Received: 22 January 2021 | Revised: 6 April 2021 | Accepted: 17 April 2021
DOI: 10.1002/ajpa.24297

RESEARCH ARTICLE

American Journal of PHYSICAL ANTHROPOLOGY
WILEY

Evidence for a sensitive period of plasticity in brown adipose tissue during early childhood among indigenous Siberians

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Funding information
Directorate for Social, Behavioral and Economic Sciences, Grant/Award Number: BCS-1455804; Leakey Foundation; Northwestern University

Abstract

Objectives: Evolutionary theorists have debated the adaptive significance of developmental plasticity in organisms with long lifespans such as humans. This debate in part stems from uncertainty regarding the timing of sensitive periods. Does sensitivity to environmental signals fluctuate across development or does it steadily decline? We investigated developmental plasticity in brown adipose tissue (BAT) among indigenous Siberians in order to explore the timing of phenotypic sensitivity to cold stress.

Methods: BAT thermogenesis was quantified using infrared thermal imaging in 78 adults (25 men; 33 women). Cold exposure during gestation, infancy, early childhood, middle childhood, and adolescence was quantified using: (1) the average ambient temperature across each period; (2) the number of times daily temperature dropped below -40°F during each period. We also assessed past cold exposure with a retrospective survey of participation in outdoor activities.

Results: Adult BAT thermogenesis was significantly associated with the average temperature ($p = 0.021$), the number of times it was below -40°F ($p = 0.026$), and participation in winter outdoor activities ($p = 0.037$) during early childhood.

Conclusions: Our results suggest that early childhood represents an important stage for developmental plasticity, and that culture may play a critical role in shaping the timing of environmental signals. The findings highlight a new pathway through which the local consequences of global climate change may influence human biology, and they suggest that ambient temperature may represent an understudied component of the developmental origins of health and disease.

KEYWORDS
adaptation, circumpolar, climate change, development, energetics

1 | INTRODUCTION

The role that developmental plasticity plays in adaptive evolution remains contested, especially for organisms with slow growth and long lifespans such as humans (DeWitt & Scheiner, 2004; Pigliucci & Murren, 2003). When an organism's phenotype responds to environmental signals during development, it runs the risk of cultivating a phenotype that is discordant with future conditions. Integral to this issue is a debate concerning the timing of sensitive periods, or a window during which exposure to environmental factors modulates the emergence of specific phenotypes (Meredith, 2015). When are humans most sensitive to environmental conditions? Studies of growth and nutrition suggest that environmental signals conveyed during gestation and infancy will have a greater effect on the phenotype than subsequent life stages due to constraints on one's ability to adjust their phenotype with increasing age (Wells, 2014). However, sensitive periods may also exist during childhood and adolescence if the biological systems that are maturing during these life stages are responsive to environmental conditions (Knudsen, 2004). For example, previous work documents that environmental signals conveyed during childhood and adolescence are crucial for the development of adaptations to high-altitude hypoxia, the microbiome, language skills, and variation in bone mass (Frisancho, 1993; Greksa, 1990; Monjardino et al., 2019; Newport et al., 2001; Yazdanbakhsh et al., 2002).

Developmental plasticity in metabolic adaptation to cold stress has not been widely explored in humans; yet, there are compelling reasons to expect that it occurs. For instance, prior investigations among indigenous and non-indigenous adults living in Siberia suggest that both genetic and developmental factors likely underlie metabolic adaptations to cold climates (Leonard et al., 2002). Previous work indicates that populations indigenous to high altitude and circumpolar regions exhibit developmental adaptation with respect to changes in skin vasoconstriction/vasodilation in response to cold (Frisancho, 1993; Miller & Irving, 1962).

One mechanism that may link early-life cold exposure with adult metabolic adaptation is developmental plasticity in brown adipose tissue (BAT). During non-shivering thermogenesis, human BAT produces heat by uncoupling oxidative phosphorylation from ATP production via uncoupling protein 1 (UCP1). This process is referred to as BAT thermogenesis and is associated with an increase in cold-induced energy expenditure (CIEE) (Levy et al., 2018; van der Lans et al., 2016). The primary BAT depot in adults is located in the supraclavicular area. Human BAT depots consist of a combination of brown and beige adipocytes (a form of adipose tissue that is similar to BAT but has a reduced thermogenic capacity), and beige adipocytes can be found scattered in white adipose tissue (Roh et al., 2018). Further research is needed to parse out the relative contribution of beige and brown fat to human variation in adipose tissue; thus, this paper will collectively refer to beige and brown fat as BAT. Past research suggest that BAT thermogenesis plays a role in acclimatization to cold stress in humans (Au-Yong et al., 2009; Huttunen et al., 1981; Yoneshiro et al., 2016). In addition, BAT stores may have protective effects against cardiometabolic diseases such as type II diabetes mellitus, while individuals with obesity may have a diminished capacity for CIEE (Becher et al., 2021; Brychta et al., 2019; Iwen et al., 2017).

BAT mass and metabolism fluctuates across the life course, and developmental changes in BAT may be sensitive to environmental conditions. Human BAT first develops around the 20th gestational week (Velickovic et al., 2014). The thermal environment of the fetus is tightly buffered by maternal thermoregulation; however, several endocrine factors that regulate brown adipogenesis, such as thyroid hormone, are sensitive to climatic conditions and pass through the placenta (Loubière et al., 2010). Thus, it is possible that differential maternal exposure to cold stress during the final 20 weeks of gestation may result in developmental programming of offspring BAT growth and metabolism. At birth, the neonate experiences the first significant cold stress. In response, BAT stores in the interscapular region, the neck, and around the trachea, esophagus, aorta, paravertebral autonomic ganglia, kidneys, and adrenals all grow significantly during the first few weeks of life (Symonds & Lomax, 1992). Over time, BAT mass gradually declines as the infant shifts from relying on non-shivering thermogenesis toward shivering as the primary response to cold stress (Naeye, 1974). BAT stores in the neck and supraclavicular region, and around the kidneys, adrenals, and aorta, however, are more resistant to regression with age (Heaton, 1972). Previous work suggests that the infancy-childhood transition is marked by distinct shifts in adipose tissue gene expression. Post-mortem biopsies of BAT taken from the perirenal adipose depot of young children exhibited higher concentrations of uncoupling protein content than biopsies from infants (Lean et al., 1986). A more recent study of epicardial adipose tissue found that the expression of genes associated with thermogenesis, such as UCP1, is higher in children ages 2–7 years old compared to infants that are under 2 years old (Ojha et al., 2016). Similar results were documented by a study of UCP1 expression in adipose tissue biopsies from perirenal, subcutaneous, and visceral depots (Rockstroh et al., 2015). These results suggest there may be a repopulation of thermogenic cells during early childhood. Studies that use infrared thermal imaging to quantify BAT thermogenesis in children suggest that the transition from early childhood to middle childhood is marked by a decline in BAT thermogenesis; this work documents a negative association between BAT thermogenesis and age in children ages 6–11 years old (Robinson et al., 2014). Interestingly, retrospective PET/CT studies of BAT in pediatric patients found that the frequency of BAT detection was higher among patients that had undergone puberty than prepubertal patients (Drubach et al., 2011; Gilsanz et al., 2012). This work suggests that there may be an increase in brown adipogenesis during puberty. Here we explore whether developmental shifts in BAT mass and metabolic activity are sensitive to variation in ambient low temperature exposure.

