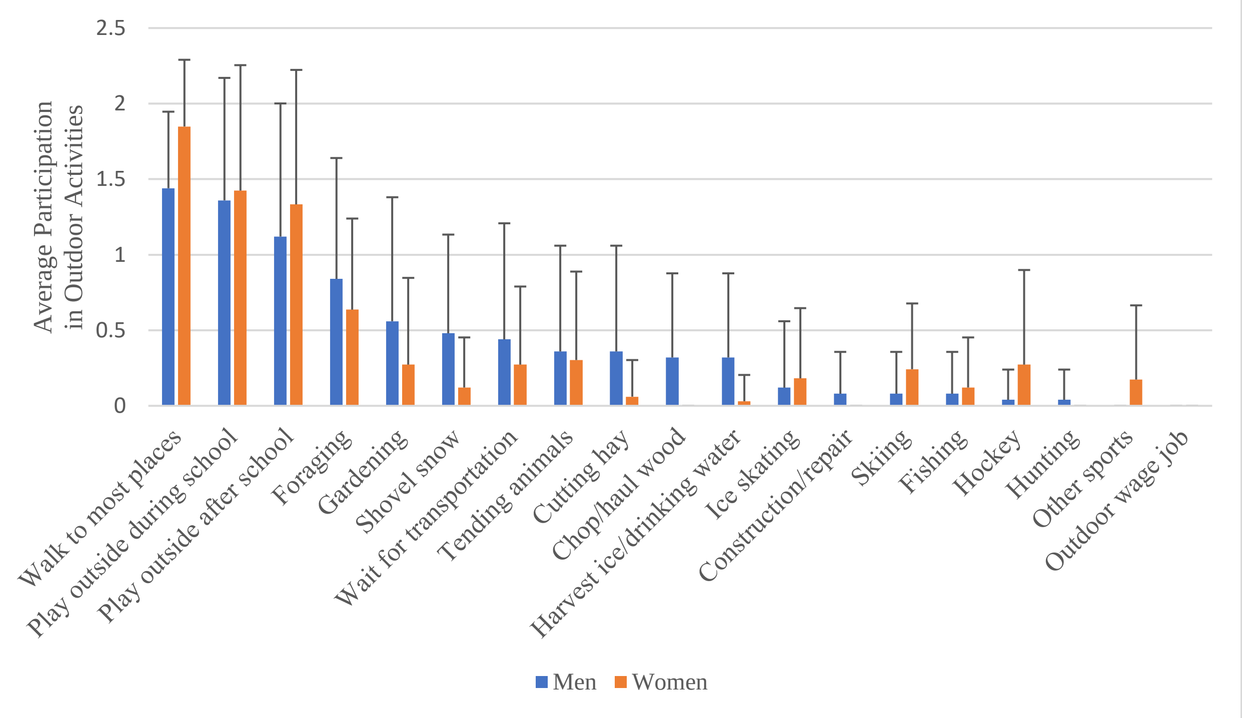
Measure	Sample C Survey Participants n = 58 Mean ± SD	Sample D Non-participants n = 16 Mean ± SD	p-value
Sex Ratio (M/F)	(25/33)	(6/10)	0.692
Age[a] (years)	24.66 ± 7.10	32.38 ± 10.23	0.003
Fat-free mass[a] (kg)	47.69 ± 8.31	44.31 ± 12.16	0.542
BMI[a]	21.50 ± 3.25	23.58 ± 4.04	0.059
Weight (kg)	58.47 ± 11.58	62.56 ± 10.70	0.208
Height (cm	164.42 ± 8.16	162.73 ± 9.56	0.482
Percent Body fat (%)	27.59 ± 7.23	30.62 ± 9.00	0.164
ΔSCV (°C)	0.02 ± 0.26	-0.11 + 0.19	0.03
Δ Sternum (°C)	-0.52 + 0.56	-0.053 + 0.51	0.938
Percent Change in EE	-1.38 + -5.57	-8.23 + 10.51	0.055
Change in RQ	0.04 ± 0.09	-0.02 + 0.06	0.017

[a] The variable is not normally distributed; therefore, a two-sample Wilcoxon rank-sum (Mann-Whitney) test was run.

Figures 8.3 to 8.7 present the results of the Childhood Outdoor Activities Survey. The frequency of participation in most activities increased with age. As expected, the types of cold-weather activities that were most common shifted with age. Activities with a mean of 1.0 or greater were included in the ELCI score for each age range (see Table 8.3). Thus, for each age range, the ELCI score is the average degree of participation across the activities included in the score.

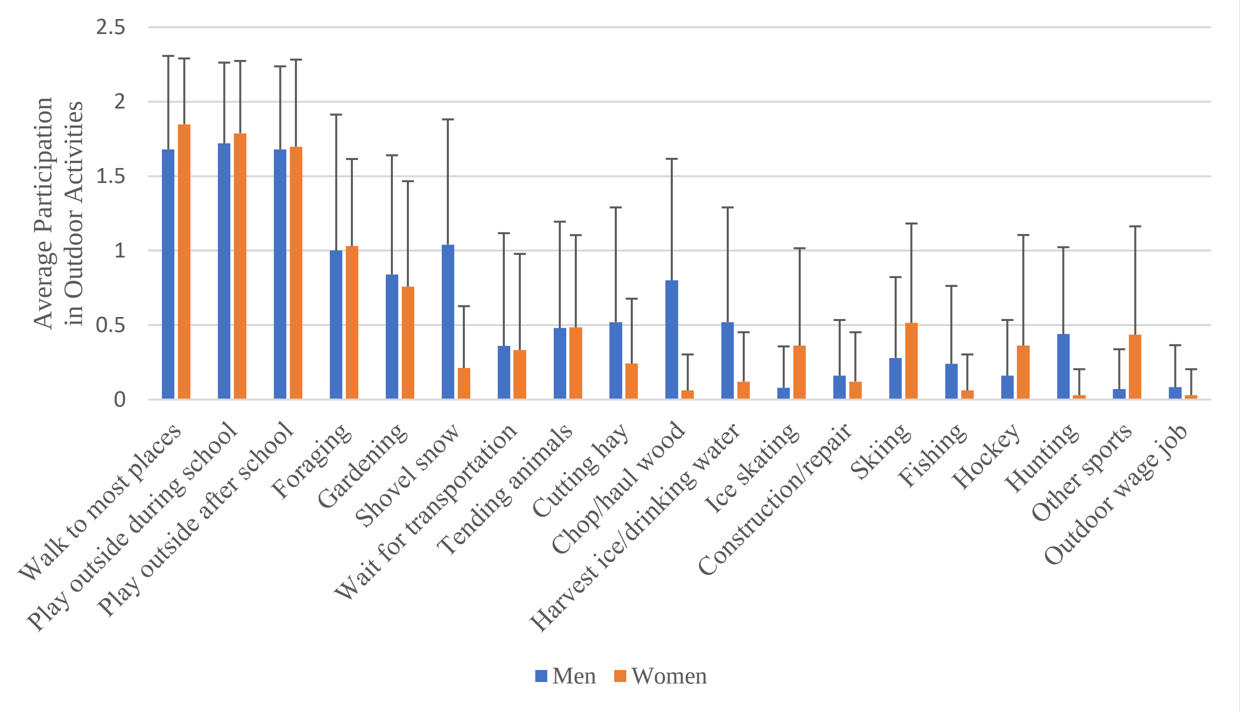
Table 8.4 compares the average ELCI score for males and females at each age range. The mean scores were not significantly different between the sexes except for the score for 14-16 years old. At this age range, males spent more time participating in outdoor activities than females. Despite this difference, the following analyses were not stratified by sex due to the small sample size. Instead sex was controlled for in multiple regression analyses. The variance inflation factors for the ELCI variables were below 10.0.

