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# Brown adipose tissue thermogenesis among young adults in northeastern Siberia and Midwest United States and its relationship with other biological adaptations to cold climates

**Stephanie B. Levy**[1,2] | **Tatiana M. Klimova**[3,4] | **Raisa N. Zakharova**[3] | **Afanasiy I. Fedorov**[3] | **Valentina I. Fedorova**[5] | **Marina E. Baltakhinova**[6] | **Madison Bondy**[7] | **Dania Atallah**[8] | **Jennah Thompson-Vasquez**[9] | **Kaylin Dong**[10] | **Anne Debertine**[11] | **William R. Leonard**[11]

[1]Department of Anthropology, CUNY Hunter College, New York City, New York, USA
[2]New York Consortium in Evolution Primatology, New York City, New York, USA
[3]North-Eastern Federal University named M.K. Ammosov, Yakutsk, Russia
[4]Yakutsk Scientific Center for Complex Medical Problems, Yakutsk, Russia
[5]Insurance Medical Company "Sakhammedstrakh", Yakutsk, Russia
[6]Aurora Medical Clinic, Yakutsk, Russia
[7]Department of Anthropology, Emory University, Atlanta, Georgia, USA
[8]College of Medicine, Kansas City University, Kansas City, Missouri, USA
[9]Department of Anthropology, CUNY Graduate Center, New York City, New York, USA
[10]School of Medicine, Boston University, Boston, Massachusetts, USA
[11]Department of Anthropology, Northwestern University, Evanston, Illinois, USA

**Correspondence**
Stephanie B. Levy, Hunter College,
659 Park Ave., New York, NY 10065, USA.
Email: stephanie.levy@hunter.cuny.edu

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## Abstract

**Objectives:** Recent research suggests that brown adipose tissue (BAT) plays a functional role in non-shivering thermogenesis; however, few studies have examined population variation in BAT or its relationship with other mechanisms of adaptation to cold stress. This study characterized BAT thermogenesis and other adaptive responses to low temperatures among Indigenous Siberian young adults and young adults living near Chicago, IL.

**Materials and methods:** We recruited 72 Yakut participants (42 females; 30 males) and 54 participants in Evanston, IL (40 females; 14 males). Anthropometric dimensions and resting metabolic rate (RMR) were measured, and we calculated percent divergence in RMR from expected values (divRMR). We also quantified change in supraclavicular temperature, sternum temperature, and energy expenditure after a mild cooling condition.

**Results:** Participants in Yakutia were less likely to shiver during the cooling condition ($p < .05$) and exhibited significantly greater evidence of BAT thermogenesis, warmer sternum temperatures, and higher divRMR than participants in Evanston ($p < .05$). Additionally, the relationship between change in

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supraclavicular temperature and energy expenditure differed between the two samples.

**Conclusions:** Yakut young adults displayed greater evidence of BAT thermogenesis in response to mild cooling compared with young adults living near Chicago, IL. Furthermore, the relationship between BAT thermogenesis and change in energy expenditure appears to be stronger among Yakut adults. Adults that exhibited greater metabolic response to cold stress, such as higher BAT thermogenesis and divRMR, maintained warmer sternum temperatures. These results highlight the degree to which adaptation to cold climates involves multiple integrated biological pathways.

## 1 | INTRODUCTION

Humans thrive in circumpolar environments by implementing a complex suite of cultural, behavioral, and biological adaptations to cold climates. For instance, high-latitude populations generate body heat through elevations in resting metabolic rates (RMR) (Leonard et al., 2002; Leonard, Snodgrass, & Sorensen, 2005; Rode & Shephard, 1995). During acute exposure to low temperatures, indigenous circumpolar groups maintain warmer skin temperatures than their nonindigenous counterparts via efficient vasoconstriction and vasodilation (Frisancho, 1993; Miller & Irving, 1962). Populations that are acclimatized to cold stress begin shivering at a lower temperature and rely more on efficient nonshivering thermogenesis (NST) for heat production since muscle activity during shivering is energetically costly (Janský et al., 1996). While researchers continue to debate the biological mechanisms that underlie NST, recent work suggests that brown adipose tissue (BAT) plays a key role (Blondin et al., 2017; Chondronikola et al., 2016). For instance, among the Yakut, a population indigenous to northeastern Siberia, adults with warmer supraclavicular skin temperatures (indicative of greater BAT thermogenesis) expend more energy during mild cooling (Levy et al., 2018). Brown adipocytes may contribute to NST by uncoupling oxidative phosphorylation from ATP production so that the proton gradient is dissipated via uncoupling protein 1 (UCP1), thus generating heat (Cannon & Nedergaard, 2004). Few studies, however, examine the relationships between multiple biological adaptations to cold climates.

Additionally, the determinants of population variation in BAT thermogenesis remain unclear. Both cold-induced energy expenditure and BAT mass decline with age (Frank, Raja, Bulcao, & Goldstein, 2000; Schosserer, Grillari, Wolfrum, & Scheideler, 2018). Investigations of the relationship between BAT and body fatness have produced mixed results (Hanssen et al., 2015; Matsushita et al., 2014). Population variation in BAT is likely shaped by developmental plasticity and seasonal acclimatization to cold climates. Yakut people that were exposed to greater cold stress during early childhood exhibit greater evidence of BAT thermogenesis in adulthood (Levy et al., 2021). Human BAT mass and metabolism increase in response to seasonal low temperatures and repeated cold exposure in an experimental setting (van der Lans et al., 2013; Yoneshiro et al., 2016). Efremova et al. (2020) collected fat cells at necropsy from individuals in Siberia and found higher UCP1 expression in cells collected from outdoor workers than indoor workers. This work suggests that differences in lifestyle characteristics may shape variation in acclimatization and BAT thermogenesis (Efremova et al., 2020). Few studies have compared BAT metabolism across multiple populations using the same methodological techniques.

The goal of this study is to characterize variation in BAT thermogenesis and its relationship with other mechanisms of adaptation to cold stress in two groups of young adults—Indigenous Siberians living in Yakutia (Republic of Sakha) and individuals living near Chicago, IL. We hypothesize that young adults in Yakutia will exhibit lower shivering thresholds, and elevations in supraclavicular skin temperature, sternum temperature, cold-induced energy expenditure, and RMR compared with measurements taken in Evanston, IL. Additionally, we predict that young adults that exhibit greater evidence of metabolic adaptations to cold stress via increases in energy expenditure will also maintain warmer skin temperatures after cooling. These predictions are based on past work documenting population differences in metabolic adaptations to low temperatures between groups living in circumpolar and temperate climates (Leonard et al., 2005). The findings of this study will shed light on the determinants of population variation in BAT thermogenesis and its metabolic correlates.

