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ORIGINAL RESEARCH ARTICLE

Brown adipose tissue, energy expenditure, and biomarkers of cardio-metabolic health among the Yakut (Sakha) of northeastern Siberia

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Abstract

Objectives: This study provides the first investigation of non-shivering thermogenesis (NST) and brown adipose tissue (BAT) activity among an indigenous circumpolar population, the Yakut of northeastern Siberia. The study also examines the health significance of BAT activity in this population by testing the relationships between BAT thermogenesis and biomarkers of cardio-metabolic disease risk, such as percent body fat and blood glucose and cholesterol levels.

Methods: Data were collected in the Sakha Republic (Yakutia) for 31 men and 43 women. Change in energy expenditure and BAT thermogenesis were quantified after a 30-minute mild cooling condition. Anthropometric dimensions, blood glucose, and lipid levels were also collected.

Results: On average, the skin temperature of the supraclavicular area was constant after cooling while the skin temperature of a point on the sternum dropped significantly ($P < .001$), thus suggesting the presence of active supraclavicular BAT among Yakut adults. Participants with evidence of greater BAT thermogenesis exhibited a larger percent change in energy expenditure (% ΔEE) and an increase in respiratory quotient (RQ) after cooling ($P \leq .05$). While there was no relationship between BAT activity and blood lipid levels, BAT thermogenesis was positively associated with blood glucose levels ($P < .01$).

Conclusions: Yakut adults exhibit evidence of active BAT deposits. Given that there is a significant relationship between BAT activity and % ΔEE, it is possible that BAT plays a role in NST among Yakut adults. While the relationship between BAT and body composition is inconclusive, participants with greater BAT seemed to preferentially utilize glucose during cold stress exposure.

1 | INTRODUCTION

Dating back to D.F. Roberts' (1952) seminal research, 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 (Froehle, 2008; Galloway, Leonard, & Ivakine, 2000; Itoh, 1980; Leonard et al., 2002; Leonard, Galloway, Ivakine, Osipova, & Kazakovtseva, 1999; Roberts, 1952, 1978; Rode & Shephard, 1995; Snodgrass, Leonard, Tarskaia, Alekseev, & Krivoshapkin, 2005), as well as shivering and non-shivering thermogenesis (NST) during acute cold exposure (van Marken Lichtenbelt & Schrauwen, 2011). Variation in NST among indigenous circumpolar populations, surprisingly, has yet to be described. This is likely in part due to the absence of a standardized protocol for quantifying NST that is appropriate for a wide variety of populations and study settings. Furthermore, the physiological mechanisms underlying NST are widely debated (Janský, 1973; Kosaka, 1930; van den Berg, van Marken Lichtenbelt, van Dijk, & Schrauwen, 2011; Wijers, Schrauwen, Saris, & van Marken Lichtenbelt, 2008).

Initially, the liver, heart, thymus, and lungs were considered to be the main sources of NST due to an increase in vascularization of these tissues during cold exposure (Janský, 1973; Kosaka, 1930). Skeletal muscle may contribute to NST by increasing mitochondrial uncoupling through the expression of uncoupling protein 3 (UCP3) (van den Berg et al., 2011; Wijers et al., 2008). More recent work hypothesizes that brown adipose tissue (BAT) may also play a role in adult human NST (Enerback, 2010).

BAT has long been recognized as the primary source of NST for human infants (Lean, James, Jennings, & Trayhurn, 1986). When an infant is exposed to low temperatures, norepinephrine triggers brown adipocytes to produce heat via the action of mitochondrial uncoupling protein 1 (UCP1) (Lowell & Spiegelman, 2000). Infant BAT deposits located in the neck and back begin to decline after the first few weeks of life (Symonds, Pope, & Budge, 2015).

Beige fat, also known as brite fat, consists of adipocytes that are similar to brown adipocytes in phenotype but are found interspersed in white adipose tissue (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, Hansen, Timmons, Cannon, & Nedergaard, 2012), although it may be possible to derive beige cells from muscle progenitors as well (Long et al., 2014). Recent work suggests that many adults have a combination of classic brown and beige adipocytes, and additional research is needed to parse out the contribution of beige and brown fat to adult variation in adipose tissue; therefore, for the sake of simplicity, this article refers to all adipose tissue with UCP1-mediated thermogenesis as BAT regardless of the beige or brown distinction.

While some adults completely lack BAT, others retain over 100 g of this tissue, primarily above the clavicle. Adult human BAT can also be found around the heart, esophagus, kidneys, pancreas, liver, spleen, and scattered within white fat deposits (Sacks & Symonds, 2013). Adults with active BAT depots exhibit significantly greater increases in energy expenditure during cold exposure than adults without BAT, suggesting that this tissue plays a mechanistic role in NST (Symonds et al., 2015; van der Lans et al., 2015; Yoneshiro, Aita, Matsushita, Kameya, et al., 2011).