Figure 8.3 Childhood outdoor activity participation between 5 and 7 years old[a].



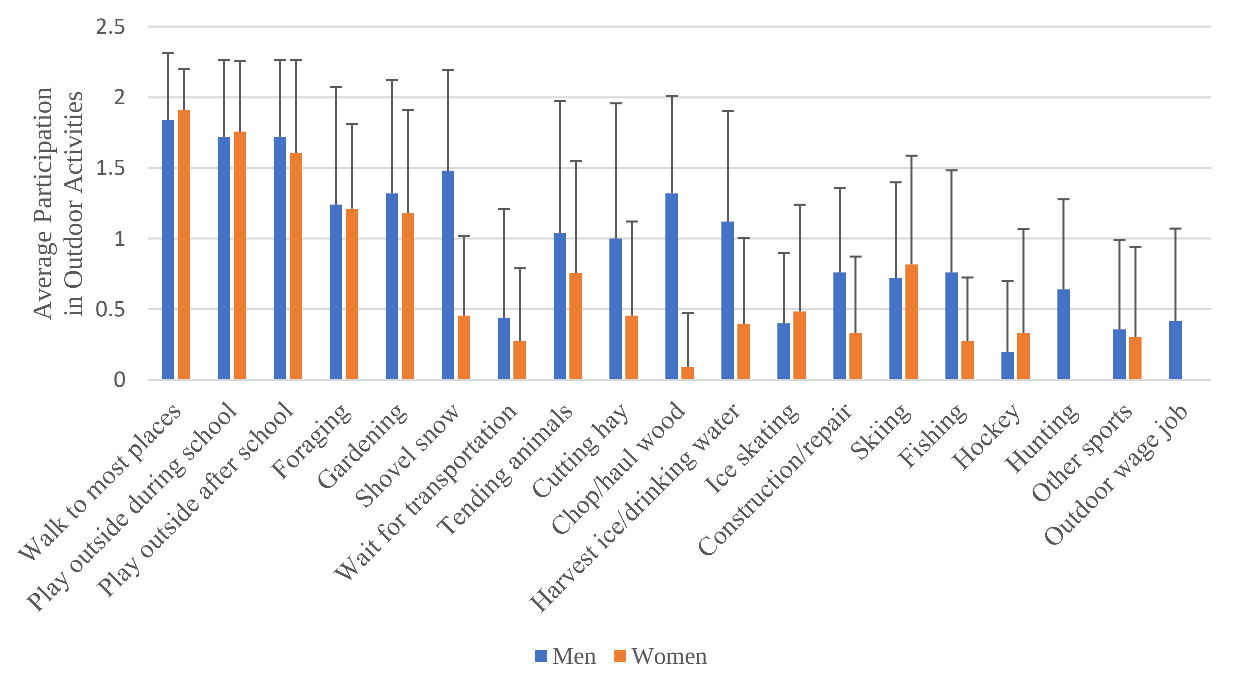
[a]Coding of the survey: 0 – never; 1 – occasionally; 2 – often.

Figure 8.4 Childhood outdoor activity participation between 8 and 10 years old[a].



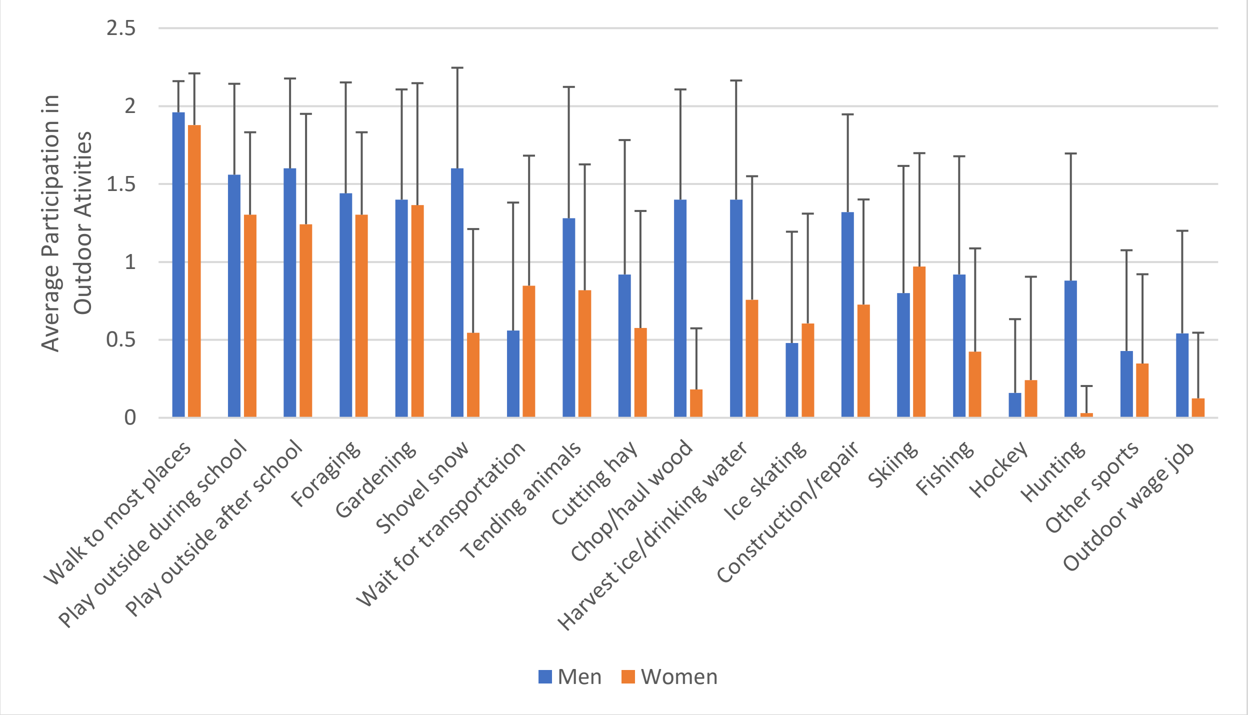
[a]Coding of the survey: 0 – never; 1 – occasionally; 2 – often.