Previously, our research team has examined variation in BAT among the Yakut, a population that is indigenous to northeastern Siberia. This work found that Yakut adults with greater BAT thermogenesis exhibit significantly greater CIEE and preferentially metabolize carbohydrates during mild cold exposure (Levy et al., 2018). In the Lena River Valley of the Sakha Republic (Yakutia), infants are well bundled from the cold and primarily kept indoors while children and adolescents assist with outdoor subsistence activities and play outside throughout the winter (Crate, 2006). While it is clear that human BAT undergoes dynamic changes across the life course, the degree to which BAT plasticity is sensitive to environmental conditions during particular life stages is unknown. We quantified variation in adult BAT thermogenesis and early-life cold exposure among Yakut (Sakha) adults in order to examine which developmental stages represent sensitive periods. Our results below highlight early childhood as a potential sensitive period in BAT plasticity among the Yakut.

2 | METHODOLOGY

2.1 | Study population

The Sakha Republic, also known as Yakutia, is a semi-autonomous state within the Russian Federation. It is located in northeastern Siberia and has a population of over 958,000 people. Ambient temperature regularly drops below −40°C (−40°F) in the winter and surpasses 30°C (86°F) in the summer. A majority of the population, around 450,000 people, are Yakut, a population indigenous to this region (Russian Census, 2010). Data collection took place in the capital city, Yakutsk (62°N, 129°E; population 269,600) and the village of Berdygestiakh (62°N, 127°E; population 6400), both of which are located in the Lena River Valley (Russian Census, 2010).

Prior to Russian expansion in the 17th century, Yakut people in the Lena River Valley practiced a semi-nomadic transhumant pastoralism (Forsyth, 1994). In 1930s, the Soviet Union organized Yakut families into herding and farming collectives. 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. Thus, Yakut villagers faced a variety of both challenges and opportunities related to defining new subsistence strategies (Crate, 2006).

Today, a majority of Yakut households depends on a mixed cash economy that consists of a combination of subsistence practices and cash inputs (Crate, 2006). There is a wide diversity of economic strategies at the community, household, and even the individual level. Common subsistence practices include raising cattle and horses, picking berries, herbs and other naturally growing foods, growing vegetables, hunting and fishing. The degree of participation in these activities ranges across a wide spectrum and typically shifts with the season.

2.2 | Participants

Data were collected at the Gorny Regional Medical Center in Berdygestiakh, Sakha Republic (Yakutia), Russia from September 5–11, 2015, and at M.K. Ammasov North-Eastern Federal University (NEFU) in Yakutsk, Sakha Republic (Yakutia), Russia from September 12–23, 2015. During this time period, the average high temperature was 55°F (12.8°C) and the average low was 33°F (0.6°C). The study was advertised in the local newspaper, local radio station, and via word of mouth. 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 7 h 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 Northwestern University Institutional Review Board granted permission to conduct this study (IRB 00200092) and all participants provided informed consent. The sample included 25 men and 33 women (Table 1). The project's deidentified data is stored in a password-protected data repository managed by Northwestern University (Northwestern Box). The data are available for further analysis to researchers who have received ethics approval from the Northwestern University IRB by contacting Dr. Stephanie Levy.

2.3 | Anthropometry

Anthropometric dimensions were taken using standardized techniques (Lohman et al., 1992). Stature was measured to the nearest millimeter using a portable field stadiometer (Seca). Triceps, biceps, subscapular, and suprailiac skinfold thicknesses were measured to the nearest 0.5 mm using calipers (Lange), and the sum of the four skinfolds was calculated. Body mass, percent body fat, and fat-free mass (FFM) were measured using a digital bioimpedence analysis (BIA) scale (Tanita) set to the non-athlete setting. Tanita does not release body composition algorithms due to proprietary claims.

TABLE 1 Anthropometric dimensions, age, and BAT thermogenesis for Yakut men and women in sample

	Males ($n = 25$)		Females ($n = 33$)	
Measure	Mean	SD	Mean	SD
Age (years)[a]	23.1	6.3	25.8	7.5
Weight (kg)	65.5***	11.7	53.2	8.3
Fat-free mass (kg)	55.5***	6.2	41.8	3.1
Sum of skinfolds (mm)	59.1***	29.0	75.2	18.9
Body mass index[a]	22.2	3.8	21.0	2.8
BAT thermogenesis (°C)[a]	0.013	0.227	0.027	0.291

Note: Unpaired *t*-tests of sex differences are significant at: *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$.

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

2.4 | Infrared thermal imaging

We quantified change in maximum supraclavicular skin temperature (°C) and sternum skin temperature (°C) (a location without BAT) during two temperature conditions—a baseline 20-min room-temperature condition (20–28°C), and after a 30-min cooling condition (15°C). The change in skin temperature of the supraclavicular area was taken as an indirect measure of BAT thermogenesis (Chondronikola et al., 2016; van der Lans et al., 2016). We also calculated the change in temperature of a point on the sternum in order to control for effect of vasoconstriction of the core on skin temperature. Participants were fasted for at least 7 h prior to data collection. Participants wore lightweight clothing (average clo value of 0.35) underneath a water-perfused suit (Allen-Vanguard) for temperature manipulation.

An infrared thermal imaging camera (FLIR, E60bx) was positioned 1 m above the supine participant away from walls and other objects that might produce interfering infrared light. The emissivity was set at 0.98 and the ambient temperature and humidity were set to values taken from the study room. BAT thermogenesis was estimated by infrared thermal imaging using the techniques described by Levy (Levy, 2019).