Variation in NST and BAT activity may have important implications for cardio-metabolic disease risk by increasing energy expenditure (EE), limiting the accumulation of WAT, or by altering blood glucose and cholesterol levels. Some individuals experience an increase in EE of 30% or more during cold-induced NST, while others experience a decline in overall EE (Blondin et al., 2014; Celi et al., 2010; van der Lans et al., 2015; van Marken Lichtenbelt, Schrauwen, van de Kerckhove, & Westerterp-Plantenga, 2002; Yoneshiro et al., 2013). There are two possible explanations for why EE may decline in response to mild cooling. First, whole-body EE may decline during mild cold stress when vasoconstriction and cooling of the periphery leads to a reduction in the rate of reactions within the peripheral tissues (ie, the Q10 effect). If the resultant decline in metabolic rate of the periphery outweighs the increase in metabolism at the core, then there is a net decline in EE (Barany, 1967; Bennett, 1985; Wakabayashi, Nishimura, Wijayanto, Watanuki, & Tochihara, 2017). Alternatively, mild cooling may elicit a habituation response in some individuals, characterized by blunted vasoconstriction and a blunted metabolic response (Mäkinen et al., 2004; Young, 1996). Adults with greater BAT thermogenesis are less likely to experience an overall decline in EE (Blondin et al., 2014; van der Lans et al., 2015; van der Lans, Vosselman, Hanssen, Brans, & van Marken Lichtenbelt, 2016).

Recent research reports that the change in skin temperature of the supraclavicular area (ΔSCV) after a cooling condition can act as an indirect biomarker of BAT thermogenesis (Boon et al., 2014; Chondronikola et al., 2016; Salem et al., 2015; van der Lans et al., 2015; Yoneshiro et al., 2016). In response to cold stress, BAT deposits within the neck are activated by norepinephrine, which warms the skin above the clavicle. Adults with active supraclavicular BAT exhibit either a minimal decline or an increase in skin temperature—ranging between −0.9°C and + 0.3°C—depending on the time length and severity of cooling condition (Boon et al., 2014; Chondronikola et al., 2016; Salem et al., 2015; van der Lans et al., 2015; Yoneshiro et al., 2016). In comparison, adults without detectable supraclavicular BAT experience a decline in skin temperature of around −1.5°C in this area (Chondronikola et al., 2016; Yoneshiro et al., 2016).

Currently, population variation in BAT is poorly characterized. 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 the functional and health significance of BAT in an indigenous circumpolar group. We hypothesize that Yakut adults with a greater ΔSCV will expend more energy during a cooling condition. This would suggest that BAT thermogenesis plays a role in NST. Additionally, we predict that Yakut adults with greater ΔSCV will exhibit healthier biomarkers of cardio-metabolic disease risk.

2 | METHODS

2.1 | Study population

The Sakha Republic, also known as Yakutia, is a semiautonomous state within the Russian Federation, located in northeastern Siberia. The Sakha Republic has a population of over 958 000 people and is home to the coldest human inhabited places on Earth (Crate, 2006). Temperatures can range from −40°C (−40°F) in the winter to 25°C (77°F) in the summer. A majority of the population of the Sakha Republic is Yakut, an indigenous population of over 450 000 people (Численность и размещение населения, 2010).

Prior to Russian expansion in the 17th century, Yakut people in the Lena River Valley practiced a seminomadic transhumant pastoralism (Forsyth, 1992). In the 1930's, the Soviet Union organized Yakut families into herding and farming collectives (Forsyth, 1992). By the mid-1980s, nearly all residents of Yakutia were either employed by the state or dependent upon government welfare (Slezkine, 1994). Soviet collectivization led to a loss of economic self-sufficiency, a decline in subsistence participation, increased alcoholism, isolation, and psychological stress, demographic decline, and deterioration of the healthcare infrastructure (Pika, 1999). The collapse of the Soviet Union dramatically altered the lives of rural Siberians, many of whom depended on the government for wages and essential goods (Fondahl, 1998). Thus, Yakut villagers faced a variety of both challenges and opportunities related to defining new subsistence strategies (Crate, 2006).

Some households have chosen to adopt a lifestyle that relies heavily on subsistence strategies (Takakura, 2015). However, not everyone wished to return to subsistence lifestyles practiced prior to the Soviet era or had the appropriate knowledge (Jordan & Jordan-Bychkov, 2001; Snodgrass, 2004). Today, however, most Yakut people depend on a mixed cash economy that consists of a combination of subsistence practices and cash inputs (Crate, 2006). 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). The degree of participation in these activities ranges across a wide spectrum and often shifts with the season.

2.2 | Participants

Data collection took place in two locations. First, data were collected in the village of Berdygestiakh, Gorny District, Sakha Republic (Yakutia), Russia at the Gorny Regional Medical Center from September 5 to 11, 2015. Berdygestiakh has a population of around 6400 and is located 180 km (111 miles) west of the capital city, Yakutsk (Russian Census, 2010). Data were also collected in the city of Yakutsk, Sakha Republic (Yakutia), Russia at the Research Institute of Health and the Medical Clinic at M.K. Ammasov North-Eastern Federal University (NEFU). Yakutsk has a population of 269 600 people. The study was advertised in the local newspaper, local radio station, and via word of mouth, and the study setting and timeline prevented recruiting a random sample. Potential participants were told to arrive at either the Gorny Regional Medical Center or NEFU in the morning having fasted and refrained from smoking for 12 hour prior to arrival. Pregnant and lactating women were excluded and all participants were healthy at the time of data collection and had no known acute conditions. The sample included 31 men and 43 women that self-identified as Yakut. The Northwestern University Institutional Review Board granted permission to conduct this study (IRB 00200092).