## 2 | METHODS

### 2.1 | Study populations and participants

The present study quantifies and compares BAT thermogenesis and other biological responses to cold stress among indigenous young adults living in Yakutia (Republic of Sakha) and young adults living near Chicago, IL. Yakutia is located in northeastern Siberia and has a population of over 958 000 people (Russian Census, 2010). A majority of the population is Yakut, an indigenous population of over 450 000 people. In the winter, ambient temperatures in Yakutia regularly drop below −40°C (−40 °F), and in the summer temperatures can rise above 30°C (86 °F). Data were collected at two locations within the Lena River Valley—in Yakutsk (62°N, 129°E; population 269 600), the capital of Yakutia, and in Berdygestiakh (62°N, 127°E; population 6400), a rural village west of Yakutsk.

Prior to Russian expansion in the 17th century, Yakut people in the Lena River Valley practiced a semi-nomadic transhumant pastoralism (Forsyth, 1994). Beginning in the 1930s, the Soviet Union organized Yakut families into herding and farming collectives (Forsyth, 1994). A majority of Yakut adults were employed by the state or dependent upon government welfare by the mid-1980s (Slezkine, 1994). When the Soviet Union collapsed, the people of Siberia were suddenly without the wages and essential resources that were provided by the government, and many people were forced to find new lifeways.

The current economic system is unique to Yakutia, and it blends together aspects of a reciprocal kin-based subsistence system, Soviet collectivization, and recent privatization initiatives (Takakura, 2015). Today, most Yakut people depend on a mixed cash economy that consists of a combination of cash inputs and subsistence practices (Crate, 2006). A single Yakut household, or even individual, may rely on earnings from both wage or salary positions and subsistence practices including raising cattle or horses, picking berries, herbs, and other naturally growing foods, growing vegetables, hunting, and fishing (Snodgrass, 2004; Sorensen, 2003). The degree of participation in these subsistence activities ranges across a wide spectrum and depends on the season. As state farms were dismantled, the distribution of livestock was not equitable, and differences in livestock ownership have led to an increase in economic inequality (Crate, 2006; Snodgrass, 2004). Yakut 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 downtime (Takakura, 2015). Food produced from subsistence activities not only supplements the needs of the household, but also serves in the development of social relationships (Takakura, 2015). This system of lifestyle heterogeneity has allowed Yakut people to maintain their cultural networks while adapting to privatization initiatives under the Russian government (Takakura, 2015).

Data collection in Yakutia took place at the Gorny Regional Medical Center in Berdygestiakh from September 5 to 11, 2015, and at the Regional Institute of Health and the Medical Clinic at M.K. Ammosov North-Eastern Federal University (NEFU) from September 12 to 23, 2015. The study was advertised in the local newspaper, local radio station, and via word of mouth. The setting and timeline of the study prevented recruitment of a random sample. Individuals interested in participating were told to arrive at either the Gorny Regional Medical Center or NEFU in the morning having fasted and refrained from smoking and exercising for at least 7 h prior to arrival. Pregnant and lactating people were excluded and all participants were healthy at the time of data collection and had no known acute conditions. The study sample in Yakutia includes 72 participants (42 females; 30 males). A majority of the participants were either university students or NEFU employees. Around 88% of the participants had at least some college-level education.

Data collection in Evanston, IL took place at the Department of Anthropology at Northwestern University from July 7 to August 3, 2015, and June 26 to August 25, 2017. Evanston (42°N, 88°W; population 74 590) is located just north of the city of Chicago. Typical temperatures in Chicago are around 1.5°C (35 °F) in the winter and around 26°C (79 °F) in the summer; however, with the wind-chill the winter "real-feel" is often below freezing.

Participants in Evanston were recruited by posting fliers around the university and a digital advertisement on Craigslist.com. A majority of the participants were students and employees of Northwestern University living in either Evanston or Chicago. Approximately 11% of participants primarily lived in an arid/tropical climatic zone and around 19% of participants primarily lived in a subtropical climatic zone prior to moving to the Chicago area. The remaining participants in Evanston primarily lived in a temperate climatic zone.

Participants were fasted for at least 7 h and had refrained from exercise and smoking prior to arrival at the Department of Anthropology for data collection. Like in Yakutia, pregnant and lactating people were excluded and all participants were healthy at the time of data collection and had no known acute conditions. The Evanston study sample included 54 participants (40 females; 14 males).

The Northwestern University Institutional Review Board granted permission to conduct the study in both Evanston and Yakutia (IRB 00200092). All subjects in both study locations provided documented informed consent prior to participating in this research.

## 2.2 | Anthropometry

Anthropometric dimensions were taken using standardized techniques (Lohman, Roache, & Martorell, 1992). Stature was measured to the nearest millimeter using a Seca portable standiometer. 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 bioimpedance analysis (BIA) scale. Percent body fat was also calculated from the sum of four skinfolds (triceps, biceps, subscapular, suprailiac) using the equations of Durnin and Womersley (1974).

## 2.3 | Indirect calorimetry

Energy expenditure was measured using open-circuit indirect calorimetry following the standards described in Leonard (2012). Participants rested quietly in a supine position so that they could adjust to breathing in the mask prior to metabolic measurements. Heart rate (HR, beats/min) was simultaneously measured using a Polar S610 heart rate monitor (Woodsbury, NY) in order to track participant anxiety. MedGraphics VO2000 metabolic analyzers (St. Paul, MN) were used to assess oxygen consumption ($VO_2$, l/min) and carbon dioxide production ($VCO_2$, l/min). Energy expenditure (kcal/day) was calculated by converting $VO_2$ based on respiratory quotient using the modified Weir formula (McArdle, Katch, & Katch, 2010; Weir, 1949).