During the room-temperature condition, participants rested quietly in a supine position. At the end of the 20-min room-temperature condition, we captured thermal images of the left and right sides of the supraclavicular area and the sternum using the infrared thermal imaging camera. The cooling condition took place immediately after the room-temperature condition. During the cooling condition, cold water (mean temperature: 10.3°C ± 2.9°C) was pumped through the tubing of the water-perfused suit for 30 min. The temperature of the water was monitored throughout the cooling condition and ice water was added as necessary in order to ensure that the inside lining of the suit was maintained at approximately 15°C. Thermal images of the neck and shoulder area were captured every 5 min. 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 non-shivering thermogenesis and minimize shivering. A total of five out of 58 participants shivered.

We used FLIR Tools Software (FLIR) to analyze the thermal images that were captured at the end of the room-temperature condition and the cooling condition (Figure 1). We calculated the change in maximum skin temperature of the supraclavicular area as a measure of BAT thermogenesis and the change in temperature of the sternum as a control.

2.5 | Selection of possible sensitive periods

Our analyses examine the relationship between adult BAT thermogenesis and ambient temperature exposure during five potential sensitive periods during development. The potential sensitive periods include gestation (the final 20 weeks), infancy (birth to less than 2 years old), early childhood (2 years old to less than 7 years old), middle childhood (7 years old to less than 12 years old), and adolescence (12 years old to less than 17 years old). The timing of the potential sensitive periods was chosen based on previous literature describing changes in adipose tissue physiology across development and the timing of puberty among Yakut among women (Douglas et al., 2014).

2.6 | Ambient temperature exposure

The NOAA Climate Data Online (NOAA National Center for Environmental Information) database maintains daily climate data captured at a weather station in Yakutsk, Russia beginning on March 3, 1888. We downloaded a data file that included average daily temperature in Yakutsk from 1950 to 2016. The weather data were used to calculate

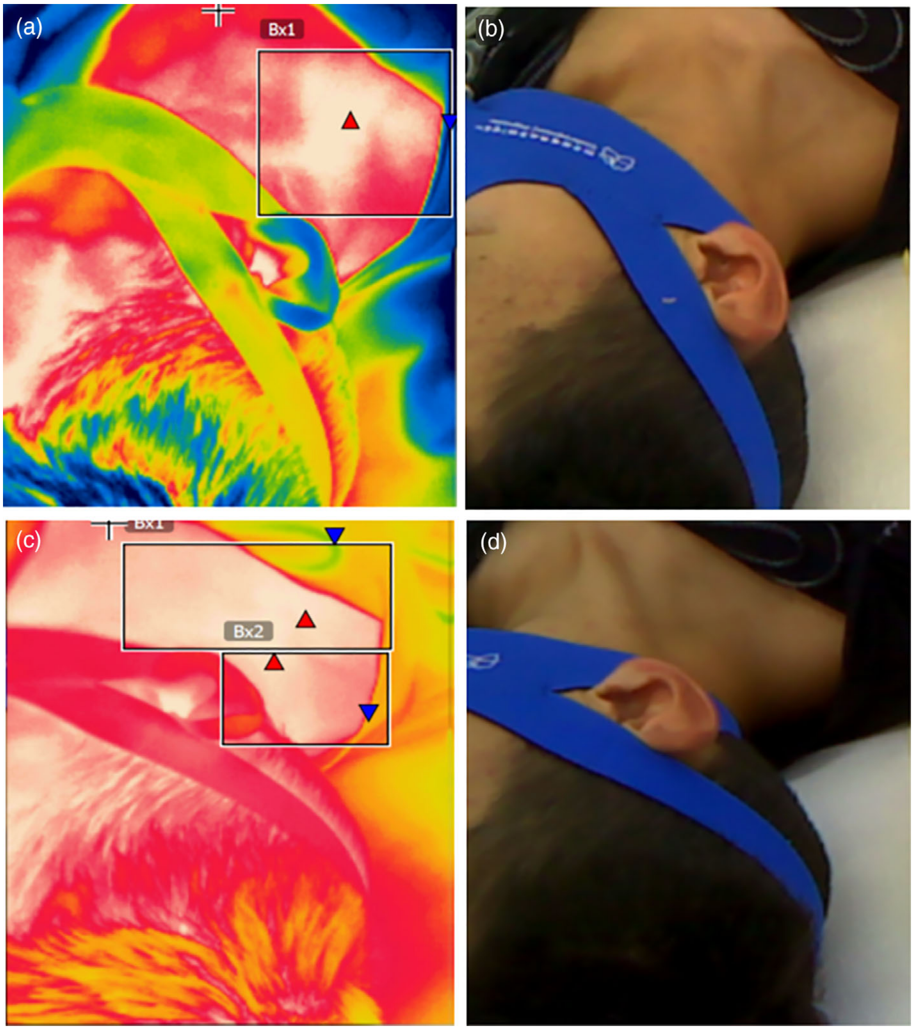

FIGURE 1 Thermal and digital images captured during the room-temperature and cooling conditions. (a) Thermal image captured during the room-temperature condition with box tool and spot tool added from FLIR tools software. The maximum temperature is signified by the red triangle. (b) Digital image captured during the room-temperature condition. (c) Thermal image captured at the end of the cooling condition with box tools and spot tool added from FLIR tools software. Two box tools were sometimes necessary to determine the maximum temperature without encompassing the inner ear temperature. (d) Digital image captured at the end of the cooling condition

for each participant the mean temperature of each potential sensitive period. We also counted the total number of days the average temperature was below −40°F for each potential sensitive period. The cutoff of −40°F was chosen because it is approximately two standard deviations below the average winter temperature. Table S1 displays descriptive statistics for these variables.

2.7 | Childhood outdoor activities survey

We administered a survey of participation in wintertime childhood outdoor activities. The survey design was based on previous work assessing how children spend their time (Silvers et al., 1994) and was modified to be suitable for the Siberian cultural context. We asked participants to report whether they participated in a list of winter outdoor activities and how often they performed each activity between ages 5–7, 8–10, 11–13, and 14–16 years old. The frequency of each activity is coded 0 through 2 according to how often the activity was performed (0: never; 1: occasionally; 2: often). Participants also reported whether the home(s) in which they lived were heated by a radiator (coded as 0) or a wood burning stove (*pechka*) (coded as 1).