2.3 | Anthropometry

Anthropometric dimensions were taken using standardized techniques (Frisancho, 2008; Lohman, Roche, & Martorell, 1988). Stature was measured to the nearest millimeter using a Seca portable field stadiometer. Triceps, biceps, subscapular, and suprailiac skinfold thicknesses were measured to the nearest 0.5 mm using Lange calipers. Body mass, percent body fat, and fat-free mass (FFM) were 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).

2.4 | Indirect calorimetry and thermal imaging

Resting metabolic rate (RMR; kcal/day), respiratory quotient ($RQ = VCO_2/VO_2$) 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 and RQ were measured using open circuit indirect calorimetry following a standard protocol outlined by Leonard (2012). RQ is the ratio of carbon dioxide production to oxygen consumption and is a proxy of the relative proportion of carbohydrate or fat that is being metabolized. An RQ that is close 1.0 indicates that carbohydrates are the primary substrate for metabolism, while an RQ value close to 0.70 connotes fat is the primary metabolic fuel source.

BAT heat production was estimated by infrared thermal imaging using a technique modified from Symonds et al. (2012). Participants wore a water-perfused suit (Allen-Vanguard, Ottawa, Ontario) 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 to track anxiety during metabolic measurements.

During the thermoneutral condition, participants rested quietly in a supine position. Measurements of oxygen consumption (VO_2, L/min.) and carbon dioxide production (VCO2, L/min.) were recorded using MedGraphics $VO_2$000 open-circuit metabolic analyzers (Medical Graphics UK Ltd., Gloucester, United Kingdom) interfaced with MedGraphics Breeze Lite software. RMR was calculated by converting VO_2 to kcal/day based on the respiratory quotient using the modified Weir (1949) formula (McArdle, Katch, & Katch, 2001). At the end of the 20-minute thermoneutral condition, thermal images were captured of the left and right sides of the neck using an infrared thermal imaging camera (E60bx, FLIR).

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 minute. 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 and 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 NST and minimize shivering. A total of 6 out of 74 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 at the end of the cooling condition.

The maximum skin temperature of the supraclavicular area of the thermoneutral and cold condition images were determined using FLIR Tools Software (FLIR) and used to calculate ΔSCV. Change in temperature of a point on the sternum (Δ sternum) was also calculated between the thermoneutral and cooling conditions as a point of comparison, as human BAT is not found on the sternum. 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 $\left[\%\Delta EE = \left(\frac{EE_c - EE_{TN}}{EE_{TN}}\right)*100\right]$.

2.5 | Analysis of blood biomarkers

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, Indiana). Low density lipoprotein (LDL) levels were calculated from total cholesterol, HDL, and triglycerides using the Friedwald, Levy, and Fredrickson (1972) equation. The CardioChek PA professional lipid and glucose testing system meets clinical guidelines for accuracy and precision.

2.6 | 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, College Station, TX, USA) and considered statistically significant at P-value ≤.05. Energy expenditure and thermal imaging data were collected for a total of 74 participants. Blood biomarkers of cardio-metabolic disease risk were determined for a subsample of 62 individuals.

A combination of unpaired Student's t-tests and two-sample Wilcoxon rank-sum tests were used to determine whether the group for which we gathered blood biomarker data was significantly different from the participants for which we did not collect blood samples. Unpaired Student's t-tests and two-sample Wilcoxon rank-sum tests were also used to determine if there were significant differences between Yakut men and women. Paired t-tests were used to determine if maximum supraclavicular temperature, sternum temperature, and metabolic parameters changed significantly between temperature conditions.

Stepwise multivariate analyses were used to examine the relationship between ΔSCV and anthropometric dimensions, age, gender, trial start time, and sternum temperature. Multivariate regression analyses were also used to test the relationship between ΔSCV and %ΔEE, change in RQ, and biomarkers of cardio-metabolic disease risk. Power analyses were conducted using the "powerreg" command in StataIC 13.0, and for the regressions listed above the statistical power ranged between 0.58 and 0.95.

3 | RESULTS

3.1 | Descriptive statistics for anthropometric dimensions, metabolism, and ΔSCV

Table 1 displays the mean age and anthropometric dimensions for the sample of Yakut men and women. The age range for men was 18–48 years old and the age range for women was 18–47 years old. As expected, Yakut men were significantly taller, heavier, and had greater FFM than Yakut women. While body mass index (BMI) did not differ between men and women, Yakut women had significantly greater percent body fat.