Figure 8.5 Childhood outdoor activity participation between 11 and 13 years old[a].



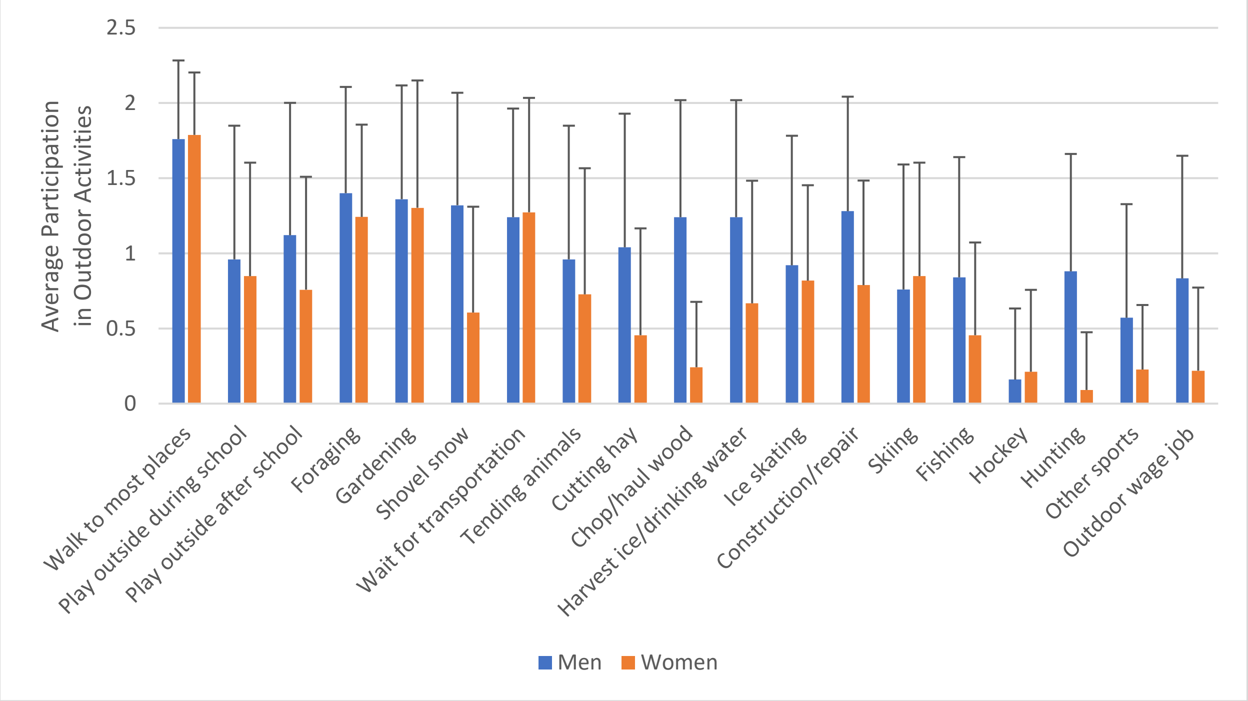
[a]Coding of the survey: 0 – never; 1 – occasionally; 2 – often.

Figure 8.6 Childhood outdoor activity participation between 14 and 16 years old[a].



[a]Coding of the survey: 0 – never; 1 – occasionally; 2 – often.

Figure 8.7 Childhood outdoor activity participation between 17 and 19 years old[a].



[a]Coding of the survey: 0 – never; 1 – occasionally; 2 – often.

Table 8.3 Outdoor activities included in the Early Life Cold Index score for each age range.

Age Range	Activities Included in ELCI
5-7 years old	Walking to most places Playing outside during school Playing outside after school
8-10 years old	Walking to most places Playing outside during school Playing outside after school Foraging
11-13 years old	Walking to most places Playing outside during school Playing outside after school Foraging Gardening/Raking leaves
14-16 years old	Walking to most places Playing outside during school Playing outside after school Foraging Gardening/Raking leaves Tending livestock/pets Harvesting drinking water/ice
17-19 years old	Walking to most places Foraging Gardening/Raking leaves Tending livestock/pets Waiting for transportation

Table 8.4 Comparisons[a] of average Early Life Cold Index score at different age ranges for Yakut men and women.

Measure	Men Mean ± SD	Women Mean ± SD	p-value
ELCI Score Ages 5-7 Years Old	1.31 ± 0.12	1.54 ± 0.10	0.121
ELCI Score Ages 8-10 Years Old	1.52 ± 0.10	1.59 ± 0.06	0.961
ELCI Score Ages 11-13 Years Old	1.57 ± 0.09	1.53 ± 0.05	0.326
ELCI Score Ages 14-16 Years Old	1.52 ± 0.09	1.24 ± 0.06	0.006
ELCI Score Ages 17-19 Years Old	1.15 ± 0.06	1.12 ± 0.05	0.657

[a] Early life cold index variables were not normally distributed; therefore, a two-sample Wilcoxon rank-sum (Mann-Whitney) test was run.

Results

Table 8.5 presents the results of a multiple regression analysis of the mean temperature of the first through seventeenth year of life on ΔSCV controlling for age, sex, anthropometric dimensions, trial start time, and vasoconstriction of the core. The results in Table 8.5 show a significant relationship between ΔSCV and mean temperature of the thirteenth year of life. Additionally, there is a trend suggesting a relationship between ΔSCV and mean temperature of the fourth, sixth, and fifteenth year of life. These results indicated that puberty may represent a critical period for developmental plasticity in BAT activity. Additionally, the standardized beta coefficient for the mean temperature of the thirteenth year of life was the largest of all the temperature variables, followed by the fifteenth year and then the sixth year. Thus, temperature exposure around the time of puberty explains the largest portion of the variation in BAT thermogenesis compared to exposure at other time periods.

The results of a multiple regression analysis of ELCI scores on ΔSCV are presented in Table 8.6. Participants with a higher ELCI score at ages five to seven exhibit greater BAT thermogenesis. This suggests that participants that spent more time participating in outdoor activities from five to seven years old later exhibit greater BAT thermogenesis in adulthood. In other words, five to seven may be a critical period for developmental adaptation to cold stress.

Table 8.5 Multiple regression analysis[a] of mean temperature of the first through seventeenth years of life on change in SCV controlling for age, sex, body composition, trial start time and vasoconstriction of the core.