The frequency of participation in most activities increased with age. As expected, the types of cold-weather activities that were most common differed between the age groups. Activities with a mean of 1.0 or greater were used to calculate the activity score for each age group (Table S2). Thus, for each age group, the activity score is the average degree of participation across the activities included in the score. Table S3 presents the average activity score for males and females and the entire sample at each age range. The mean scores were not significantly different between the sexes except for the score for 14–16 years old.

2.8 | Statistical analysis

Statistical tests were run using StataIC 13.0 (Statacorp LLC) and were considered statistically significant at p value ≤0.05. We assessed the distribution of each variable using Shapiro–Wilk and Shapiro–Francis tests for normality. Our small sample size prohibited us from running sex-specific analyses. Thus, we tested for differences in age, anthropometric dimensions, BAT thermogenesis and CIEE between males and females using either Student's t-tests or Wilcoxon rank-sum (Mann–Whitney) tests (Table 1). All regressions were checked for normally distributed residuals and heteroscedasticity and run with robust standard errors as needed. Age, sex, percent-body fat, fat-free mass, trial start time, and change in sternum temperature were chosen as potential covariates in multiple regression analyses, and variance inflation factors were calculated for each variable (Levy, 2019).

We were interested in whether the methods we used to assess cold exposure during development (i.e., average temperature during each potential sensitive period, the total number of days below −40°C during each potential sensitive period, and activity score at each age group) were closely associated with each other. We therefore created a table that presents a matrix of the associations (Spearman's rho values) between each of these variables (Table S4).

3 | RESULTS

First, we explored the relationship between early-life cold exposure and adult BAT thermogenesis by calculating the mean temperature that each participant was exposed to during gestation, infancy, early childhood, middle childhood, and adolescence using data that were recorded by a weather station in Yakutsk between 1950 and 2016 (Table S1). We explored the relationship between adult BAT thermogenesis and the mean temperature of each potential sensitive period using Spearman's rank correlations. There was a trend suggesting a positive relationship with mean temperature during infancy (p = 0.057), while mean temperature during early childhood was negatively associated with adult BAT thermogenesis (p = 0.020) (Figure S1). To test whether early childhood represents a sensitive period in BAT plasticity, we ran a multiple regression of adult BAT thermogenesis on the mean temperature of each potential sensitive period and other confounding variables. Mean temperature during early childhood was negatively associated with BAT thermogenesis (p = 0.021), and there was a significant negative relationship between mean temperature during adolescence and adult BAT thermogenesis (p = 0.027), (Figures 2(a) and 3; Table 2).

To further examine the timing of sensitive periods in BAT plasticity, we counted the total number of times the daily average temperature dropped below −40°F (−40°C) during each sensitive period (Table S1). We chose this cutoff because −40°F is approximately two standard deviations below the mean winter temperature between 1950 and 2016. We ran a multiple regression of adult BAT thermogenesis on the number of days below −40°F during each potential sensitive period, controlling for covariates (Figure 2(b)). Participants that experienced a larger number of days below −40°F during early childhood exhibited significantly greater BAT thermogenesis in adulthood (p = 0.026) (Figure 4, Table 3).

We also examined whether differences in lifestyle during childhood and adolescence may be associated with adult BAT thermogenesis due to differential cold exposure during these life stages. Using the Childhood Winter Outdoor Activities Survey, we calculated an activity score that quantifies participation in winter outdoor activities for each of the following sequential age groups: 5–7, 8–10, 11–13, and 14–16 years old (see Tables S2 and S3). A higher activity score connotes greater reported participation in outdoor activities. We explored the relationship between adult BAT thermogenesis and the activity score for each age group using Spearman's rank correlations. There was a significant association between adult BAT thermogenesis and activity score for the five to seven (p = 0.036) and the 11 to 13 age groups (p = 0.023), and a trend suggesting a positive relationship with the activity score for the 8–10 age group (p = 0.055) and the 14–16 age group (p = 0.086) (Figure 5). Next, we ran a multiple regression of adult BAT thermogenesis on the activity scores for each age group controlling for covariates (Figure 2(c)). Adults reporting greater participation in

