Received: 20 April 2021 | Revised: 18 August 2021 | Accepted: 21 August 2021

DOI: 10.1002/osp4.559

ORIGINAL ARTICLE

Obesity Science and Practice Open Access WILEY

Impact of brown adipose tissue vascular density on body adiposity in healthy Japanese infants and children

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Funding information
Grant-in-Aid Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, Grant/Award Numbers: 19H04061, 19K20123

Abstract

Background and Objective: The importance of brown adipose tissue (BAT) is well recognized in healthy infants and children. However, information regarding age-related changes in BAT vascular density (BAT-d) and the impact of BAT-d on body adiposity are lacking. This study aimed to evaluate the normal values of BAT-d, factors influencing BAT-d, and the impact of BAT-d on body adiposity in healthy infants and children.

Methods: This study included 240 participants (127 girls and 113 boys) aged 1 month to 5 years. The tissue total hemoglobin concentration in the supraclavicular region adjusted according to the subcutaneous adipose tissue thickness (SAT) ([total-Hb-Adj]$_{sup}$) as BAT-d. SAT in the deltoid and interscapular regions (SAT$_{del+int}$), the Kaup index (body weight [g]/height or length [cm]/height or length [cm] $\times$ 10) as body adiposity, and fertilization season were also measured.

Results: The [total-Hb-Adj]$_{sup}$ of boys was higher than that of girls (r = 0.277, p = 0.009). Younger children had a significantly higher Kaup index (r = 0.495, p < 0.001) and SAT$_{del+int}$ (r = 0.614, p < 0.001) than older children. Children who had higher [total-Hb-Adj]$_{sup}$ had a significantly lower Kaup index (r = 0.495, p = 0.037) and SAT$_{del+int}$ (r = 0.614, p < 0.001).

Conclusion: The [total-Hb-Adj]$_{sup}$, as a parameter of BAT-d, is negatively correlated with body adiposity in children aged 1 month to 5 years, and BAT might affect human obesity to a much greater extent than expected. To prevent or treat obesity in early childhood, the level of BAT-d should be considered when using a dietary intervention.

KEYWORDS
adiposity, brown adipose tissue, obesity, pediatrics

1 | INTRODUCTION

The thermogenic activity of brown adipose tissue (BAT) is well known. BAT is critical in infants to sufficiently maintain a core body temperature through shivering thermogenesis, particularly at birth, considering their immature skeletal muscles.[1,2] Despite the importance of BAT for heat production in healthy infants and children, studies covering different aspects of BAT are limited because of the lack of appropriate methodologies to measure BAT.[2–4] Regarding the normal values of BAT volume in infants and children, BAT volume has been evaluated in autopsies, but participants were few and might have suffered from certain diseases.[5–8] Studies have demonstrated the presence of uncoupling protein 1-positive adipocytes in children and adults during elective surgery and autopsy.[6,8]

BAT has been evaluated using several methods, and the parameters of BAT, such as BAT activity and volume, differ according to the method of measurement.[3,4,9–15] ^{18}F-fluorodeoxyglucose positron emission tomography combined with computed tomography (FDG-PET/CT) is used to measure BAT activity.[9–13] However, FDG-PET/CT is unsuitable for healthy infants because of exposure to ionizing radiation and the cold. Infrared thermography is used to measure BAT activity in children aged 6 to 11 years via the temperature of the supraclavicular region.[14] Alternatively, magnetic resonance imaging is used to evaluate BAT characteristics in infants aged 0 and 6 months,[3,15] and in children aged 9 to 19 years.[4] However, no data are available on the age-specific distribution of BAT volume in healthy infants and children aged 6 months to 5 years, presumably because of the difficulties of using noninvasive measurements such as motion artifacts in the magnetic resonance signal and annoying sounds.

In this study, near-infrared time-resolved spectroscopy (NIR_{TRS}), a relatively new methodology, was used to monitor BAT vascular density (BAT-d).[16–18] Near-infrared is applied to evaluate BAT-d because the microvascular bed, evaluated using the total hemoglobin concentration in the supraclavicular region ($[total\text{-}Hb]_{sup}$), is more abundant in BAT than in white adipose tissue. The sensitivity (75.0%), specificity (100%), and accuracy (82.8%) of $[total\text{-}Hb]_{sup}$ compared with other BAT activity parameters determined using cold-induced FDG-PET/CT measurements were good for determining the reliability of $[total\text{-}Hb]_{sup}$.[16–18] Thus, $[total\text{-}Hb]_{sup}$ is a reflection of BAT activity determined using cold-induced FDG-PET/CT.