Measure	β Coef.	p-value	Standardized β Coef.
1st Year Mean Temp. (°F)	-0.003	0.917	-0.0211
2nd Year Mean Temp. (°F)	-0.003	0.951	-0.017
3rd Year Mean Temp. (°F)	-0.044	0.209	-0.305
4th Year Mean Temp. (°F)	-0.05	0.089*	-0.285
5th Year Mean Temp. (°F)	-0.052	0.171	-0.294
6th Year Mean Temp. (°F)	-0.065	0.083*	-0.438
7th Year Mean Temp. (°F)	-0.01	0.762	-0.055
8th Year Mean Temp. (°F)	0.012	0.749	0.064
9th Year Mean Temp. (°F)	-0.032	0.362	-0.171
10th Year Mean Temp. (°F)	0.055	0.258	0.285
11th Year Mean Temp. (°F)	-0.006	0.848	-0.041
12th Year Mean Temp. (°F)	0.03	0.408	0.172
13th Year Mean Temp. (°F)	-0.082	0.05**	-0.575
14th Year Mean Temp. (°F)	0.016	0.724	0.092
15th Year Mean Temp. (°F)	-0.084	0.082*	-0.533
16th Year Mean Temp. (°F)	-0.058	0.277	-0.325
17th Year Mean Temp. (°F)	-0.038	0.435	-0.179
Age (years)	-0.05	0.157	-1.342
Sex (1-M; 2-F)	0.275	0.282	0.515
Fat-free Mass (kg)	0.013	0.245	0.4
Percent Body Fat (%)	-0.008	0.573	-0.208
Trial Start Time	-0.974	0.045**	-0.31
Δ Sternum (°C)	0.174	0.058*	0.366
Constant	7.945		

Relationship with change in SCV indicated a trend at: *$p \leq 0.10$

Relationship with change in SCV were significant at: **$p \leq 0.05$

[a] Adjusted $R^2 = 0.270$

Table 8.6 Multiple[a] regression analysis of early life cold index scores at various ages on change in SCV controlling for age, sex, body composition, trial start time and vasoconstriction of the core.

Measure	β Coef.	p-value
Early Life Cold Index Ages 5-7	0.12	0.05
Early Life Cold Index Ages 8-10	0.036	0.664
Early Life Cold Index Ages 11-13	-0.032	0.799
Early Life Cold Index Ages 14-16	0.159	0.163
Early Life Cold Index Ages 17-18	0.046	0.704
Age (years)	-0.01	0.173
Sex (1-M; 2-F)	-0.152	0.451
Fat-free Mass (kg)	0.0003	0.976
Percent Body Fat (%)	0.02	0.085
Trial Start Time	-0.937	0.029
Δ Sternum (°C)	0.052	0.354

[a]Adjusted $R^2 = 0.195$

Discussion

The present study examined developmental plasticity in BAT thermogenesis with the aim of identifying possible critical periods during which the body may be particularly sensitive to low temperatures. Early life cold exposure was quantified from two sources: (1) historical weather data (used to determine the average temperature at each year of a subject's life), and (2) a survey of subjects' participation in a range of outdoor activities during childhood and adolescence. These data provided the first evidence that humans exhibit developmental plasticity in BAT thermogenesis. Furthermore, mid-childhood and adolescence were identified as possible critical periods during which environmental inputs may shape adult BAT activity.

Participants with a higher ELCI score for ages five to seven exhibited significantly greater BAT thermogenesis (see Table 8.5). In other words, Yakut adults that spent more time participating in outdoor cold-weather activities showed higher levels of BAT activity. Additionally, there is a trend suggesting a negative relationship between BAT thermogenesis and average temperature of the fourth and sixth year of life (see Table 8.5). These results imply that mid childhood may represent a critical period for BAT plasticity.

Adult BAT thermogenesis was negatively correlated with the average temperature of the 13th year of life suggesting that individuals that were exposed to lower temperatures during this time period exhibit greater BAT activity later in life. Additionally, there was a trend suggesting that BAT thermogenesis is negatively associated with mean temperature of the 15th year of life. These results are particularly interesting given that, in humans, BAT appears to increase during puberty (Deng et al., 2015; Drubach et al., 2011; Gilsanz et al., 2016). Additionally, this age range coincides with the typical age of menarche in the Sakha Republic, Russia (Kucher et al., 2006). Thus, it is possible that puberty may represent a critical period for plasticity in BAT activity among Yakut people.

Surprisingly, the average temperatures of the first few years of life were not significantly correlated with BAT activity in adulthood. One possible explanation is that there may not be much variation in cold exposure across Yakut infants because they are largely buffered from cold stress through bundling. Comparative ethnographic evidence suggests that in colder climates, infant carrying and bundling patterns play a critical role in protecting vulnerable infants from cold stress (Leonard et al. 2009). In the high Peruvian Andes, for example, Tronick and colleagues (1994) showed that the traditional ‘manta’ carrying pouch used by Quechua mothers allowed for their infants to remain in a consistent ‘thermoneutral’ environment. In Finland, it is common for parents to set napping infants outside in a stroller during the winter months (Tourula et al., 2007). The practice is typically initiated when the infant is about two weeks old and is stopped at around one or two years old. Parents in Finland keep their napping infant outside when the temperature is anywhere from 5°C to -27°C and report that infants sleep for a longer period of time when outside in the cold (Tourula et al., 2007). Thus, developmental plasticity and the length of critical windows may be shaped by local infant-care practices and cultural contexts.

An examination of the standardized beta coefficients in Table 8.5 suggests that low temperature conditions around puberty have important consequences for BAT activity later life. The standardized beta coefficient for the thirteenth year of life was larger than the effect size of earlier years. This is interesting given that developmental plasticity is hypothesized to be more sensitive during the first few years of life compared to later years of development. For example, previous work has hypothesized that offspring plasticity is only viable within the niche of maternal care and that critical windows will close around the time of weaning (Wells, 2014). This is because metabolic programming that integrates a longer time depth of information by including cues that convey the mother’s (and perhaps grandmother’s) experience are more likely to accurately predict future conditions (Kuzawa, 2005; Kuzawa and Quinn, 2009; Wells, 2014).

While it is likely that human phenotypes are sensitive to maternal biological signals passed during pregnancy and lactation, human development is also likely sensitive to environmental cues that are separate from maternal biology. For example, the hygiene hypothesis proposes that exposure to environmental microbes may shape the development of the immune system (Yazdanbakhsh et al., 2002). Belsky and colleagues (2007) hypothesize that childhood psychosocial stress programs stress reactivity in adulthood. Substantial evidence suggests that the process of developmental adaptation to hypoxia continues into adolescence in populations living at high altitude (Frisancho, 1977, 2009; Greska, 1990). The results of this study demonstrate that developmental adaptation to cold stress may be added to this list.