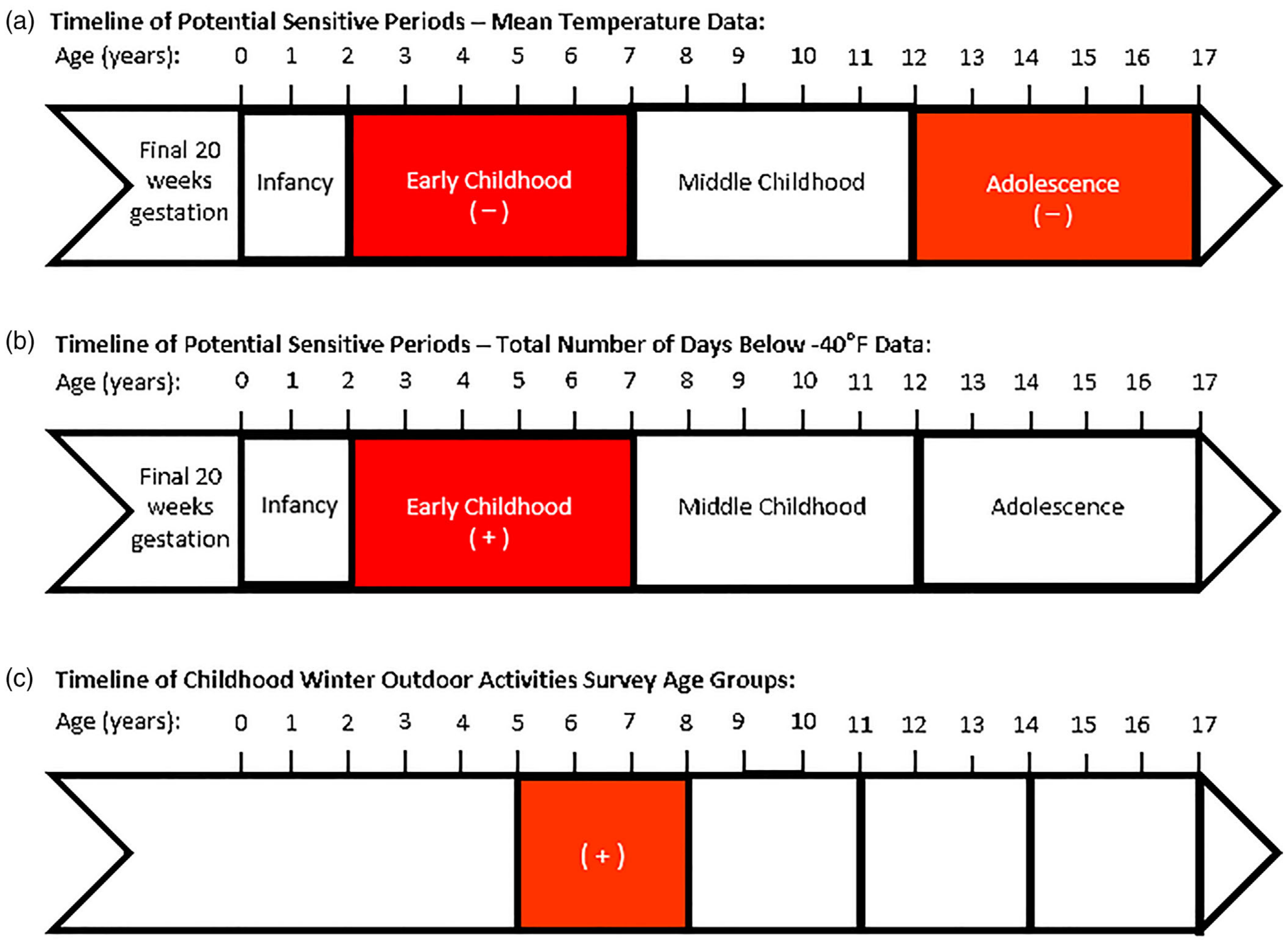

FIGURE 2 Timelines depicting the results of multiple regressions examining the relationship between cold exposure during development and adult BAT thermogenesis, controlling for covariates. Red denotes a relationship with adult BAT thermogenesis with a significance level of $p \le 0.05$ and orange indicates a relationship with $p \le 0.1$. The (+) and (−) convey the direction of the association. (a) Results of a multiple regression of adult BAT thermogenesis on the mean temperature of each sensitive period. (b) Results of a multiple regression of adult BAT thermogenesis on the total number of days below −40°F during each potential sensitive period. (c) Results of a multiple regression of adult BAT thermogenesis on the activity score for each age group

outdoor activities between ages five and seven exhibited significantly greater BAT thermogenesis ($p = 0.037$) (Table 4). We also examined whether there were differences in BAT thermogenesis between individuals that grew up with a wood burning stove (*pechka*) versus central heating. Adult BAT thermogenesis was not associated with how the home was heated. In addition, there were no associations with either individual or family income (Table S5).

4 | DISCUSSION

Our results suggest that, among the Yakut, BAT developmental plasticity is most sensitive to cold stress exposure during early childhood. As seen in Figure 1, our analyses of historic weather data suggest that exposure to lower temperatures during early childhood (ages 2–6 years old) is associated with greater BAT thermogenesis in adulthood. Similarly, adult BAT thermogenesis is significantly correlated with greater participation in outdoor winter activities during ages 5–7 years old—a timeframe that overlaps with the early childhood sensitive period. Cold exposure during early childhood may program developmental pathways that influence BAT thermogenesis by either promoting brown adipocyte proliferation or BAT metabolic activity.

There are, however, several reasons we should approach this interpretation of the results with circumspection. First, the significance of these results is limited by the fact that this is a retrospective study that does not establish causality. The study sample was not randomly selected. Our recruitment techniques were likely biased toward individuals with high education levels and an interest in health. Thus, the lifestyles of the study participants may differ from the general population of Berdygestiakh and Yakutsk in important ways that might influence adult BAT thermogenesis. Given the small sample size, the multivariate linear regression models include a large number of variables, and so the amount of variation explained by our models may be inflated.

Our study used an indirect method for quantifying BAT thermogenesis. This approach uses the change in skin temperature of the supraclavicular area as an indicator 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 skin temperature of the supraclavicular area as a biomarker for quantifying BAT metabolic activity (Chondronikola et al., 2016; van der Lans et al., 2016).

Our approach to quantifying early-life cold exposure has multiple limitations. The final 20 weeks of gestation may not correspond with the fetal development of BAT for each individual due to variation in gestation length. In addition, the ambient temperature data were collected at a weather station in Yakutsk, Russia and many of the participants grew up in surrounding villages of Yakutia. Thus, many of the participants may have experienced temperatures that differed from those in Yakutsk. We did not find significant differences in BAT thermogenesis between individuals that grew up in a rural village versus in Yakutsk. The number of days the average temperature dropped below −40°F was treated as an additional line of evidence to examine the potential sensitive periods in BAT plasticity; however, the average temperature and the number of days below −40°F for each potential sensitive period are correlated with each other (Table S4). In addition,

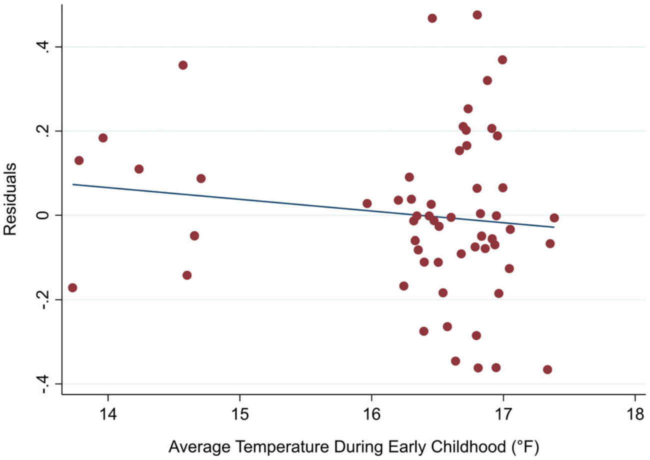

FIGURE 3 Scatterplot of the relationship between average temperature of early childhood (°F) and the residuals of potential covariates regressed on BAT thermogenesis. Covariates in the multiple regression include average temperature of gestation (°F), average temperature of infancy (°F), average temperature of middle childhood (°F), average temperature of adolescence (°F), age (years), sex (1 = M; 2 = F), fat-free mass (kg), sum of skinfolds (mm), trial start time, and sternum temperature change (°C)