Tables 2 and 3 show the mean SCV temperature, sternum temperature, RMR, and RQ for 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. Men experienced a small but significant decline in RMR after cooling while women did not experience a significant change on average. The RQ of women increased significantly during cooling while men did not exhibit a significant change in RQ. Figure 1 displays the % ΔEE after cooling for Yakut men

TABLE 1 Anthropometric dimensions, age and change in maximum supraclavicular skin temperature for Yakut men and women

Measure	Men (n = 31) Mean ± SD	Women (n = 43) Mean ± SD	t-statistic/z-statistic
Age (years)[a]	28.8 ± 8.0	27.4 ± 8.7	−1.35
Height (cm)	171.7 ± 5.4	158.5 ± 5.3	10.50*
Weight (kg)	66.2 ± 11.1	54.4 ± 8.9	5.05*
BMI[a]	22.4 ± 3.6	21.6 ± 3.5	0.300
Percent body fat	21.4 ± 5.5	33.2 ± 4.6	−10.09*
Fat free mass (kg)[a]	55.8 ± 5.8	41.0 ± 5.4	7.11*

t-tests of gender differences are significant at: *$P \leq 0.001$.
[a] The variable is not normally distributed; therefore, P-value is derived from a two-sample Wilcoxon rank-sum (Mann–Whitney) test.

and women. The % ΔEE was not significantly different between genders. Similarly, the ΔSCV temperature and change in sternum temperature were not significantly different between men and women (see Figure 2).

Table 4 displays stepwise multivariate regression analyses assessing body composition and other variables as predictors of BAT thermogenesis (ΔSCV). In model 1, ΔSCV is regressed on age, gender, 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 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.

3.2 | ΔSCV and percent change in energy expenditure

Figure 3 is a scatter plot of ΔSCV after 30 minute of cooling and % ΔEE. The significant positive relationship ($R = 0.421$; $P < .05$) suggests that, as expected, individuals with greater ΔSCV (suggesting more BAT thermogenesis) exhibit a greater increase in energy expenditure after cooling. Removing the participant with an increase in energy expenditure of more than 50% did not significantly change the results ($R = 0.275$; $P < .05$); therefore, the participant was included in the analyses. In contrast, the change in skin temperature of the sternum, which lacks BAT, exhibits a weak negative relationship with percent change in energy expenditure ($R = -0.074$; see Figure 4).

Table 5 displays the relationship between percent change in energy expenditure and ΔSCV after controlling for potential confounding variables, including age, sex, time of data collection, and Δ sternum. There was a significant, positive association between % ΔEE and ΔSCV and a significant negative relationship between % ΔEE and change in sternum skin temperature.

3.3 | ΔSCV and change in respiratory quotient

Figure 5 is a scatterplot of the relationship between ΔSCV and change in RQ. Table 6 displays the results of the multivariate regression of ΔSCV, age, gender, FFM, percent body fat, time of data collection, and change Δ sternum on change in RQ. There is a significant positive relationship between ΔSCV and change in RQ. These data suggest that individuals with greater BAT thermogenesis may preferentially utilize carbohydrates as a metabolic substrate during NST.

3.4 | ΔSCV and biomarkers of cardio-metabolic health

Fasting cholesterol, triglyceride, and glucose levels were measured for a subsample of 62 participants (24 males; 38 females). Table 7 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

TABLE 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	t-statistic
SCV (°C)	36.629 ± 0.066	36.622 ± 0.074	0.434
Sternum (°C)	34.812 ± 0.129	34.239 ± 0.138	−6.96*
RMR (kcal/day)	1129 ± 31	1094 ± 43	−1.07
RQ	0.8 ± 0.010	0.84 ± 0.015	3.63*

Paired *t*-tests of differences between conditions are significant at: *$P \leq 0.001$.

TABLE 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	t-statistic
SCV (°C)	36.793 ± 0.068	36.782 ± 0.061	0.260
Sternum (°C)	34.773 ± 0.136	34.315 ± 0.126	−4.60*
RMR (kcal/day)	1575 ± 48	1528 ± 49	−1.84*
RQ	0.846 ± 0.015	0.86 ± 0.019	0.750

Paired *t*-tests of differences between conditions are significant at: *$P \leq 0.001$.

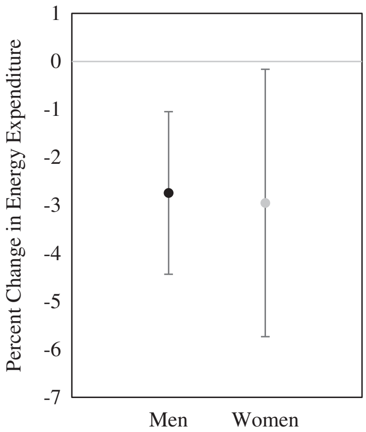

FIGURE 1 Percent change in energy expenditure after cooling for men (n = 31) and women (n = 43). The error bars denote standard error (SE) values

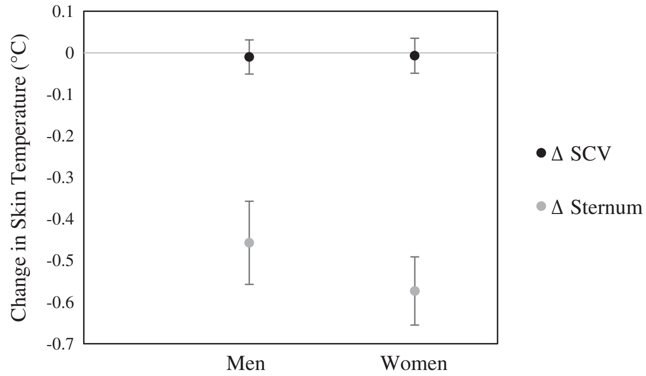

FIGURE 2 Change in supraclavicular and sternum skin temperature after cooling for Yakut men (n = 31) and women (n = 43). The error bars denote standard error (SE) values

subjects that were excluded from the blood tests. The following analyses were conducted using Sample A.