Energy expenditure was quantified during two temperature conditions—a room-temperature condition and a mild cooling condition. Throughout the metabolic measurements, participants wore a water-perfused cooling suit that consists of pants and a jacket that are each lined with tubing (Med-Eng, Ottawa, ON). Participants wore lightweight clothing (average clo value of 0.35) underneath the water-perfused suit. During the room-temperature condition, measurements were taken at room temperature (23.4°C ± 1.0 in Evanston and 24.9°C ± 1.7 in Yakutia) without cold water flowing through the suit, and RMR measurements were recorded for 20 min. A steady-state period of at least 10 min was used to calculate RMR. Previous work has demonstrated that 5-min or more of steady-state measurements are sufficient to generate a precise estimate of RMR (Irving, Eggett, & Fullmer, 2017; Popp, Tisch, Sakarcan, Bridges, & Jesch, 2016). The percentage of divergence in RMR from predicted values (divRMR) was calculated from the estimated RMR based on FFM (eRMR) using the Cunningham (1991) equation ($divRMR = [(RMR - eRMR)/eRMR] \times 100$). The divRMR estimate was used to evaluate the degree to which an individual's RMR measurement was above or below the expected metabolic rate based on the participant's body size and composition.

The cooling condition protocol followed the standards described in Levy (2019). Coldwater (10°C) was pumped through the tubing of the cooling suit so that the inside of the suit was kept at 15°C. If the participant reported that they were beginning to shiver, the time, and 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. Of note, there is currently no evidence that NST peaks at the onset of shivering; thus, the temperature just above shivering is likely to elicit the most NST with the least amount of shivering. The cooling condition was 30 min long. The average cold-induced energy expenditure (CIEE, kcal/day) was estimated from a steady–state period after excluding the first 10 min of cooling and any time points when the participant was shivering. Change in energy expenditure (ΔEE) was calculated by subtracting RMR from CIEE. Percent change in energy expenditure (%ΔEE) was calculated by subtracting RMR from CIEE and dividing by RMR $\left[\%\Delta EE = \left(\frac{CIEE - RMR}{RMR}\right) \times 100\right]$.

## 2.4 | Infrared thermal imaging

Supraclavicular and sternum skin temperature were quantified using an infrared thermal imaging camera (E60bx, FLIR, Nashua, NH) as described in Levy (2019). The camera was positioned 1 m away from the participant and no heat-emitting objects (i.e., radiator) were in the area. Emissivity was set to 0.98 (the emissivity of dry skin) and room temperature and humidity were recorded and entered into each image's parameters. Thermal images of the left and right side of the supraclavicular area were captured at the end of the room-temperature and cooling conditions (Figure S1). The maximum skin temperature of the supraclavicular area of each image was determined using FLIR Tools Software's (FLIR, Nashua, NH) box tool. The temperatures of the left and right side images were averaged together, and the change in maximum supraclavicular skin temperature between the room-temperature and cooling conditions was calculated and used as an estimate of BAT thermogenesis (Levy, 2019). The average temperature of a point at the top of the sternum was calculated using the spot tool in FLIR Tools in the room-temperature and cooling condition images. We then calculated the change in skin temperature of the sternum between the temperature conditions. Since the sternum does not carry any BAT deposits, change in skin temperature of the sternum was measured in order to assess variation in skin temperature of the core due to differences in skin blood flow via vasoconstriction/vasodilation. Intra-observer error was previously assessed and a coefficient of variation of 12% was determined based on nine repeated skin measurements.

### 2.5 | Statistical analysis

Statistical tests were run using StataIC 16.0 (Statacorp LLC, College Station, TX), and tests were considered statistically significant at *p*-value $\leq .05$. All variables were examined for outliers, which were removed as appropriate, and checked for a normal distribution using the Shaprio-Wilk W test (Stata command swilk). FFM was not normally distributed and thus was log transformed. Age was also not normally distributed and was transformed using the following equation: $Age\,transformed = 1/(Age^2)$.

Unpaired Student's *t* tests were used compare anthropometric dimensions between males and females within each study location and across the Yakutia and Evanston study samples. Age and FFM were not normally distributed and, thus, were transformed. Because of the small sample sizes, subsequent analyses are not separated by sex. A chi-squared test was used to test for differences in the number of participants that shivered in the two study samples. Subsequent analyses were limited to participants that did not shiver in order to limit the influence of shivering on metabolic measurements. Unpaired Student's *t* tests were used to examine differences in RMR, divRMR, change in supraclavicular temperature, change in sternum temperature, ΔEE, and %ΔEE. Then multiple regression analyses were used to further explore the relationship between change in supraclavicular temperature and ΔEE as well as %ΔEE in each of the samples controlling for possible confounding factors. All regressions were checked for heteroscedasticity and run with robust standard errors as needed. Finally, we explored the predictors of variation in change in supraclavicular temperature, change in skin temperature of the sternum, ΔEE, %ΔEE, and divRMR using multivariate regression analyses. The residuals of the multiple regressions presented in Tables 3, 4, and S2 were not normally distributed, and so age and FFM were transformed.

## 3 | RESULTS

### 3.1 | Descriptive statistics of anthropometric dimensions

Table 1 displays the mean transformed age, height, weight, log of FFM, and sum of skinfolds of females and males in the study samples in Evanston and Yakutia. The Yakutia sample (mean age: 26.0 ± 8.5 y/o) was significantly older than the Evanston sample (mean age: 23.0 ± 4.9 y/o) in part because females included in the Evanston sample (mean age: 22.3 ± 4.3 y/o) were significantly younger than the sample of females in Yakutia (mean age: 27.5 ± 8.8 y/o). Males and females in the Evanston sample were significantly taller, heavier, and had a larger FFM than males and females in the Yakutia sample ($p < .05$). While the sum of skinfolds was not significantly different between males and females in the Yakutia sample compared with males and females in Evanston, respectively, overall the Evanston sample had significantly greater sum of skinfolds than the Yakutia sample ($p < .05$).

### 3.2 | Comparisons of metabolic and skin temperature variables

First, we performed a chi-squared test to compare the number of individuals that shivered during the cooling condition in the Evanston sample (4 females; 9 males; 24% of sample) compared with the Yakutia sample (6 females; 0 males; 8% of sample). Participants in Evanston were significantly more likely to shiver during the cooling condition than participants in Yakutia ($p = .015$). The small sample limited our ability to statistically characterize differences in anthropometric dimensions between participants that did and did not shiver.