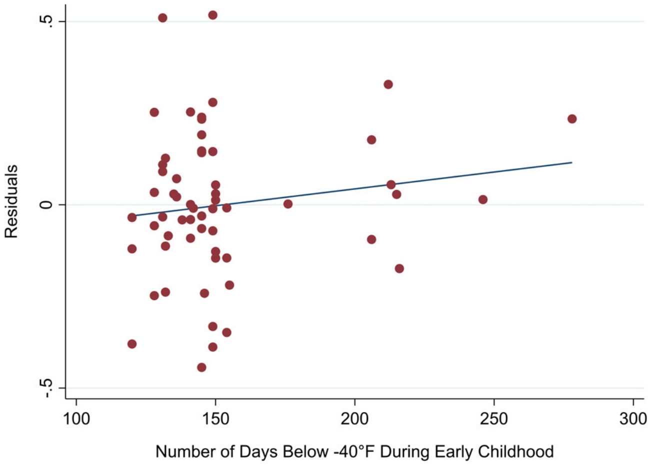

FIGURE 4 Scatterplot of the relationship between number of days below −40°F during early childhood and the residuals of potential covariates regressed on BAT thermogenesis. Covariates in the multiple regression include total number of days below −40°F during gestation, infancy, middle childhood, adolescence, age (years), sex (1 = M; 2 = F), fat-free mass (kg), sum of skinfolds (mm), trial start time, and sternum temperature change (°C)

TABLE 2 Multiple linear regression analysis of the relationship between mean temperature of each potential sensitive period and adult BAT thermogenesis controlling for potential covariates

Measure	Coefficient	Robust standard error	*p* Value
Gestation (°F)	0.0002	0.0009	0.825
Infancy (°F)	−0.006	0.035	0.866
Early childhood (°F)	**−0.175**	**0.073**	**0.021**
Middle childhood (°F)	0.112	0.064	0.087
Adolescence (°F)	**−0.210**	**0.092**	**0.027**
Age (years)	−0.033	0.026	0.205
Sex (1 = M; 2 = F)	0.001	0.127	0.992
Fat-free mass (kg)	0.002	0.009	0.849
Sum of skinfolds (mm)	0.001	0.001	0.347
Sternum temperature change (°C)	0.082	0.057	0.155
Trial start time	**−1.334**	**0.337**	**0.000**
Room temperature (°C)	**0.087**	**0.022**	**0.000**

Note: The sample size is 58, *p* values ≤0.05 are bolded, the residual degrees of freedom is 46, and the adjusted R^2 of the model is 0.380.

TABLE 3 Multiple linear regression analysis of the relationship between total number of days below −40°F during each potential sensitive period and adult BAT thermogenesis controlling for potential covariates

Measure	Coefficient	Robust standard error	*p* Value
Gestation	0.001	0.002	0.523
Infancy	0.003	0.002	0.189
Early childhood	**0.004**	**0.002**	**0.026**
Middle childhood	−0.001	0.001	0.186
Adolescence	0.003	0.002	0.154
Age (years)	−0.024	0.017	0.164
Sex (1 = M; 2 = F)	0.030	0.140	0.831
Fat-free mass (kg)	0.001	0.010	0.943
Sum of skinfolds (mm)	0.002	0.002	0.272
Sternum temperature change (°C)	0.053	0.061	0.306
Trial start time	**−1.30**	**0.342**	**0.000**
Room temperature (°C)	**0.084**	**0.022**	**0.000**

Note: The sample size is 58, *p* values ≤0.05 are bolded, the degrees of freedom is 46, and the adjusted R^2 of the model is 0.332.