There are several reasons to hypothesize why critical periods may extend past infancy and even childhood. First, by continuing to integrate environmental cues into the developing phenotype, the organism will decrease the chances that the adult phenotype will be poorly suited for future environmental conditions. This is especially the case when the predictive accuracy of each cue is only moderately high (Panchanathan and Frankenhuis, 2016). The predictive accuracy of ambient temperature will depend on the degree of variability. At high latitudes, ambient temperature varies widely, thus indigenous circumpolar populations like the Yakut may be more likely to exhibit extended critical periods in response to cold stress.

The adult phenotype may be sensitive to cues conveyed during childhood and adolescence, not because they necessarily improve fitness, but because of biological constraints within the developing system. Each stage of development represents a shift in energy allocation across biological systems (see Figure 8.1). It is possible that environmental inputs may alter the hormonal pathways that are responsible for changes is energy allocation across developmental stages without incurring an improvement in fitness.

It appears that the critical period for plasticity in BAT thermogenesis extends across a period of time when BAT first decreases and then increases in mass. Future work should investigate whether environmental inputs across this time range shape the rate at which BAT volume changes across development and the consequences for adult BAT activity and energy balance.

Currently, heat production is the only known function of human BAT; however, the fact that BAT mass may track changes in skeletal muscle and bone density and increases during puberty highlights the need for additional investigations into the function (or lack of function) of this tissue in humans. As described in Chapter 5, evidence indicates that the tissue-specific metabolic rate of BAT in humans may represent a minimal contribution to whole-body energy expenditure during cooling (Muzik et al., 2013; Din et al., 2016); however, BAT thermogenesis is correlated with changes in total energy expenditure during cooling (Chen et al., 2013; Muzik et al., 2017; van der Lans et al., 2013; van Marken Lichtenbelt et al., 2015; Yoneshiro et al., 2016). Additionally, the relationship between cold exposure early in life and adult BAT activity does suggest that BAT metabolism is somehow mechanistically tied to the metabolic pathways involved in non-shivering thermogenesis.

Hormonal regulation of BAT in humans is not well understood (Ramage et al., 2016); however, it is possible hormones responsible for puberty upregulate BAT mass. For example, estradiol activates BAT thermogenesis in mice (de Morentin et al., 2014). Caution must be applied when extrapolating metabolic patterns found in rodents to humans given the extreme differences in size, thermoregulatory demands, and energetic pathways. For instance, glucocorticoids are found to stimulate thermogenesis in human brown adipocytes, while it downregulates activity in BAT of mice (Ramage et al., 2016).

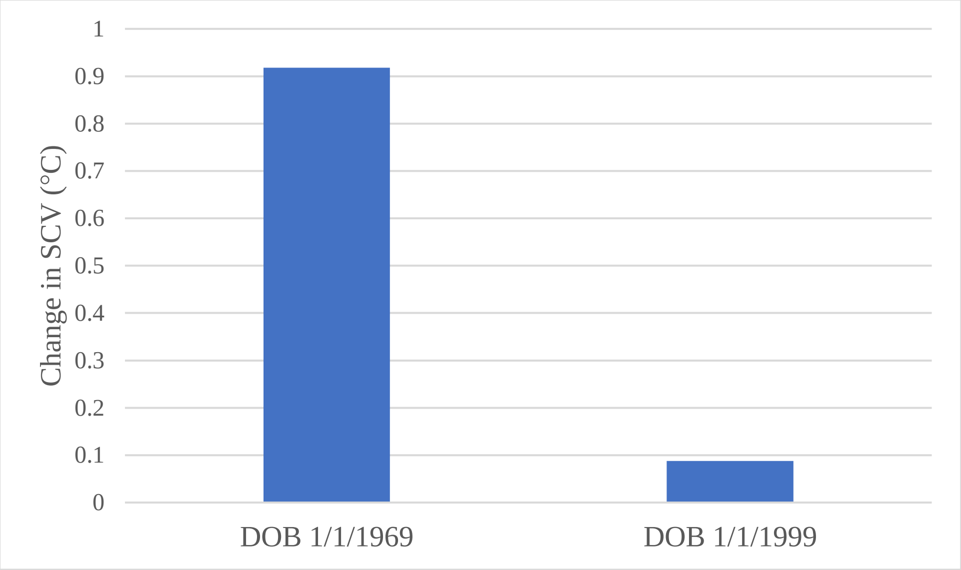
Nevertheless, the dynamics of thyroid hormone, which upregulates BAT metabolism in rodents (Cannon and Nedergaard, 2004), likely triggers thermogenesis in human BAT and may change during puberty, sometimes referred to as thyroidarche (Michaud et al., 1993). Michaud et al. (1993) measured thyroid stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3), and reverse T3 (rT3) in children and adolescents. The authors report an increase in TSH before puberty and an increase in T3 and T4 during puberty (Michaud et al., 1993). Changes in rT3 suggest that these developmental shifts are due to an increase in the conversion of fT4 to fT3 by peripheral tissues (Michaud et al., 1993). Some studies report a similar pattern (Lem et al., 2012; Marwaha et a., 2012; Para et al., 1980), while other studies fail to report significant changes in thyroid hormones during puberty (Chaler et al., 2012; Elmlinger et al., 2001; Nelson et al., 1993; Radicioni et al., 2013).

Understanding the timing and duration of critical periods will not only shed light on the development of energy budgets but also the creation of effective disease prevention strategies and health interventions. Public health has emphasized the crucial nature of the first 1000 days of life for shaping adult phenotypes (Save the Children, 2012). While many environmental inputs appear to have dramatic effects during this stage, the duration of critical periods may vary across stressors. Future research should explore the determinants of critical periods and how they vary between environmental inputs and across individuals or populations.

The results of this study highlight a new pathway through which lifestyle and environmental conditions may interact to shape energy budgets. Subjects that spent more time playing and walking outdoors in childhood exhibited greater BAT thermogenesis as adults. Thus, shifts in the lifestyle of children that lead to more time spent indoors may have consequences for energy expenditure and balance later in life. Additionally, Figure 8.2 demonstrates that while the weather in Yakutsk fluctuates from year-to-year, the climate is clearly warming – likely due to global climate change. The primary ecological consequences of global climate change in this region include flooding, shifts in the distribution of wildlife, and degradation of the permafrost (Hinzman et al., 2005; Nelson et al., 2002). Degraded permafrost inhibits naturally growing hay fields that Yakut people rely on for feeding livestock (Crate, 2006). Thus, climate change patterns may indirectly influence energy expenditure and energy balance of Yakut people by prompting economic decisions and lifestyle choices.