Acceleration in body mass index (BMI) in early childhood can lead to sustained obesity.[19,20] Moreover, BAT volume is significantly reduced in children with obesity.[8] Infants with a higher BAT volume exhibit smaller gains in total body fat from birth to 6 months of age.[3] Thus, increasing BAT activity or volume may be helpful for combating obesity and chronic diseases such as type 2 diabetes mellitus not only in adults but also in children.

This study had three objectives: (a) to evaluate the normal values of BAT-d in children aged 1 month to 5 years; (b) to confirm factors associated with BAT-d, such as age, sex, and fertilization season; and (c) to elucidate the impact of BAT-d on body adiposity. The hypothesis of this study was that BAT-d in children aged 1 month to 5 years would have an impact on body adiposity.

2 | PARTICIPANTS AND METHODS

2.1 | Participants and study design

This study was conducted during winter (December 2018 to April 2020). A total of 240 healthy Japanese participants aged 1 month to 5 years were recruited in the Kanto region in Japan via a poster in five child-rearing support centers and six nursery schools, and a social network service. All participants were compensated. Children who were of multiple races or were foreign-born were excluded from the study because they were too few in number. The participants arrived at the laboratory, wherein the temperature was regulated from 23°C to 26°C using an air conditioner. The following parameters were measured: $[total\text{-}Hb]_{sup}$ as BAT-d, subcutaneous adipose tissue thickness (SAT) in the supraclavicular, deltoid, and interscapular regions, height or length, and body weight. From the Maternal and Child Health Handbook, records of prenatality, labor, and postnatality were obtained. The study design and protocols were approved by the institutional review boards of Tokyo Medical University (IRB 2017-199) and are in accordance with the ethical principles in the Declaration of Helsinki. Written informed consent was obtained for all participants from one of their parents. An explanation was provided in the research consent statement and assent document.

2.2 | Measurements of BAT-d

Before starting the measurement, the NIR_{TRS} (TRS-20; Hamamatsu Photonics K.K.) was calibrated to test its accuracy. After a 10-min rest in a room at 23°C to 26°C, the NIR_{TRS} probes were placed on the skin of the supraclavicular region, which could potentially contain BAT, and the participants were required to remain in a sitting position on their parent's lap on a chair or being held by their parent during the measurements. Children were required to be calm and stable during the measurement, and to ensure this, they were offered toys or tablets to watch their favorite videos. Children who were crying during the measurement were allowed 10 min to regain calmness; otherwise, they were excluded from the measurement. The optode separation for NIR_{TRS} was 2 cm for children older than 12 months and 1.5 cm for infants younger than 12 months in this study. The reason for the difference in optode separation was that 2 cm was too large to use in the supraclavicular region in infants younger than 12 months. Furthermore, according to a recent study,[21] the mean depth of light penetration was greater (approximately 2/3 of optode separation) and more homogeneous when NIR_{TRS} was used. Thus, a 2-cm optode separation probe could reach a mean depth of light penetration of 1.3 cm and a 1.5-cm of 1.0 cm, where BAT is potentially located.[22]

The tissue was illuminated using a 200-µm core diameter optical fiber that generated picosecond light pulses, with a 100-ps full width at half-maximum, a 5-MHz repetition rate, and average power of 80 µW for each wavelength. The emitted photons penetrated the tissue and reflected a 3-mm diameter optical bundle fiber, through which they were sent to a photomultiplier tube for single-photon detection and a signal processing circuit for time-resolved measurement. The digitized temporal profile data from an in vitro sample or tissue using the nonlinear least-squares method were fitted with a theoretical temporal profile derived from the analytical solution of the photon diffusion theory with a semi-infinite homogeneous reflectance model. After convolution with the instrumental response function, the time response of the instrument itself could be compensated for, and the absorption coefficient values and reduced μ_s' values at 760, 800, and 830 nm were obtained using the least-squares fitting method. The absolute [total-Hb] was then calculated as the sum of [oxy-Hb] and [deoxy-Hb].[16,23] The data were collected every 10 s for 60 s using the NIR_{TRS}. The coefficient of variation for repeated measurements of the $[\text{total-Hb}]_{sup}$ was 4.9%.[16]

2.3 | Measurements of anthropometric parameters

The SAT in the supraclavicular (SAT_{sup}) and deltoid and interscapular ($SAT_{del+int}$) regions was monitored using B-mode ultrasonography (Vscan Dual Probe; GE Vingmed Ultrasound AS). SAT was measured by an investigator using the attached distance measuring system and calculated as the mean value of two measurements.