In order to reduce the influence of shivering on variation in metabolic and skin temperature variables, the following analyses were limited to participants that did not report shivering (66 participants in Yakutia; 41 participants in Evanston). Table 2 and Figure 1 present the results of paired and unpaired *t* tests comparing the RMR, divRMR, change in supraclavicular temperature, change in skin temperature of the sternum, ΔEE, and %ΔEE. Participants in Yakutia had a significantly higher average RMR than participants in Evanston ($p < .01$). Similarly, the degree to which measured RMR values differed from expected values based on FFM (i.e., divRMR)

**TABLE 1** Age and anthropometric dimensions of males and females in sample from Evanston and Yakutia

| | Evanston | | | | | | Yakutia | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Males ($n$=14) | | Females ($n$=40) | | Total ($n$=54) | | Males ($n$=30) | | Females ($n$=42) | | Total ($n$=72) | |
| **Measure** | **Mean** | ***SD*** | **Mean** | ***SD*** | **Mean** | ***SD*** | **Mean** | ***SD*** | **Mean** | ***SD*** | **Mean** | ***SD*** |
| Age (transformed) | 0.002 | 0.001 | 0.002 | 0.001 | 0.002 | 0.001 | 0.002 | 0.001 | 0.002‡ | 0.001 | **0.002** | 0.001 |
| Height (cm) | 176.3*** | 5.5 | 164.0 | 7.1 | 167.2 | 8.6 | 171.7***‡ | 5.5 | 158.7§ | 5.3 | **164.1** | 8.4 |
| Weight (kg) | 74.7*** | 13.8 | 62.5 | 12.5 | 65.7 | 13.8 | 66.1***† | 11.3 | 54.5‡ | 9.1 | **59.3** | 11.5 |
| Log of Fat-free mass (kg) | 1.79*** | 0.06 | 1.66 | 0.05 | 1.69 | 0.08 | 1.74***‡ | 0.05 | 1.62§ | 0.03 | 1.67 | 0.07 |
| Sum of skinfolds (mm) | 65.4** | 19.1 | 84.3 | 22.8 | 79.4 | 23.3 | 58.2*** | 28.7 | 79.1 | 20.6 | **70.4** | 26.3 |

*Note*: Unpaired *t* tests of between-sex differences within each population are significant at: *$p$<.05; **$p$<.01; ***$p$<.001. Unpaired *t* tests of within-sex differences between each population are significant at † $p$<.05; ‡ $p$<.01; § $p$<.001. Unpaired *t* tests of total samples comparisons with a *p*-value < .05 are shown as bolded means in the Yakutia total column.

were significantly higher in the Yakutia sample compared with the Evanston sample ($p < .01$). Both samples exhibited negative divRMR values suggesting that, on average, measured RMRs were lower than expected based on FFM; however, values were closer to the expected RMRs among Yakut participants than among participants in Evanston. Both samples maintained significantly warmer supraclavicular temperatures than sternum temperatures ($p < .001$). Yakut participants had significantly greater change in supraclavicular temperature ($p = .015$) and maintained warmer skin temperatures of the sternum ($p < .001$) than participants in the Evanston sample. Differences in the change in skin temperature of the sternum between the two samples were particularly pronounced (Yakutia mean: $-0.53 \pm 0.06$°C; Evanston mean: $-2.14 \pm 1.47$°C). Interestingly, ΔEE and %ΔEE between the room-temperature and cooling conditions were not significantly different between the two groups.

## 3.3 | Examination of the correlates of percent change in energy expenditure

Next, we ran regressions to analyze the predictors of variation in ΔEE and %ΔEE. Figure 2 presents scatterplots of the relationship between change in supraclavicular temperature and ΔEE as well as %ΔEE in the Yakutia and Evanston samples. Among Yakut participants, change in supraclavicular temperature was significantly associated with ΔEE ($p = .043$) after controlling for variation due to age, sex, sum of skinfolds, FFM, time of data collection, change in skin temperature of the sternum, and room temperature (see Table S1). Similarly, there was a significant relationship between change in supraclavicular temperature and %ΔEE ($p = 0.044$) after controlling for potential covariates (see Table S2). The relationship between %ΔEE and change in supraclavicular temperature remained significant after the data point for the individual with a %ΔEE of over 50% was removed. Among participants in Evanston, change in supraclavicular temperature was not significantly associated with ΔEE ($p = .921$) nor %ΔEE ($p = .999$) after controlling for possible covariates (see Tables S3 and S4).

## 3.4 | Examination of the correlates of change in supraclavicular temperature, change in skin temperature of the sternum, and divRMR

Table 3 presents the results of a multivariate regression model examining the predictors of variation in change in supraclavicular temperature. In particular, the model included study location, change in skin temperature of

**TABLE 2** Comparisons of RMR, divRMR, change in supraclavicular temperature and sternum temperature, ΔEE and %ΔEE for the Evanston and Yakutia samples

| | **Evanston ($n$=41)** | | **Yakutia ($n$=66)** | |
|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** |
| RMR (kcal/day) | 1156.5 | 346.8 | 1348.8** | 314.5 |
| divRMR (%) | −19.94 | 18.08 | −4.69*** | 15.24 |
| Change in supraclavicular temperature (°C) | −0.166 | 0.430 | −0.002* | 0.252 |
| Change in sternum temperature (°C) | −2.139 | 1.470 | −0.527*** | 0.464 |
| ΔEE (kcal/day) | −1.54 | 31.91 | −41.39 | 23.51 |
| %ΔEE | −0.617 | 17.049 | −2.930 | 15.327 |

*Note*: Unpaired *t* tests of means are significant at: *$p$<.05; **$p$<.01; ***$p$<.001.