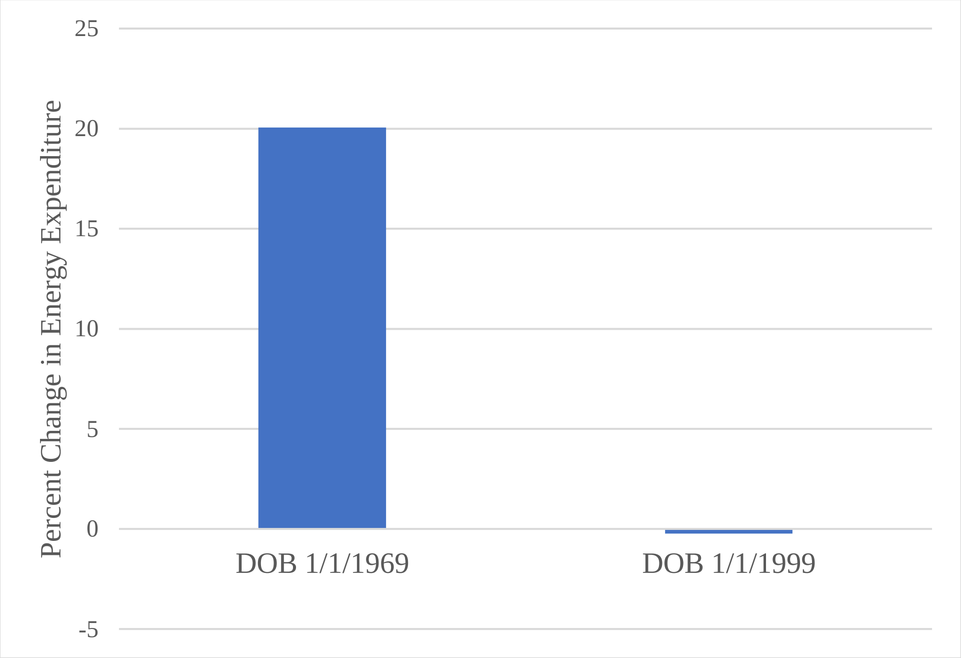
The results indicate that plasticity in human BAT is sensitive to ambient temperature. This raises the following question: does global climate change have a direct effect on the biology of circumpolar populations? Using the results of the multiple regression analysis presented in Table 8.5 and the ambient temperature data presented in Figure 8.2, I calculated the predicted BAT thermogenesis of two women with the same age (26 years), fat-free mass (41.755 kg), percent body fat (32.234%), change in sternum temperature (-0.593°C), and trial start time – one born on January 1, 1969 and one born January 1, 1999 (see Figure 8.7). The parameters were chosen based on the average values for women in the sample. Based on differences in average temperature of the 1st – 17th year of life, the woman born on January 1, 1969 is predicted to exhibit a change in SCV of 0.918°C, while the woman born on January 1, 1999 is predicted to exhibit a change in SCV of only 0.088°C. Using the results of the multiple regression presented in Table 8.3 and the same parameters, a change is SCV of 0.918°C is predicted to correspond to an increase in energy expenditure of about 20% during cooling, while a change of 0.088°C would result in little to no change in energy expenditure (see Figure 8.8). While this exercise is purely hypothetical, it highlights the possibility that climate change may influence the cardiometabolic health of circumpolar populations via indirect and direct pathways.

Figure 8.8 Estimated change in supraclavicular skin temperature of two women[a] born in Yakutsk after 30 minutes of cooling – one born on January 1, 1969 and one born on January 1, 1999.



[a]Predictions were based on two 26-year-old women (F=2) with a fat-free mass of 41.755 kg, percent body fat of 32.234%, change in sternum temperature of -0.593°C, and a numerical trial start time of 0.458.

Figure 8.9 Estimated percent change in energy expenditure of two women[a] born in Yakutsk after 30 minutes of cooling – one born on January 1, 1969 and one born on January 1, 1999.



[a]Predictions were based on two 26-year-old women (F=2) with a fat-free mass of 41.755 kg, percent body fat of 32.234%, change in sternum temperature of -0.593°C, and a numerical trial start time of 0.458.

Limitations

There are several critical limitations to this study. First, infrared thermal imaging was used to quantify BAT thermogenesis, which is an indirect measure and is sensitive to differences in vasoconstriction and adiposity. Second, the sample size was relatively small and this restricted the ability to run sex-specific analyses. The Childhood Outdoor Activities Survey is limited by participants' ability to recall their past participation in various activities. Finally, the historical weather data was collected at the meteorological station in Yakutsk. Many of the participants grew up in villages outside of the capital and may have experienced annual temperatures that differed from those in Yakutsk.

Summary

This chapter examined the relationship between early life cold exposure and BAT thermogenesis among a sample of Yakut adults. The study presented the first evidence of developmental plasticity in BAT in reaction to low temperatures during developmental stages. In particular, the data indicated that mid-childhood and puberty may act as critical periods for shaping adult BAT thermogenesis. Furthermore, cold exposure during adolescence accounted for a significant portion of the variation in BAT activity among Yakut adults. Environmental signals experienced during adolescence may program adult BAT function and thus improve the adaptive fit between adult phenotypes and environmental conditions. Alternatively, this pattern may be rooted in biological constraint linked to hormonal changes during puberty and their effect on BAT function.

For circumpolar populations like the Yakut, developmental plasticity in BAT thermogenesis represents an important pathway linking lifestyle and cardiometabolic disease risk. Yakut adults that spent more time playing and walking outside during the winter as children grew up to have greater BAT activity. Childhood experience will, therefore, shape adult energy expenditure and cardio-metabolic disease risk via its effects on BAT.

This chapter also presents evidence that the local effects of global climate change may influence developmental plasticity in BAT among circumpolar populations via direct and indirect pathways. The local ecological consequences of global climate change may affect Yakut people’s lifestyle choices due to the consequences for subsistence activities like raising cattle. Shifts in subsistence practices would likely have important implications for cold exposure and BAT plasticity. Additionally, developmental plasticity in BAT appears to be sensitive to warming temperatures. Warmer weather may directly alter BAT development over the life course with important implications for adult energy balance.

CHAPTER 9

CONCLUSION

The goal of the thesis was to explore how the environment shapes energy expenditure by investigating multiple timescales of adaptation to cold stress among the Yakut of northeastern Siberia. As rates of cardio-metabolic disease increase among indigenous circumpolar populations and across the globe, understanding the determinants of energy expenditure and energy balance is an ever-more pressing issue. Recent research questions the accuracy of simple estimations of energy expenditure based on just age, sex, body size and composition (Johnstone et al., 2005; Leonard et al., 2002; Ocobock, 2014, 2016a, b). Rather, energy expenditure is the result of a complex amalgamation of genetic factors and changes in gene expression, hormonal signaling, and cellular metabolism in response to shifts in diet, physical activity, and environmental conditions that occur over a wide range of timescales. In an attempt to tease apart how the environment becomes embodied in human energy budgets, this thesis uses the timescales of adaptation model as a framework for examining how energy expenditure responds to environmental change on a brief transient time period, a seasonal timescale, and over multiple years of development. This project adds to the growing body of research that emphasizes that ecological conditions, such as exposure to low temperatures, not only play an important role in shaping energy budgets, but they are also intrinsically linked to local social, cultural, political, and economic contexts. The pathways through which ecological stressors alter energy budgets must, therefore, be considered within this complex web of environmental factors.