Table 8 presents the mean lipid and glucose levels for Yakut men and women in Sample A. Yakut women have significantly higher total cholesterol and 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., 2006).

Multiple regression analyses of blood biomarkers of cardio-metabolic health on ΔSCV are presented in Table 9. After controlling for age, gender, FFM, percent body fat, trial start time, and change in sternum temperature, 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).

4 | DISCUSSION

The present study investigated the relationships between a signal of BAT thermogenesis, whole-body energy expenditure, and biomarkers of cardio-metabolic health, such as body composition, blood lipid, and glucose levels. As 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. Additionally, 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 1. It reveals that, on average, the participants were relatively short and lean. 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 significant decrease in sternum temperature (men: –0.457°C ± 0.1 °C; women: –0.573°C ± 0.082°C). 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.

The mean ΔSCV values reported in this study are similar to the ΔSCV of adults with detectable BAT using positron

TABLE 4 Stepwise multivariate regression analyses of possible correlates of change in supraclavicular skin temperature after 30 minute of a cooling condition (n = 74)

	Model 1		**Model 2**		**Model 3**	
	Adj. R^2 = 0.013		**Adj. R^2 = 0.048**		**Adj. R^2 = 0.075**	
Measure	***β Coef.***	***P-values***	***β Coef.***	***P-values***	***β Coef.***	***P-values***
Age (years)	−0.008	.09	−0.009	.084	−0.008	.141
Gender	−0.164	.291	−0.159	.291	−0.136	.343
FFM (kg)	−0.0001	.991	0.001	.929	0.001	.881
% body fat	0.016	.047	0.016	.11	0.016	.127
Start time	---	---	−0.659	.104	−0.658	.104
ΔSternum (°C)	---	---	---	---	0.092	.06

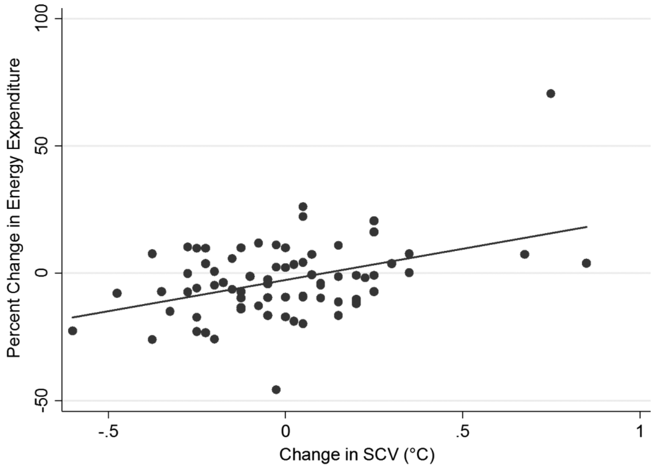

FIGURE 3 Scatterplot of the change in supraclavicular skin temperature and percent change in energy expenditure after 30 minute of cooling (n = 74). Pearson's correlation coefficient: R = 0.421

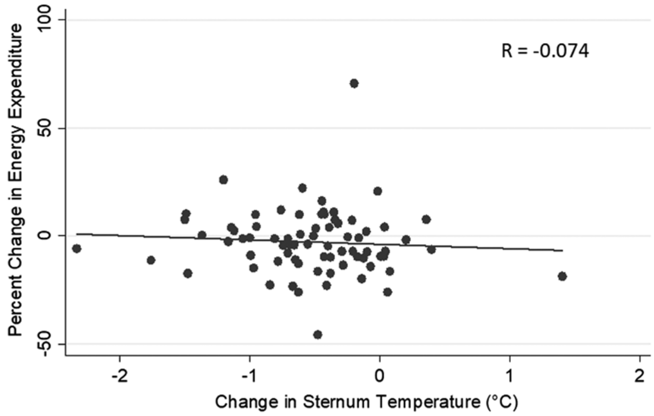

FIGURE 4 Scatterplot of the change in sternum skin temperature and percent change in energy expenditure after 30 minute of cooling (n = 74). Pearson's correlation coefficient: R = −0.074

emission tomography with computed tomography scans (PET-CT) (Chondronikola et al., 2016; Salem et al., 2015; van der Lans et al., 2016; Yoneshiro et al., 2016). The decline in sternum temperature, however, is smaller than previously reported values (Yoneshiro et al., 2016). Populations that are regularly exposed to chronic cold stress are able to maintain warmer skin temperatures by cycling between the vasoconstriction and vasodilation of peripheral blood vessels (Lee, Park, & Kim, 2017; Park et al., 1983). Thus, Yakut adults may exhibit warmer sternum temperatures due to greater vasodilation. Alternatively, greater whole-body energy expenditure among the Yakut may lead to warmer blood flow to the sternum; however, change in sternum temperature was negatively associated with percent change in energy expenditure (see model 1, Table 5).