2.4 | Statistical analyses

Data were expressed as mean (95% confidence interval [CI]) or mean (first and third quartiles). The $[\text{total-Hb}]_{sup}$ was adjusted according to the underlying SAT providing $[\text{total-Hb-Adj}]_{sup}$,[24] with the following formula: $[\text{total-Hb-Adj}]_{sup}$ = $[\text{total-Hb}]_{sup}$/EXP [−1 (SAT in the supraclavicular region [mm] × 10/6.9)^2].

The Kaup index (body weight [g]/height or length [cm]/height or length [cm] × 10) was calculated from weight and height or length. According to the Kaup index, participants were divided into groups with underweight (<14), without obesity (15 to 17), or with obesity (>18).[25] Fertilization date was calculated from the date of birth and pregnancy weeks. Fertilization seasons were divided into the cold (November to April) and warm seasons (May to October) in Japan.

To compare the participants' sex, age, Kaup index, and the $SAT_{del+int}$, the independent *t*-test, Mann–Whitney test, Kruskal–Wallis test, or one-way analysis of variance was used as appropriate. The Spearman rank correlation coefficient was used to analyze the relationship between each parameter. A univariate analysis was conducted to identify factors (sex, age, and fertilization season) influencing $[\text{total-Hb-Adj}]_{sup}$, and $p < 0.25$ was accepted for further multivariate analyses (logistic regression analysis). Logistic regression analysis was conducted to assess the factors influencing $[\text{total-Hb-Adj}]_{sup}$. Sex: 0 = boys, 1 = girls; fertilization season: 1 = Nov to Apr, 2 = May to Oct. A univariate analysis was conducted to identify factors (sex, age, fertilization seasons, and $[\text{total-Hb-Adj}]_{sup}$) influencing the Kaup index and $SAT_{del+int}$, and $p < 0.25$ was accepted for further multivariate analyses (logistic regression analysis). Logistic regression analysis was conducted to assess the factors influencing the Kaup index. The Kaup index used median in logistic regression analysis; 0 = <16.28, 1 = >16.28. Kaup index: body weight [g]/height or length [cm]/height or length [cm] × 10, sex: 0 = boys, 1 = girls. Logistic regression analysis was conducted to assess the factors influencing $SAT_{delt+int}$. $SAT_{delt+int}$ used median in logistic regression analysis; 0 = <0.65 cm, 1 = >0.65 cm. Sex: 0 = boys, 1 = girls. The analyses were performed using SPSS (IBM SPSS Statistics 27 IBM Japan), and $p < 0.05$ was considered significant.

3 | RESULTS

3.1 | Participant profiles

Figure 1 shows the flowchart for the selection of children, and Table 1 shows the profiles of 240 children. The mean age was 2.1 years (range, 1–71 months, 95% CI: 1.9–2.3). The mean gestational week was 39.3 weeks (range, 28.3–42.4, 95% CI: 39.1–39.6). The mean Kaup index, SAT_{sup}, and $[\text{total-Hb-Adj}]_{sup}$ values were 16.4 g/cm^2 × 10 (95% CI: 16.3–16.6), 0.14 cm (95% CI: 0.13–0.14), and 86.6 μM (95% CI 83.8–89.4), respectively.

3.2 | Comparison of $[\text{Total-Hb-Adj}]_{sup}$ and sex by age

The $[\text{total-Hb-Adj}]_{sup}$ of infants aged <1 year was significantly lower than that of older children (1 year old, $p < 0.001$; 2 years old, $p = 0.032$; 3 years old, $p = 0.017$; 4 years old, $p < 0.001$; 5 years old, $p = 0.007$). No significant differences were observed among the other combinations (Figure 1). The $[\text{total-Hb-Adj}]_{sup}$ was significantly higher in boys than in girls at 5 years of age ($p = 0.007$). The $[\text{total-Hb-Adj}]_{sup}$ of girls aged <1 year was significantly lower than that of girls aged 1 year ($p < 0.001$) (Figure 2).