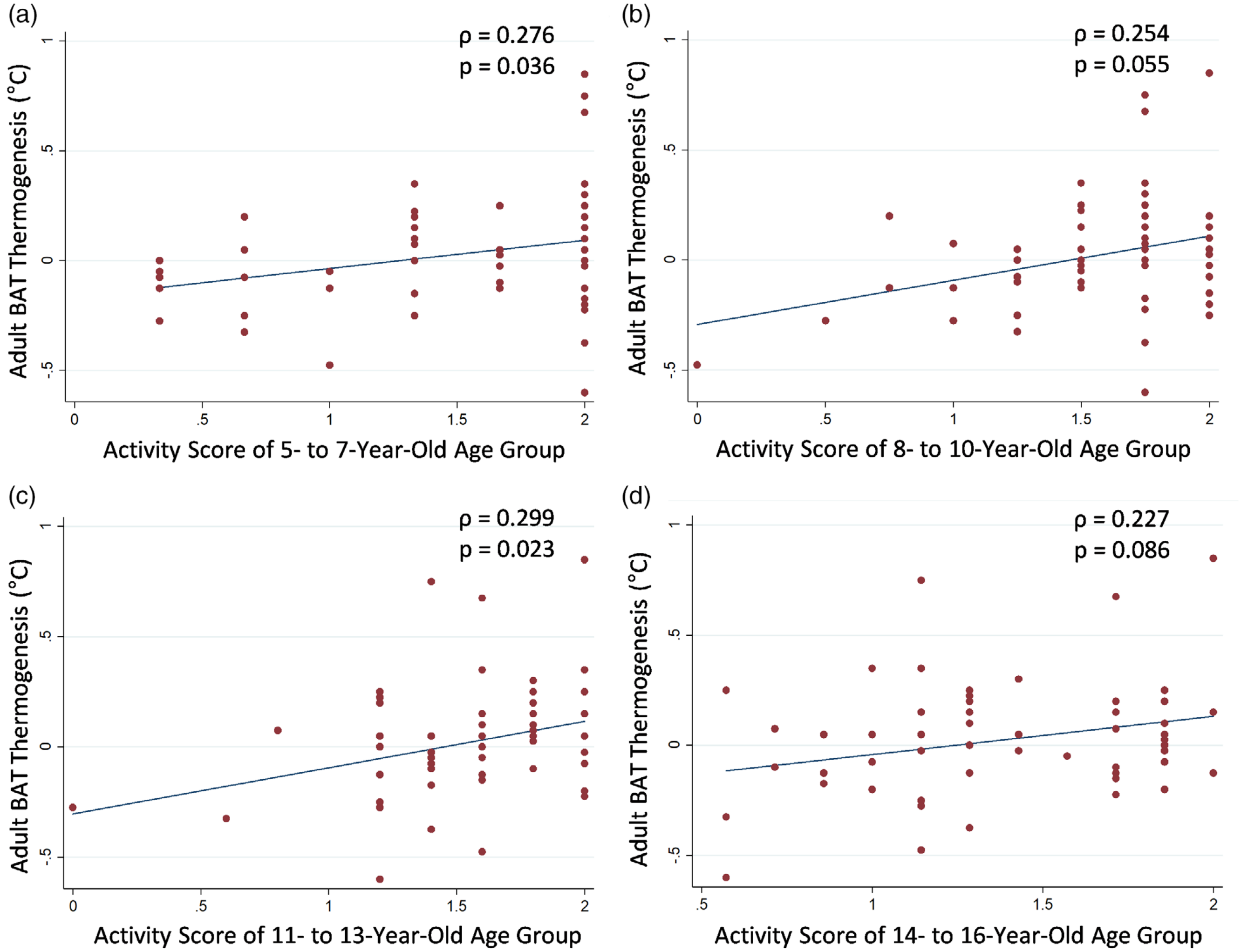

FIGURE 5 Scatterplots of the relationship between activity score of each age group and adult BAT thermogenesis and Spearman's correlation coefficients (*ρ*) (*n* = 58). (a) Activity score for the 5- to 7-year-old age group and adult BAT thermogenesis. (b) Activity score for the 8- to 10-year-old age group and adult BAT thermogenesis. (c) Activity score for the 11- to 13-year-old age group and adult BAT thermogenesis. (d) Activity score for the 14- to 16-year-old age group and adult BAT thermogenesis

TABLE 4 Multiple linear regression analysis of the relationship between activity score at each age group and adult BAT thermogenesis controlling for potential covariates

Measure	Coefficient	Robust standard error	*p* Value
Activity score for ages 5–7 y/o	**0.121**	**0.056**	**0.037**
Activity score for ages 8–10 y/o	0.072	0.075	0.343
Activity score for ages 11–13 y/o	−0.109	0.119	0.363
Activity score for ages 14–16 y/o	0.118	0.106	0.270
Age (years)	−0.002	0.005	0.778
Sex (1 = M; 2 = F)	0.027	0.138	0.844
Fat-free mass (kg)	0.001	0.009	0.393
Sum of skinfolds (mm)	0.003	0.001	0.063
Sternum temperature change (°C)	0.007	0.053	0.897
Trial start time	−**1.452**	**0.374**	**0.000**
Room temperature (°C)	**0.081**	**0.021**	**0.000**

Note: The sample size is 58, *p* values ≤0.05 are bolded, the residual degrees of freedom is 47, and the adjusted R^2 of the model is 0.327.

the Childhood Winter Outdoor Activities Survey is limited by participants' ability to recall their past participation in various activities.

Our analyses may be confounded by variation in recent cold stress exposure. Since data collection took place during early autumn when temperatures were beginning to drop, we initially controlled for date of data collection; however, the addition of this variable did not influence the predictive power of our models. In addition, our analyses maybe confounded by variation in indoor physical activity. Research in rodent models indicates that physical activity stimulates BAT metabolism, and additional research is needed in order to test this relationship in humans (Dewal & Stanford, 2019).

Finally, the effect sizes appear modest. BAT is hypothesized to play a mechanistic role in human non-shivering thermogenesis, which can result in an increase in CIEE of over 30% (Levy et al., 2018; Sanchez-Delgado et al., 2019). Yet, estimates of the tissue-specific metabolic rate of BAT are small; a study of oxygen consumption of per gram of BAT found that activated BAT deposits contribute less than 12 kcal/100 g/day to total energy expenditure (Muzik et al., 2013). Multiple studies document a significant association between adult BAT metabolism and CIEE (Blondin et al., 2015; Chen et al., 2013; Hanssen et al., 2015; Muzik et al., 2017; van der Lans et al., 2013, 2016; van Marken Lichtenbelt et al., 2015; Vosselman et al., 2012; Yoneshiro et al., 2016). Variation in the cooling protocols makes it difficult to interpret the biological significance of these results. The multiple regression model in Table 2 suggests that an increase in average early childhood temperature of 1° (F) is associated with a decline in adult BAT thermogenesis of 0.170°C. Based on our previous research in Yakutia, this decline in BAT thermogenesis corresponds to a 4% difference in CIEE (Levy et al., 2018). Similarly, following the model in Table 3, an increase in the number of days below −40°F during early childhood of one standard deviation (~32 days) would correspond to an increase in BAT thermogenesis of 0.128°C and an approximately 3% difference in CIEE (Levy et al., 2018). While the effect sizes appear modest, additional research is needed in order to determine the biological implications of BAT developmental plasticity (for instance, by exploring its relationship with core body temperature or blood glucose homeostasis). Below we provide several possible explanations for the association between early childhood cold exposure and adult BAT thermogenesis so that future studies may further investigate the timing of sensitive periods for BAT plasticity and its evolutionary and health significance.

Similar to other metabolic systems, the biological pathways that shape BAT development may be most sensitive to ambient temperature earlier in development; however, in this population, cold stress exposure during pregnancy and infancy is limited due to technological adaptations and infant care practices. For example, BAT fetal development may be sensitive to the homeostatic mechanisms that respond cold stress in the mother, such as maternal thyroid hormones, but exposure to low temperatures during pregnancy may be limited. The buffering effect of technological adaptations and infant bundling may mask any relationship between cold exposure early in development and adult BAT thermogenesis. Despite declining sensitivity across the life course, BAT programming may persist into childhood. In Yakutia, as children become more independent, they are exposed to greater cold stress. In addition to unstructured playtime and organized winter sports, Yakut children help with outdoor winter chores, such as tending to livestock, hunting, and fishing (Crate, 2006). This may lead to developmental programming of BAT thermogenesis during early childhood. Thus, in humans, cultural contexts may influence the timing of when environmental signals are conveyed to the developing offspring.

Another explanation is that during gestation and infancy the biological systems that govern BAT development are buffered from acute cold stress by maternal biology. As the child grows and gains independence, developing systems may become more sensitive to the surrounding environmental conditions that are divorced from maternal biology, such as ambient temperature. Plasticity during early childhood may further fine-tune the developing phenotype by incorporating additional environmental information that is gathered by the child independent of maternal biological signals. Environmental signals conveyed during early childhood may increase the chances that the developing phenotype will be well suited for future conditions.

This interpretation is consistent with multiple developmental hypotheses. Short-term environmental signals are unlikely to be reliable predictors of future conditions (Wells, 2007; Wells & Johnstone, 2017). The adaptive value of maternal signals is hypothesized to be enhanced by incorporating information across multiple generations (Kuzawa, 2005; Kuzawa & Quinn, 2009).

When maternal signals incorporate a longer time depth of environmental information, they are buffered from stochastic changes in the environment, and thus have greater predictive power (Kuzawa, 2005). Wells (2012, 2019) hypothesizes that during gestation and infancy, developing systems are responsive signals of maternal capital. Beginning in early childhood, the individual must then adapt to the surrounding environmental conditions.