Synthesis of Main Findings

Integrating Evolutionary and Biocultural Approaches

This dissertation research builds on recent work that integrates evolutionary and biocultural approaches to biological anthropology research. The results of this work highlight several pathways through which the local political-economic context structures the process of biological adaptation to environmental stressors. The unique political and economic shifts that have occurred in the Sakha Republic since the collapse of the Soviet Union have resulted in an economic pattern, termed lifestyle heterogeneity, that is characterized by a diversity of lifeways within Yakut communities, a single household, or even an individual (Snodgrass, 2004). This system blends a reciprocal kin-based subsistence system, characteristics of Soviet collectivization, and recent privatization initiatives (Takakura, 2015). Additionally, lifestyle heterogeneity is also a result of the extreme seasonality in the region and the specific ecological characteristics of subsistence activities like cattle and horse husbandry (Takakura, 2015). This system has allowed the Yakut to maintain their cultural networks while adapting to privatization initiatives under the Russian government (Takakura, 2015: 166-202).

This project hypothesized that lifestyle heterogeneity would interact with and structure the process of biological adaptation to cold stress such that Yakut people would vary in their degree of metabolic adaptation to cold depending on their lifestyle characteristics, such as subsistence activity participation. The results of Chapter 7 suggest that lifestyle factors may play a role in mediating seasonal thyroid responses, particularly among men. Men pursuing a more traditional lifestyle experienced more dramatic seasonal shifts in thyroid hormone dynamics.

Additionally, the results of Chapter 8 indicate that Yakut children that spend more time outside exhibit greater BAT thermogenesis in adulthood.

Social, cultural, and economic factors structure the amount of time Yakut people spend exposed to cold stress and the severity of the exposure. These factors range from an individual's dietary preferences, occupation(s), and income, to household characteristics like kin networks, to community-level economic policies, and country-wide trends in market integration and economic development. The timescales of adaptation model purports that variation in the timing and length of cold exposure will govern the process of adaptation. Based on the results of this research, I argue that investigating biological adaptation to cold stress is a useful approach to studying how political-economic contexts interact with and alter the process of adaptation and shape phenotypic variation. Future work should continue to integrate biocultural approaches when studying the process of biological adaptation. For example, what state or community-level policies promote or inhibit lifestyle heterogeneity and what are the implications for metabolism and cardiometabolic health?

Social, cultural, and economic factors also shape other components of the energy budget, such as diet and physical activity. Research in animal models indicates that diet and exercise likely alter the hormonal pathways that regulate BAT metabolism. Future research should investigate how dietary characteristics and physical activity may interact with metabolic adaptation to cold stress and alter energy budgets.

Not only do the results of this dissertation highlight new pathways through which lifestyle and environmental conditions may interact to shape energy budgets, they also have important implications regarding the consequence of global climate change for health among circumpolar populations. The primary ecological consequences of global climate change in the Sakha Republic include flooding, shifts in the distribution of wildlife, and degradation of the permafrost (Hinzman et al., 2005; Nelson et al., 2002). Climate change patterns may indirectly influence energy expenditure and energy balance of Yakut people by prompting economic decisions and lifestyle choices. Additionally, given that the results suggest that developmental plasticity in BAT may be sensitive to ambient temperature, local climate change may have direct effects on the biology and health of Yakut people.

The inability to carry out subsistence practices, damage to infrastructure, and the spread of zoonotic diseases like West Nile are likely to have more dramatic effects on the health of circumpolar populations than small declines BAT thermogenesis and total energy expenditure (United Nations, 2008). This research, however, calls attention to a pathway through which the local effects of global climate change may act synergistically with political-economic processes, such as globalization and market integration, that underlie the growing rates of cardiometabolic disease in subarctic regions and globally. In other words, the economic changes that have led to the production, distribution, and consumption of processed foods and the adoption of sedentary lifestyles, which are at the root of the obesity epidemic, also contribute to the production of greenhouse gasses and global climate change, thus resulting in a feedback loop on growing rates of obesity.

The Adaptive Significance of BAT

This dissertation strives to shed light on the significance of adult BAT for adaptation to cold stress. The results of Chapter 6 indicate that BAT thermogenesis is correlated with percent change in energy expenditure, suggesting that BAT may play a role in non-shivering thermogenesis (NST). This relationship has been replicated by multiple studies (Blondin et al., 2015; van der Lans et al., 2015; van Marken Lichtenbelt et al., 2015; Yoneshiro et al., 2011a); however, the exact physiological mechanisms that link BAT metabolism and whole-body energy expenditure during NST remain unclear. Increases in resting metabolic rate (RMR) during NST were as high as 70 % in this study; yet paradoxically, recent estimates of the tissue-specific metabolic rate of supraclavicular BAT deposits are only about ~20 kcal/day.

There are several possible explanations for this discrepancy. First, supraclavicular BAT may act as biomarker for BAT metabolism in other parts of the body, such as deposits around the heart, esophagus, kidneys, pancreas, liver, spleen, and beige adipocytes scattered within white adipose tissue (WAT) in the greater omentum and mesocolon (Sacks and Symonds, 2013). The contribution of these various BAT deposits to total energy expenditure is currently unknown.

Second, BAT thermogenesis may act as a passive, indirect biomarker for increases in metabolism in deep skeletal muscles and internal organs, such as the liver and heart, during NST. It is possible that the same hormonal mechanisms, such as norepinephrine and thyroid hormone, upregulate these other tissues during acute and chronic cold stress. The contribution of these other tissues to NST may be overlooked by recent [18F]FDG PET/CT scan studies if their primary fuel source during NST are lipids rather than glucose. Deep muscles, such as the levator scapulae and lungus colli, appear to increase their metabolic rate during NST (Din et al. 2016; Ouellet et al. 2012). Din et al. (2016) estimated that muscle of the cervico-thoracic region contributes about 86 kcal/day during cold exposure. Few studies, however, have attempted to quantify possible changes in metabolic rate during NST of the internal organs.