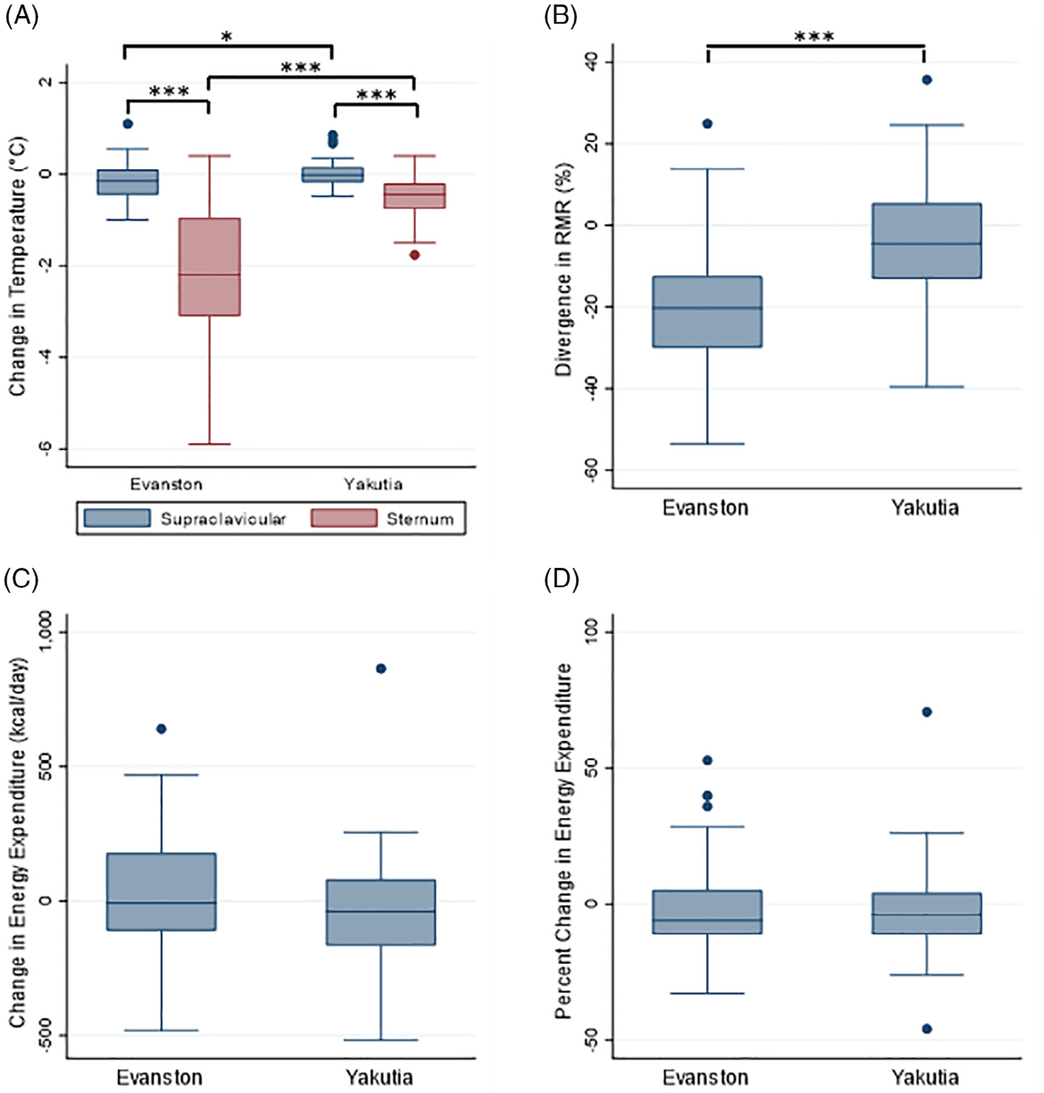

**FIGURE 1** Boxplots comparing change in supraclavicular temperature, sternum temperature, divRMR, ΔEE, and %ΔEE in the Yakutia and Evanston samples. Unpaired and paired *t* tests of means are significant at: *$p \leq .05$; **$p \leq .01$; ***$p \leq .001$. (A) Comparisons of change in supraclavicular and sternum temperatures (°C). (B) Comparison of change in sternum temperature (°C). (C) Comparison of divergence in RMR from predictions based on FFM (%). (D) Comparison of change in energy expenditure after cooling (kcal/day). (E) Comparison of percent change in energy expenditure after cooling