Yakut men experienced a small but significant decline in RMR, while Yakut women did not experience a significant change (see Tables 2 and 3); however, percent change in energy expenditure was not significantly different between men and women (see Figure 1). In fact, percent change in energy expenditure was highly variable (minimum: −45.9%; maximum: +70.6%; standard deviation (SD): 15.12%). As discussed above, whole-body energy expenditure may decline during mild cooling due to the Q_{10} effect (Barany, 1967; Bennett, 1985; Wakabayashi et al., 2017) or a habituation response characterized by blunted vasoconstriction and a blunted metabolic response (Mäkinen et al., 2004; Young, 1996).

The study detected a significant increase in RQ after cooling in women but not men (see Tables 2 and 3). A similar pattern was detected by Hadi et al. (2016) after immersing subjects' hands in 5°C water for 20 minute; however, most investigations of NST report no change in RQ (Celi et al., 2010; Hanssen et al., 2015; Muzik et al., 2017; Peterson et al., 2015; Stelly, 2015; U Din et al., 2016). 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 hour of mild cold exposure (19°C) (Celi et al., 2010) and 10 days of cold acclimatization (van Marken Licthenbelt et al., 2015), thus suggesting changes in glucose metabolism during thermogenesis.

TABLE 5 Multivariate regression analysis of change in supraclavicular temperature on percent change in energy expenditure controlling for various confounding variables (n = 74)

	Adjusted R^2 = 0.13	
Measure	**β coefficient**	***P*-values**
ΔSCV (°C)	24.46	.015
Age (years)	−0.28	.145
Gender (M-1; F-2)	−1.33	.867
Fat-free mass (kg)	0.14	.548
% body fat	0.28	.417
Trial start time	−11.16	.587
ΔSternum (°C)	−5.1	.043

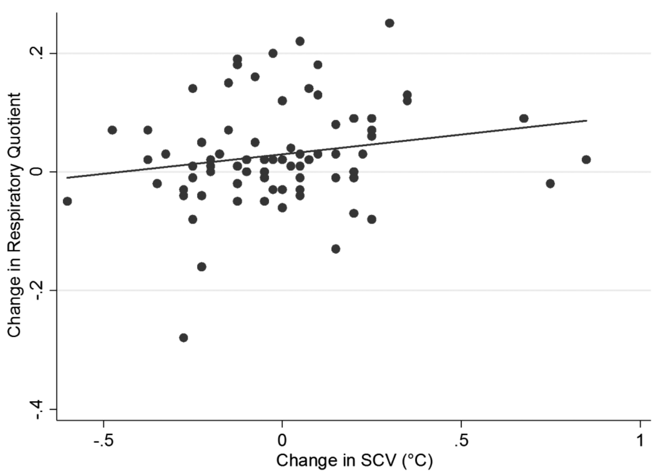

FIGURE 5 Scatterplot of change in supraclavicular temperature and change in respiratory quotient after 30 minute of cooling (n = 74). Pearson's correlation coefficient: R = 0.190

TABLE 6 Multivariate regression analyses of change in supraclavicular temperature on change respiratory quotient controlling for various confounding variables ($n = 74$)

	Adjusted $R^2 = 0.10$	
Measure	β coefficient	*P*-value
ΔSCV (°C)	0.09	.042
Age (years)	0.001	.529
Gender (M-1; F-2)	0.13	.016
Fat-free mass (kg)	0.002	.341
% body fat	−0.01	.014
Trial start time	−0.16	.175
ΔSternum (°C)	−0.02	.244

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 as adults with greater BAT metabolism may have a higher total daily energy expenditure, 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, gender, FFM, and percent body fat displayed in model 1 of Table 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. However, the relationship between ΔSCV and percent body fat became nonsignificant after controlling for the trial start time and change in sternum temperature.

Previous works investigating the relationship between BAT metabolism and body fatness have produced mixed results. Saito et al. (2009), Matsushita et al. (2014), and Hanssen et al. (2015) document that participants with greater BAT activity have lower body fatness; however, Lee et al. (2012) documented a positive association, while many studies fail to detect any relationship (Bahler et al., 2016b; Franssens, Hoogduin, Leiner, van der Graaf, & Visseren, 2017; Yoneshiro, Aita, Matsushita, Kameya, et al., 2011, Yoneshiro, Aita, Kawai, Iwanaga, & Saito, 2012). 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 documented 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 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., 2011; 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., 2017). 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., 2011; Zhang et al., 2013). Thus, issues of causality regarding the aging process, BAT metabolism, and adiposity warrant further investigation.