Finally, it is possible that BAT may be a more active biomarker for increases in metabolism of other tissues during NST via its role as an endocrine or paracrine organ. It is interesting that BAT co-locates with the deep skeletal muscles and internal organs that may contribute to increases in total energy expenditure during NST (Leitner et al., 2017). Research in animal models indicates that BAT releases several "batokines" into circulation with important implications for the metabolism of other tissues. For instance, fibroblast growth factor 21 (FGF21) produced by BAT can induce the conversion of white adipocytes to beige adipocytes and can stimulate metabolic processes associated with thermogenesis (Villarroya et al., 2016). FGF21 along with IL-6 produced in BAT can improve insulin secretion and beta-cell function in the pancreas and increase cardiac substrate oxidation (Villarroya et al. 2016). Additionally, brown adipocytes convert free thyroxine (fT4) into free triiodothyronine (fT3), the metabolically active form of thyroid hormone, through the expression and action of the enzyme type II deiodinase (DIO2). In mice, fT3 generated in BAT is released into circulation (Fernandez et al., 1987). While around 80% of fT3 in humans is generated in the periphery rather than by the thyroid gland, the exact pathways for fT3 production are still unknown (Bianco and Kim, 2013; Schimmel and Utiger, 1977).

In order to better understand the adaptive significance of BAT in humans, future research should quantify and compare the contribution of skeletal muscle and internal organs to elevations in metabolic rate during NST of adults with and without active BAT deposits. Additionally, continuing to characterize population variation in BAT thermogenesis will shed light on its adaptive significance.

The Health Significance of BAT

Strong claims have been made regarding the importance of BAT metabolism for preventing cardiometabolic disease risk (Iyengar and Scherer, 2016; Schrauwen and van Marken Lichtenbelt, 2017). Upon the discovery that adult humans have metabolically active BAT deposits, many researchers hypothesized that adults with greater BAT mass were likely to be protected against obesity due to greater total energy expenditure (van Marken Lichtenbelt and Schrauwen, 2011). The relationship between BAT mass and body composition, however, appears to be more complicated than initially hypothesized. Many studies fail to detect a relationship between BAT mass and body composition (Bahler et al., 2015; Franssens et al., 2017; Lee et al., 2012; Yoneshiro et al., 2011b, 2012), while others do report an inverse association between BAT mass and adiposity, especially those that recruited elderly participants (Hanssens et al., 2015; Saito et al., 2009; Yoneshiro et al., 2011a).

The results of Chapter 6 revealed a significant positive association between BAT thermogenesis and percent body fat after controlling for age, sex, and fat-free mass. The statistical significance disappeared after adding trail start time and change in temperature of the sternum as possible confounding variables to the multivariate regression. It is possible that a higher percent body fat may signal that there is greater energy available for BAT thermogenesis. At higher levels of adiposity or at older ages, hormonal signaling between white and brown fat deposits may change, leading to a shift in the direction of the relationship between body fatness and BAT mass (Yoneshiro et al., 2011a). In other words, the aging process may alter the relationship between BAT and adiposity (Berry et al., 2016). The mixed results across studies point to limitations tied to parsing out causality between BAT metabolism, energy balance and body fatness using observational studies.

Data presented in Chapter 6 also revealed that fasting blood glucose levels were positively associated with BAT thermogenesis independent of age, sex, body composition, trial start time and change in sternum temperature. The results also document a significant positive association between BAT thermogenesis and change in RQ, thus suggesting that participants with greater BAT activity preferentially metabolize carbohydrates during cold exposure. These results suggest that circulating glucose may act as an important fuel source for BAT thermogenesis, and higher blood glucose levels may connote that there is more energy available for BAT metabolism. Previous studies found that participants with greater BAT volume exhibit greater insulin sensitivity, lower fasting insulin (Zhang et al., 2013) and lower HB1ac levels (Matsushita et al., 2014).

Van Marken Lichtenbelt and colleagues (2014) propose that, in response to growing rates of cardio-metabolic disease risk globally, repeated exposure to mild cold may provide a healthy and sustainable alternative to increasing energy expenditure. Further investigations of the determinants of variation in energy expenditure during cold stress are critical for uncovering and preventing the pathways that lead to cardio-metabolic disease; however, based on the results of this dissertation contextualized within past work, I would exercise caution when recommending cold exposure as a weight-loss strategy. Changes in energy expenditure during mild cold exposure are highly variable, with a considerable portion of adults experiencing a decline in total energy expenditure. Future work should focus on exploring the determinants of variation in NST and uncovering the metabolic contribution BAT, skeletal muscle and other organs to total energy expenditure during cold stress.

The Timescales of Adaptation to Cold Stress

This dissertation conceptualizes adaptation as a dynamic process in which a suite of physiological and morphological changes are integrated across development. The results of this dissertation support the conclusion that the process of adaptation to cold stress includes a collection of changes in hormones such as thyroid hormones, BAT activity and the metabolism of other tissues, each of which vary in their timing across a range of timescales of cold exposure. On the shortest timescale, acute fluctuations in norepinephrine from the sympathetic nervous system trigger changes in metabolism of BAT and other tissues and stimulate NST. Seasonal cold acclimatization is facilitated by changes in thyroid hormone dynamics. Future research should investigate the role of BAT in seasonal acclimatization among indigenous circumpolar populations. Cold exposure during early developmental stages appears to have lasting consequences for BAT thermogenesis in adulthood. Additional research is needed in order to parse out the physiological mechanisms that facilitate developmental adaptation to cold stress.

The results discussed in Chapter 8 highlight the importance of childhood and adolescence as possible critical periods. The relative amount of energy allocated toward competing biological processes is not constant across human development. Thus, each life stage involves a transition in energy allocation and different biological systems develop and mature at different rates. The results in Chapter 8 suggest that circumpolar populations may integrate information from the environment, such low temperature exposure, across the life course, and this may result in critical periods extending into childhood and adolescence. Critical windows that extend into childhood and adolescence may represent a strategy for better calibrating energy allocation for future life stages. Based on the data presented in this dissertation, I argue that researchers investigating adaptive plasticity should consider both the timing of the stressor exposure and the developmental timing of sensitive biological systems. Additionally, future research should consider the relationship between the various timescales of adaptation in order to explore whether phenotypic plasticity facilitates genetic adaptation as predicted by the phenotype-first evolution hypothesis (Kuzawa and Bragg, 2012; West-Eberhard, 2003).

Concluding Remarks

The data presented in this thesis demonstrates that the pathways through which the environment alters energy budgets will depend on the timescale of the environmental change and the social, cultural, and economic factors that structure stressor exposure. Variation in cold exposure and adult BAT appears to have important consequences for energy balance and cardiometabolic health. Energy balance and cardio-metabolic disease risk fluctuates seasonally due to the interaction of seasonal changes in lifestyle, diet and ecological conditions. Exposure to cold stress during development has energetic and health consequences for adults living in circumpolar regions. Ongoing changes in the economic, lifestyle and ecological conditions in the Sakha Republic will have important implications for energy balance and cardiometabolic disease risk for Yakut people.

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