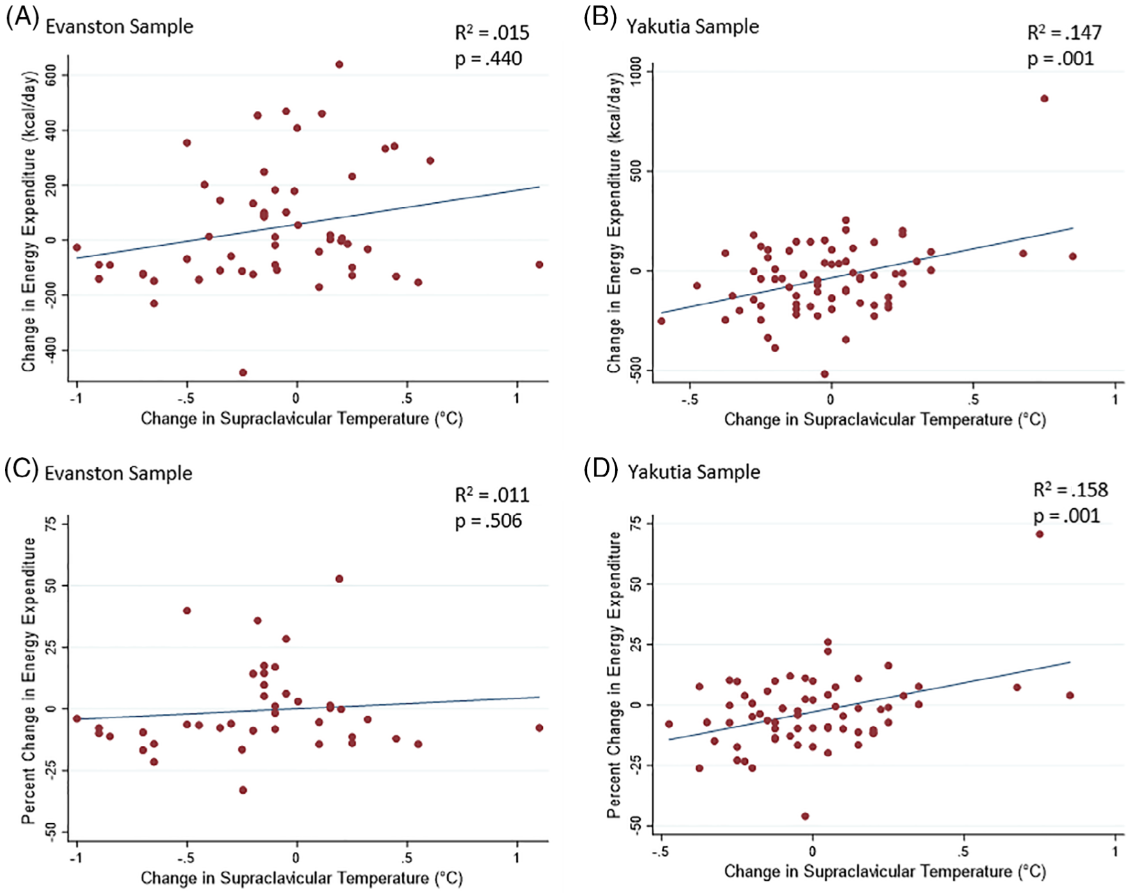

**FIGURE 2** Scatterplots of change in supraclavicular temperature and ΔEE and %ΔEE in Evanston and Yakutia. (A) Scatterplot of change in supraclavicular temperature and ΔEE data from Evanston ($n = 41$; $R^2 = .015$; $p = .440$). (B) Scatterplot of change in supraclavicular temperature and ΔEE data from Yakutia ($n = 66$; $R^2 = .147$; $p = 0.001$). (C) Scatterplot of change in supraclavicular temperature and %ΔEE data from Evanston ($n = 41$; $R^2 = .011$; $p = .506$). (B) Scatterplot of change in supraclavicular temperature and %ΔEE data from Yakutia ($n = 66$; $R^2 = .158$; $p = .001$)

the sternum, divRMR, age, sex, sum of skinfolds, FFM, time of data collection, and room temperature. Change in skin temperature of the sternum was positively associated with change in supraclavicular temperature ($p < .001$) and the time of data collection was negatively associated with change in supraclavicular temperature ($p < .001$). The time of data collection was not significantly different between the two study locations. Room temperature was significantly associated with change in supraclavicular temperature ($p = .01$), and the room temperature was significantly warmer during data collection in Yakutia ($p < .000$).

Next we examined the predictors of variation in change in skin temperature of the sternum using multiple regression analysis (Table 4). Study location was a significant predictor of change in skin temperature of the sternum ($p < .001$), suggesting that Yakut participants were more likely to exhibit warmer sternum temperatures after cooling. There was a significant positive association between change in supraclavicular temperature and change in skin temperature of the sternum ($p = .020$). There was also a significant positive association between divRMR and change in skin temperature of the sternum ($p = .013$).

Finally, Table 5 presents the results of a multivariate regression analysis of possible correlates of divRMR. Change in skin temperature of the sternum was positively associated with divRMR ($p = .010$). None of the other variables in the model were significantly associated with divRMR.

## 4 | DISUCSSION

The present study characterized differences in BAT thermogenesis and its relationship with other biological adaptations to cold stress among Yakut adults living in Northeastern Siberia and adults in Midwestern

**TABLE 3** Multiple linear regression analysis of the possible predictors of variation in change in supraclavicular temperature

| Measure | Coefficient | Robust *SE* | *p*-value |
|---|---|---|---|
| Sample location (Evanston: 0; Yakut: 1) | −.07 | 0.08 | .403 |
| Change in sternum temperature (°C) | .126 | 0.035 | **.000** |
| divRMR (%) | −.002 | 0.002 | .250 |
| Age (transformed) | 33.15 | 37.75 | .382 |
| Sex (M=1; F=2) | .03 | 0.10 | .771 |
| Log of fat-free mass (kg) | .002 | 0.005 | .641 |
| Sum of skinfolds (mm) | .001 | 0.002 | .480 |
| Time of data collection | −1.40 | 0.35 | **.000** |
| Room temperature (°C) | .05 | 0.08 | **.010** |

*Note*: The sample size is 107, *p*-values <.05 are bolded, and the adjusted $R^2$ of the model is .22.

**TABLE 4** Multiple linear regression analysis of the possible predictors of variation in change in sternum thermogenesis

| Measure | Coefficient | Robust *SE* | *p*-value |
|---|---|---|---|
| Sample location (Evanston: 0; Yakut: 1) | 1.30 | 0.25 | **.000** |
| Change in supraclavicular temperature (°C) | 1.15 | 0.49 | **.020** |
| divRMR (%) | .015 | 0.006 | **.013** |
| Age (transformed) | −1.92 | 99.96 | .985 |
| Sex (M = 1; F = 2) | −.13 | 0.33 | .706 |
| Log of Fat-free mass (kg) | −.01 | 0.02 | .724 |
| Sum of skinfolds (mm) | −.001 | 0.004 | .703 |
| Time of data collection | 1.60 | 1.18 | 1.350 |
| Room temperature (°C) | −.09 | 0.06 | −1.540 |

*Note*: The sample size is 107, *p*-values < .05 are bolded, and the adjusted $R^2$ of the model is .475.

**TABLE 5** Multiple linear regression analysis of the possible predictors of variation in the percent difference between predicted and measured RMR (divRMR)

| Measure | Coefficient | *SE* | *p*-value |
|---|---|---|---|
| Sample location (Evanston: 0; Yakut: 1) | 6.9 | 4.9 | .156 |
| Change in supraclavicular temperature (°C) | −4.6 | 5.2 | .382 |
| Change in sternum temperature (°C) | 4.4 | 1.7 | **.010** |
| Age | −.02 | 0.23 | .929 |
| Sex (M=1; F=2) | −2.8 | 6.1 | .652 |
| Fat-free mass (kg) | .42 | 0.32 | .189 |
| Sum of skinfolds (mm) | .002 | 0.07 | .978 |
| Time of data collection | 3.0 | 21.3 | .889 |
| Room temperature (°C) | 1.2 | 1.19 | .303 |

*Note*: The sample size is 107, *p*-values < .05 are bolded, and the adjusted $R^2$ of the model is .255.

United States. Our results indicated that Yakut adults exhibited significantly greater evidence of BAT thermogenesis than adults in Evanston, IL. Furthermore, the relationship between brown fat and other adaptive responses to cold stress may differ between these two populations.

We found that participants in Evanston were more likely to shiver during the cooling condition than participants in Yakutia. Additional research is needed in order to delineate the degree to which differences in shivering threshold between these two groups are linked to genetic adaptations to cold climates and acclimatization to repeated exposure to low temperatures. Previous work documents that populations with a history of repeated cold exposure exhibit a lower shivering threshold (Frisancho, 1993). Studies of female breath-hold divers from the Korean island of Jeju (referred to as *haenyo*) highlight the role of acclimatization to cold stress in lowering the shivering threshold. Historically, *haenyo* divers wore cotton bathing suits while diving at temperatures as lows 10°C (46°C) (Lee, Park, & Kim, 2017). Physiological studies documented that diving women exhibited significantly lower shivering thresholds than non-diving women (Frisancho, 1993). Over the past few decades, however, *haenyo* divers have begun to wear wetsuits, and recent studies no longer detected significant differences in shivering threshold between diving and non-diving women (Lee et al., 2017).