We also hypothesized that Yakut adults with greater ΔSCV would expend more energy during the cooling condition. The present study reports in Table 5 a significant

TABLE 7 Selected anthropometric dimensions, change in skin temperature and percent change in energy expenditure of sample A and sample B

	Sample A: Blood biomarker Particicipants $n = 62$	Sample B: Nonparticipants $n = 12$	
Measure	Mean ± SD	Mean ± SD	t-statistic/z-statistic
Gender ratio (M/F)	(24/38)	(7/5)	
Age[a] (years)	27.0 ± 8.4	23.1 ± 8.0	−2.13*
Fat-free mass[a] (kg)	47.0 ± 9.6	48.3 ± 7.6	0.53
BMI[a]	22.2 ± 3.5	20.8 ± 3.7	−1.47
Weight (kg)	59.6 ± 11.7	58.1 ± 10.6	−0.43
Height (cm	163.5 ± 8.4	167.0 ± 8.6	1.33
Percent body fat (%)	29.1 ± 7.2	23.7 ± 8.7	−2.28*
Change in SCV (°C)	−0.02 + 0.24	0.04 ± 0.31	0.77
Change in sternum (°C)	−0.5 + 0.6	−0.4 + 0.3	0.88
Percent change in EE	−4.3 + 12.3	4.8 ± 24.5	1.95
Change in RQ	0.03 ± 0.09	0.02 ± 0.08	−0.26

t-tests of the differences between Sample A and B are significant at: $*P \leq 0.05$.

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

TABLE 8 Mean blood biomarkers of cardio-metabolic disease risk for men and women

Measure	Males $n = 24$ Mean ± SD	Females $n = 38$ Mean ± SD	t-statistic/z-statistic
Total Cholesterol[a] (mg/dL)	132.1 ± 30.7	151.4 ± 32.6	−2.46*
HDL cholesterol (mg/dL)	51.3 ± 10.8	73.3 ± 14.6	−6.35***
LDL cholesterol (mg/dL)	63.9 ± 26.3	64.0 ± 26.4	−0.02
Triglycerides[a] (mg/dL)	84.3 ± 23.6	76.9 ± 16.8	0.98
Glucose (mg/dL)	86.7 ± 8.4	88.2 ± 12.2	−0.53

t-tests of the gender differences are significant at: *$P \leq .05$; **$P \leq .01$; ***$P \leq .001$.
[a] The variable is not normally distributed; therefore, Two-sample Wilcoxon rank-sum (Mann–Whitney) test was run.

positive relationship between ΔSCV and % ΔEE after controlling for age, gender, FFM, percent body fat, trial start time, and change in sternum temperature. These results suggest that BAT thermogenesis may be linked to NST among Yakut adults. In contrast, the change in skin temperature of a point on the sternum, which lacks BAT deposits, was negatively associated with change in energy expenditure. The positive relationship between ΔSCV and energy expenditure during cold exposure is consistent with previous investigations (Chen et al., 2013; Muzik et al., 2017; van der Lans et al., 2013; van Marken Licthenbelt et al., 2015; Yoneshiro et al., 2016). Interestingly, participants who experienced an increase in SCV temperature had a mean % ΔEE of +1.41%, while participants who experienced a decrease in SCV temperature had a mean % ΔEE 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 U 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 vary 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., 2014; 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. Deep muscles, such as the levator scapulae (U Din et al., 2016) and lungus colli (Ouellet et al., 2012), which co-locate with BAT, do exhibit an increase in metabolism during NST. U Din et al. (2016) estimated that muscle of the cervico-thoracic region contributes about 86 kcal/day during cold exposure. The tissue-specific metabolic rate of other deep muscle tissues, such as the lungus colli, have 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.

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 including skeletal muscle, the heart, and liver. Thus, BAT may be a biomarker for variation in the metabolic action of these hormones or differences in innervation (Muzik & Diwadkar, 2017).

BAT may also influence NST 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

TABLE 9 Multivariate regression analyses of biomarkers of cardio-metabolic disease risk on change in supraclavicular skin temperature ($n = 62$)

Measure	Total Cholesterol (mg/dL) Adj. $R^2 = 0.50$ β Coef.	P-values	HDL Cholesterol (mg/dL) Adj. $R^2 = 0.44$ β Coef.	P-values	LDL Cholesterol (mg/dL) Adj. $R^2 = 0.41$ β Coef.	P-values	Triglycerides (mg/dL) Adj. $R^2 = 0.06$ β Coef.	P-values	Glucose (mg/dL) Adj. $R^2 = 0.20$ β Coef.	P-values
Δ SCV (°C)	14.08	.212	3.01	.676	11.02	.238	9.96	.479	14.97	.017
Age (years)	2.81	0	0.73	.007	1.94	.000	0.40	.361	−0.08	.629
Gender (M-1; F-2)	11.86	.300	28.43	.001	−11.89	.220	−7.50	.459	8.76	.134
Fat-free mass (kg)	−0.16	.676	−0.16	.605	−0.02	.966	0.43	.370	0.50	.003
% body fat	−0.23	.733	−1.04	.022	0.66	.175	0.56	.298	0.14	.630
Trial start time	5.56	.855	6.08	.756	5.46	.851	−9.99	.691	−5.04	.651
Δ sternum (°C)	−2.95	.636	−1.75	.561	0.21	.964	0.56	.879	4.06	.059