Developmental changes in adipose tissue gene expression further support this interpretation. Early childhood represents a stage when white adipose stores decrease in favor of energy allocation toward brain development (Kuzawa et al., 2014). In addition, the expression of thermogenic genes is upregulated in adipose tissue during early childhood compared to infancy (Ojha et al., 2016). Shifts in adipose tissue gene expression during the infancy-childhood transition may play a mechanistic role in BAT developmental programming, leading to greater sensitivity to ambient temperature at this life stage.

We found mixed evidence suggesting a potential sensitive period during adolescence. Pediatric studies have found that BAT mass increases during puberty (Gilsanz et al., 2012). Synergistic shifts in BAT, bone, and muscle development during puberty may be sensitive to environmental conditions (Ponrartana et al., 2012).

It is possible that parental exposure to cold climates may influence the BAT metabolism of offspring through the inheritance of epigenetic marks across generations. A recent study found that male mice that were exposed to repeated cold stress exhibit differentially methylated regions in their sperm and greater UCP1 expression in their offspring (Sun et al., 2018). Additional research is needed in order to explore whether human BAT development is sensitive to transgenerational epigenetic inheritance.

Our results imply that developmental plasticity in BAT may be sensitive to social, cultural, and economic contexts which mediate exposure to weather conditions. Cross-population comparisons suggest that cultural norms surrounding infant carrying and bundling practices play a critical role in controlling the thermal environment of infants (Leonard et al., 2009). For instance, in Finland it is common for parents to set napping infants outside during winter, while in the Lena River Valley of the Sakha Republic infants are kept indoors (Tourula et al., 2010). Furthermore, by structuring the daily activities of a child, the cultural and economic context of one generation is likely to influence the developing biology of the next through reinforcing biological and social mechanisms (Hoke & McDade, 2014). Parents' cultural and subsistence practices will determine how children play, do chores, and get from place to place—all of which influence cold exposure and may modify the developing BAT of Yakut children.

Prior research indicates that BAT metabolism may have protective effects against cardiometabolic diseases such as type II diabetes (Becher et al., 2021; Iwen et al., 2017). We previously demonstrated that Yakut adults with greater BAT thermogenesis expend more energy and utilize a larger proportion of carbohydrates as a metabolic substrate during acute cold exposure (Levy et al., 2018). Here we show that exposure to low temperatures during development program adult BAT activity and energy budgets in adulthood. Our results suggest that ambient temperature may represent an understudied component of the developmental origins of health and disease.

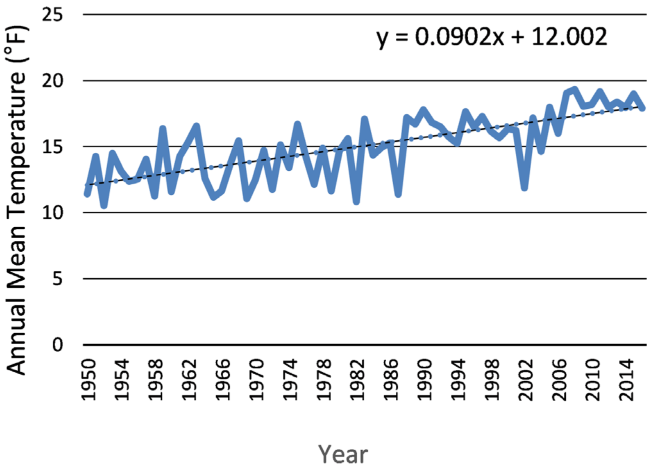

FIGURE 6 Annual mean temperature (°F) in Yakutsk, Russia from 1950–2016

Finally, this study highlights new direct and indirect pathways through which climate change may affect the biology and health of circumpolar populations. The accumulation of human-generated greenhouse gases in the atmosphere is causing annual temperatures to climb in Yakutsk, Russia, as seen in Figure 6. The primary ecological consequences of global climate change in this region include flooding and degradation of the permafrost (Revich, 2007). These local effects may lead children to spend more time indoors and may have consequences for energy expenditure later in life. We recognize that other consequences of circumpolar climate change, such as the inability to carry out subsistence practices, damage to infrastructure, and the spread of zoonotic diseases, are likely to have more dramatic effects on the health of circumpolar populations than small declines BAT thermogenesis (Revich, 2007). However, this work contributes to a growing body of research that highlights how the local effects of global climate change may act synergistically with political-economic processes, such as globalization and market integration, which underlie the growing rates of cardiometabolic disease in subarctic regions (Gildner & Levy, 2020).

ACKNOWLEDGMENTS

The authors are most grateful to all the participants of this study. In addition, they thank the staff at the Gorny Regional Medical Center, the Research Institute of Health at NEFU, and the Medical Clinic at NEFU for their assistance and support. We thank K. Arslanian, C. Beall, C. Chaney, K. Daiy, P. Ellison, R. Fried, M. Hoke, K. McCabe, K. Wiley and the reviewers for their helpful feedback on the manuscript and V. Figueroa for his assistance with the tables. This study was supported by the NSF BCS-1455804, the Leakey Foundation, and Northwestern University.

CONFLICT OF INTEREST

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

AUTHOR CONTRIBUTIONS

Stephanie Levy: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; visualization; writing-original draft; writing-review & editing. **Tatiana Klimova:** Investigation; methodology; project administration; resources. **Raisa Zakharova:** Investigation; methodology; project administration; resources. **Afanasiy Fedorov:** Investigation; methodology; project administration; resources. **Valentina Fedorova:** Investigation; methodology; project administration; resources. **Marina Baltakhinova:** Investigation; methodology; project administration; resources. **William Leonard:** Investigation; methodology; resources; software; supervision; writing-review & editing.

DATA AVAILABILITY STATEMENT

The Northwestern University Institutional Review Board granted permission to conduct this study (IRB 00200092) and all participants provided informed consent. The project's deidentified data is stored in a password-protected data repository managed by Northwestern University (Northwestern Box). The data are available for further analysis to researchers who have received ethics approval from the Northwestern University IRB by contacting Dr. Stephanie Levy.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Levy SB, Klimova TM, Zakharova RN, et al. Evidence for a sensitive period of plasticity in brown adipose tissue during early childhood among indigenous Siberians. *Am J Phys Anthropol*. 2021;175:834–846. https://doi.org/10.1002/ajpa.24297