Young adults in Yakutia maintained significantly warmer supraclavicular temperatures during mild cooling than young adults in Evanston suggesting greater BAT thermogenesis. The study location, however, was not a significant predictor of change in supraclavicular temperature after controlling for change in skin temperature of the sternum, time of data collection, and room temperature. Fatty acid uptake and metabolism within murine BAT shows a distinct diurnal rhythm that peaks at wakening (van den Berg et al., 2018). The time of data collection was not significantly different between the two study locations; however, average room temperature was significantly warmer in Yakutia. Differences in supraclavicular temperature between the two study samples may be linked to variation in subcutaneous adipose tissue thickness (Gatidis et al., 2016). Sum of skinfolds, however, was not a significant predictor of variation in supraclavicular temperature.

It is also possible that population differences in BAT thermogenesis may be linked to developmental plasticity or recent acclimatization to low temperatures. Yakut individuals that were exposed to greater cold stress during early childhood exhibit greater evidence of BAT thermogenesis in adulthood (Levy et al., 2021). Huttunen, Hirvonen, and Kinnula (1981) document that outdoor workers in Finland have greater BAT stores around the neck and heart compared with indoor workers. BAT mass and metabolic activity increases after 10 days of cold exposure in a lab setting and from the summer to winter season (van der Lans et al., 2013; Yoneshiro et al., 2016). Since data collection in Yakutia took place during the transition from summer to early autumn, population differences may be confounded by variation in recent cold stress exposure. More dramatic population differences in BAT thermogenesis may be detected by studies conducted in the winter.

Participants in Yakutia also maintained significantly warmer sternum temperatures after cooling. This is consistent with previous work documenting warmer skin temperatures after cold exposure among indigenous circumpolar populations compared with other groups (Frisancho, 1993; Miller & Irving, 1962). Indigenous populations of the North American Arctic maintained warmer hand and foot temperatures than other participants (Brown & Page, 1952; Frisancho, 1993; Page & Brown, 1953). Little, Thomas, Mazess, and Baker (1971) found that Quechua adults in highland Peru, exhibited significantly warmer skin temperatures than Quechau children after cooling, while nonindigenous children and adults displayed similar skin temperatures after cold exposure. This suggests that developmental plasticity may shape variation in vasoconstriction/vasodilation responses to low temperatures (Frisancho, 1993).

Change in skin temperature of the sternum was positively associated with multiple mechanisms of adaptation to low temperatures including change in supraclavicular temperature and divergence of RMR. These results speak to the degree to which the process of adaptation to cold climates involves multiple integrated biological pathways. The ability to maintain warmer skin temperatures by quickly cycling between vasoconstriction and vasodilation, known as hunting response, provides crucial protection against frostbite (Daanen, Van de Linde, Romet, & Ducharme, 1997). Heat lost during intermittent vasodilation may be replaced by thermogenesis due to elevations in RMR or BAT metabolic and endocrine activity.

Interestingly, ΔEE and %ΔEE after cooling were not significantly different between the two study locations. Neither sample exhibited a significant change in cold-induced energy expenditure. Additionally, both samples exhibited a wide degree of variation in %ΔEE ranging from a decrease of more than 25% in some individuals and an increase of over 50% in others. Celi et al. (2010), Muller et al. (2014), van der Lans et al. (2015), and other studies reviewed by Yurkevicius, Alba, Seeley, and Castellani (2021), also document increases as well as declines in energy expenditure in response to acclimation to mild cooling. A decline in energy expenditure during mild cooling is a key characteristic of a habituation response (Yurkevicius et al., 2021). Habituation to cold stress is hypothesized to benefit the organism by conserving energy that would otherwise be spent responding to sub-lethal stimuli (Yurkevicius et al., 2021). Yurkevicius et al. (2021) provides a useful review of the human habituation response to cold stress. Multiple experimental studies document declines in metabolic rate in response to a mild cooling condition, such as 12°C water immersion. More severe or repeated cold exposure is more likely to induce a hypermetabolic response (Yurkevicius et al., 2021). Given the wide range of metabolic responses to the mild cooling condition in both study locations, additional research is needed to investigate the determinants of hypo- versus hypermetabolic responses to mild cooling.

Change in supraclavicular temperature was a significant predictor of ΔEE and %ΔEE in Yakutia but not in Evanston suggesting that the biological mechanisms that underlie energy expenditure during NST may differ between these two populations. The mechanisms responsible for NST are currently debated (Carpentier et al., 2018). Previous work among populations outside circumpolar regions have documented a significant correlation between BAT metabolic activity and change in energy expenditure after cooling suggesting that BAT plays a mechanistic role in NST (Chondronikola et al., 2016; Muzik et al., 2013; u Din et al., 2016; van der Lans et al., 2013). These studies differ from our protocol in that the cooling condition was significantly longer (2–6 h) and/or involved repeated cold exposure over multiple days. Despite evidence for a significant relationship between BAT metabolic activity and cold-induced energy expenditure, the tissue-specific metabolic rate of BAT is estimated to contribute less than 12 kcal/100 g/day to total energy expenditure (Muzik et al., 2013). BAT may contribute to cold-induced energy expenditure through its action as an endocrine organ by triggering an increase in metabolism within other tissues during NST (Bal et al., 2017). For instance, BAT secretes interleukin-6, 3-methyl-2-oxovaleric acid, 5-oxoproline, β-hydroxyisobutyric acid, and 12,13-diHOME which upregulate oxidative metabolism in skeletal muscle (Bal et al., 2017; Shamsi, Wang, & Tseng, 2021; Stanford et al., 2018; Whitehead et al., 2021). Deep muscles that co-locate with BAT, such as levator scapulae, exhibit an increase in metabolism during NST (u Din et al., 2016). Thus, it is possible that BAT and muscle act synergistically during NST.