(Villarroya, Cereijo, Villarroya, & Giralt, 2017). 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., 2017). 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, Mampel, Villarroya, & Iglesias, 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 unclear (Bianco & Kim, 2006; Schimmel & Utiger, 1977). Finally, greater supraclavicular BAT volume may be associated with the presence of BAT deposits in other regions of the body, such as around the spine and heart, or brown adipocytes scattered within white adipose tissue (Becker, Nagel, Wolfrum, & Burger, 2016). 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 9 revealed that serum lipids were not correlated with ΔSCV; however, blood glucose levels were positively associated with BAT thermogenesis independent of age, gender, body composition, trial start time, and vasoconstriction of the core. Additionally, this is the first study to document a significant positive correlation between ΔSCV and change in RQ, thus suggesting that participants with greater BAT activity might 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%. Two hours of mild cooling is associated with an increase in small LDL and HDL particles (Hoeke et al., 2017). In a transgenic mouse model of dyslipidemia, thermogenic adipocytes exposed to cold stress exhibit accelerated plasma cholesterol efflux and fecal excretion (Bartelt et al., 2017). In particular, lipoprotein lipase activity within the adipocytes promotes HDL turnover and hepatic clearance, thus suggesting that BAT may influence lipid metabolism and removal. A study of elderly humans 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.

Historically, indigenous circumpolar populations have exhibited a low prevalence of cardiovascular disease mortality and diabetes, as well as low levels of blood lipids and glucose (Bang & Dyerberg, 1980; Chateau-Degat, 2011; Kozlov, Vershubsky, & Kozlova, 2007; Rode, Shephard, Vloshinsky, & Kuksis, 1995; Young, Moffatt, & O'Neill, 1993; Young et al., 1995). However, a number of studies of cardiovascular disease risk factors among circumpolar groups in Siberia, North America, and Greenland have documented a strong association between processes of acculturation and cardio-metabolic disease risk (de Knijff et al., 1992; Kozlov et al., 2007; Sorensen et al., 2009; Young et al., 1995). In circumpolar regions, the relationship between health and 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. An elevated metabolic rate in response to low temperature exposure is also linked to higher blood pressure (Luke, Adeyemo, Kramer, Forrester, & Cooper, 2004; Snodgrass, Leonard, Sorensen, Tarskaia, & Mosher, 2008).

Our understanding of the relationships between BAT thermogenesis, energy expenditure and biomarkers of cardio-metabolism in this subarctic population would be greatly enhanced by examining fluctuations in BAT activity within the same individual across seasons. Rates of BAT detection using PET-CT scans are higher in the winter than the summer among adults living in a temperate climate (Bahler et al., 2016b; Bahler, Deelen, Hoekstra, Holleman, & Verberne, 2016a). 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.

Yakut lifestyles that include more frequent cold exposure, such as greater participation in winter-time subsistence activities, may influence cardio-metabolic disease risk via BAT thermogenesis. Yakut men who 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, future research should 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 highly active adults participating in National Outdoor Leadership School in hot, temperate, and cold climates. Total energy expenditure in the hot and temperate 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 not directly quantified, rather change in the SCV temperature was used as a probable signal of BAT thermogenesis. Several PET-CT studies of BAT suggest that ΔSCV may act as an indirect measure of BAT activity considering the strong relationship between ΔSCV and the BAT standardized uptake value (SUV) of ^{18}F-FDG (Chondronikola et al., 2016; van der Lans et al., 2016); however, skin temperature of this region is influenced by adiposity and vasoconstriction as well as BAT thermogenesis. The study sample was skewed toward young, lean individuals, and on average the biomarkers of cardiovascular and metabolic disease risk were within recommended ranges. This pattern limits the study's ability to make conclusions regarding how BAT changes with age and its relationship with body composition and cardio-metabolic health. Finally, the study sample was small and recruitment was nonrandom. This restricts our interpretations regarding BAT thermogenesis among Yakut adults. Participant recruitment was biased toward women and individuals with high education levels. The lifestyles of the study participants may differ from the general population of Berdygestiakh and Yakutsk in important ways that might influence BAT thermogenesis, body composition, and health.

In short, this study is the first to describe the adaptive and health significance of BAT among an indigenous circumpolar population. 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. Additionally, the results suggest greater BAT activity may lead to preferential utilization of carbohydrates as a fuel source for oxidative phosphorylation and that BAT may alter blood biomarkers of cardio-metabolic health. Future research should explore variation in the relationships between BAT activity, metabolism and cardio-metabolic disease risk across populations.

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AUTHOR CONTRIBUTIONS

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Recruited participants: Klimova, Zakharova, Federov, Fedorova, Baltakhinova.
Data collected: Levy, Leonard, Klimova, Zakharova, Federov, Fedorova, and Baltakhinova.
Directed analysis of blood samples: Klimova, Zakharova, Federov, Fedorova, and Baltakhinova.
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