While participants in Evanston and Yakutia both exhibited average RMRs that were lower than expected based on FFM, divRMR was significantly higher in Yakutia than in Evanston. This suggests that adults in Yakutia exhibit greater adaptive elevations in RMR in response to chronic cold exposure than adults in Evanston. Previous research has documented elevations in RMRs among Indigenous Siberian groups, including the Yakut, Evenki and Buryat (Leonard et al., 2002; Snodgrass, 2004). Leonard et al. (2005) documented that average percent deviations in RMR above norms based on FFM were + 18.8 among Indigenous Siberian women and + 16.4 among men. Deviations in RMR among Yakut adults may be lower in the present study than previous work due to differences in lifestyle of the study sample or changes in heating infrastructure. In the past few decades, a growing number of households in Yakutia have adopted central heating in place of a wood-burning stoves (*pechka*). Shifts in lifestyle and subsistence practices due to market integration in Yakutia may lead to differences in metabolic adaptation to cold climates over time. Previous work Shephard and Rode (1996) suggest that shifts in market integration, access to new technologies, and lifestyle change may influence variation in RMR among indigenous circumpolar groups (Galloway, Leonard, & Ivakine, 2000; Ocobock, Soppela, Turunen, Stenbäck, & Herzig, 2020; Shephard & Rode, 1996).

Our results suggest that the relationship between BAT and cardiometabolic health may vary across populations. Change in supraclavicular temperature was significantly associated with %ΔEE among adults in Yakutia but not in Evanston. If the relationship between BAT thermogenesis and energy expenditure differs across populations, the relationship between BAT and biomarkers of cardiometabolic health, such as fasting blood glucose and cholesterol levels, may also vary. For example, our previous work documented higher fasted blood glucose levels among Yakut adults with greater BAT thermogenesis; however, Becher et al. (2021) found that adults with greater BAT mass and metabolism exhibit lower blood glucose levels. Additional research is needed to investigate the environmental and evolutionary origins of population variation in BAT and its health correlates.

The methodological approach of this study presents several key limitations. First, the study uses an indirect method for quantifying BAT thermogenesis. The standard approach for quantifying BAT mass and metabolic activity is to use a combination of positron emission tomography (PET) and computed tomography (CT); however, this method was not feasible for this study sample due to both access and cost. Instead, we quantified changes in skin temperature of the supraclavicular area as an indirect marker of BAT thermogenesis. Because this is an indirect measure, it is difficult to disentangle the contribution of BAT thermogenesis to shifts in supraclavicular skin temperature from thermogenesis generated elsewhere in the body (Levy, 2019). Recent work, however, has used PET/CT scans to validate change in supraclavicular temperature as a biomarker for quantifying BAT metabolic activity (Chondronikola et al., 2016; van der Lans, Vosselman, Hanssen, Brans, & van Marken Lichtenbelt, 2016). The sum of skinfolds was used to assess body fatness and BIA was used to quantify variation in fat-free mass. While dual-energy x-ray absorptiometry (DXA) is considered the gold standard for assessing body composition parameters such as percent body fat and fat-free mass, access to this method was not feasible in the study locale. Additionally, shivering was detected through participant self-report rather than via electromyography (EMG).

Additional research is needed in order to delineate the role that genetic mechanisms, developmental plasticity, and acclimatization play in shaping population variation in BAT and other mechanisms of adaptation to cold stress. Future work should examine seasonal shifts in BAT metabolism among circumpolar populations and their relationship with other metabolic adaptations. Additionally, little is known about developmental changes in BAT across the human life course and how environmental factors may influence developmental plasticity in this tissue. Future work investigating these topics will shed light on the relationship between BAT and energy expenditure as wells its significance for metabolic health.

In summary, the present study indicates that Yakut young adults exhibit greater BAT thermogenesis than young adults in the Midwest, United States. Additionally, Yakut adults exhibit a stronger relationship between BAT thermogenesis and cold-induced energy expenditure. This work sheds light on the synergistic relationships between metabolic adaptations and skin temperature control via vasoconstriction/vasodilation and highlights the degree to which the process of biological adaptation to cold climates integrates multiple biological mechanisms that act on a range of timescales.

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## CONFLICT OF INTEREST

The authors do not have any conflicts of interest to declare.

## AUTHOR CONTRIBUTIONS

**Stephanie B. Levy:** Conceptualization (lead); data curation (lead); formal analysis (lead); funding acquisition (lead); investigation (equal); methodology (equal); project administration (equal); visualization (lead); writing – original draft (lead); writing – review and editing (lead). **Tatiana M. Klimova:** Conceptualization (supporting); investigation (equal); methodology (equal); project administration (equal); resources (lead); writing – review and editing (supporting). **Raisa N. Zakharova:** Investigation (equal); methodology (equal); project administration (equal); resources (supporting). **Afanasiy I. Fedorov:** Investigation (equal); methodology (equal); project administration (equal); resources (supporting). **Valentina I. Fedorova:** Investigation (equal); methodology (equal); project administration (equal); resources (supporting). **Marina E. Baltakhinova:** Investigation (equal); methodology (equal); project administration (equal); resources (supporting). **Madison Bondy:** Investigation (equal); methodology (equal); project administration (equal); writing – review and editing (supporting). **Dania Atallah:** Investigation (equal); methodology (equal); project administration (equal). **Jennah Thompson-Vasquez:** Investigation (equal); methodology (equal); project administration (equal); writing – review and editing (supporting). **Kaylin Dong:** Investigation (equal); methodology (equal); project administration (equal); writing – review and editing (supporting). **Anne Debertine:** Investigation (equal); methodology (equal); project administration (equal). **William R. Leonard:** Conceptualization (supporting); funding acquisition (supporting); investigation (equal); methodology (equal); project administration (equal); resources (supporting); writing – review and editing (supporting).

## DATA AVAILABILITY STATEMENT

The project's de-identified data are stored in a password-protected data repository managed by Northwestern University. The data are available for further analysis to researchers who have received ethics approval from the Northwestern University IRB by contacting Stephanie B. Levy.

## ORCID

*Stephanie B. Levy* https://orcid.org/0000-0003-2828-2014
*Tatiana M. Klimova* https://orcid.org/0000-0003-2746-0608
*Raisa N. Zakharova* https://orcid.org/0000-0002-1395-8256
*Afanasiy I. Fedorov* https://orcid.org/0000-0002-7973-6103
*Valentina I. Fedorova* https://orcid.org/0000-0002-6147-4643
*Marina E. Baltakhinova* https://orcid.org/0000-0003-0986-7754
*William R. Leonard* https://orcid.org/0000-0002-6233-604X

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## SUPPORTING INFORMATION

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