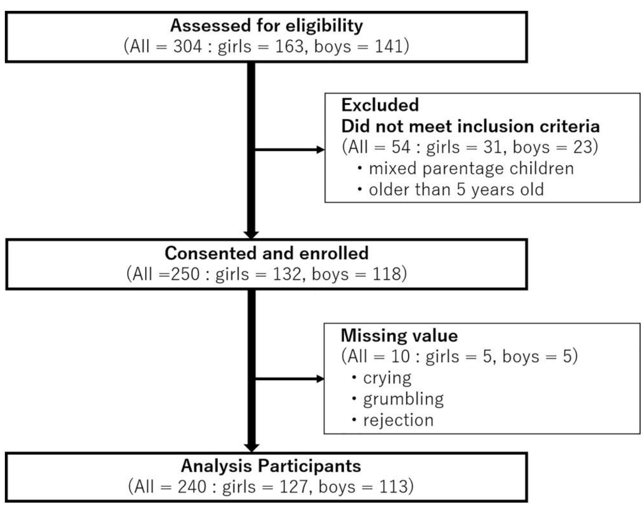

FIGURE 1 Flowchart for the selection of participants

TABLE 1 Profiles of the participants

n (girls/boys)	All 240 (127/113)	<1 year old 46 (30/16)	1 year old 52 (34/18)	2 years old 51 (27/24)	3 years old 34 (23/11)	4 years old 31 (19/12)	5 years old 26 (13/13)
Age (months)	30.9 (28.4–33.3)	7.0 (6.2–7.8)	16.8 (15.9–17.6)	29.2 (28.2–30.2)	40.5 (39.3–41.7)	54.1 (52.9–55.3)	64.1 (63.0–65.2)
Gestational weeks (weeks)	39.3 (39.1–39.6)	39.4 (39.0–39.8)	39.5 (39.1–40.0)	39.1 (38.5–39.7)	39.5 (39.1–40.0)	38.7 (37.5–39.9)	39.5 (38.8–40.1)
Height or length (cm)	87.2 (85.3–89.0)	67.8 (66.4–69.3)$^{*1, *2, *3, *4, *5}$	77.8 (76.6–79.0)$^{*0, *2, *3, *4, *5}$	86.9 (85.9–87.9)$^{*0, *1, *3, *4, *5}$	95.9 (93.6–98.1)$^{*0, *1, *2}$	103.8 (101.9–105.7)$^{*0, *1, *2}$	109.3 (107.0–111.7)$^{*0, *1, *2}$
Body weight (kg)	12.7 (12.2–13.2)	8.0 (7.6–8.3)$^{*1, *2, *3, *4, *5}$	10.3 (9.9–10.7)$^{*0, *2, *3, *4, *5}$	12.4 (12.0–12.8)$^{*0, *1, *4, *5}$	14.5 (14.0–15.0)$^{*0, *1}$	17.3 (16.4–18.2)$^{*0, *1, *2}$	18.5 (17.4–19.7)$^{*0, *1, *2}$
Kaup index (g/cm^2 × 10)	16.4 (16.3–16.6)	17.3 (16.9–17.7)$^{*2, *3, *4, *5}$	16.9 (16.5–17.3)$^{*3, *4, *5}$	16.3 (16.0–16.7)$^{*0, *5}$	15.8 (15.3–16.4)$^{*0, *1}$	16.0 (15.6–16.4)$^{*0, *1}$	15.4 (14.9–16.0)$^{*0, *1, *2}$
$SAT_{delt+int}$ (cm)	0.67 (0.64–0.70)	0.90 (0.81–0.99)$^{*2, *3, *4, *5}$	0.71 (0.67–0.75)$^{*3, *4, *5}$	0.66 (0.61–0.70)$^{*0, *5}$	0.59 (0.54–0.64)$^{*0, *1}$	0.56 (0.48–0.63)$^{*0, *1}$	0.48 (0.41–0.56)$^{*0, *1, *2}$
SAT_{sup} (cm)	0.14 (0.13–0.14)	0.18 (0.16–0.20)$^{*2, *3, *4, *5}$	0.16 (0.14–0.18)$^{*3, *5}$	0.12 (0.11–0.14)$^{*0, *5}$	0.12 (0.10–0.14)$^{*0, *1,}$	0.11 (0.08–0.12)^{*0}	0.089 (0.07–0.11)$^{*0, *1, *2}$

Note: Values are expressed as mean (95% confidence interval). Height was used in participants who were able to stand up and length in participants who were unable; Kaup index, body weight [g]/height or length [cm]/height or length [cm] × 10; $SAT_{delt+int}$, subcutaneous adipose tissue thickness in the deltoid and interscapular regions; SAT_{sup}, subcutaneous adipose tissue thickness in the supraclavicular region; *0, $p < 0.05$ versus 0 year; *1, $p < 0.05$ versus 1 year; *2, $p < 0.05$ versus 2 years; *3, $p < 0.05$ versus 3 years; *4, $p < 0.05$ versus 4 years; *5, $p < 0.05$ versus 5 years.

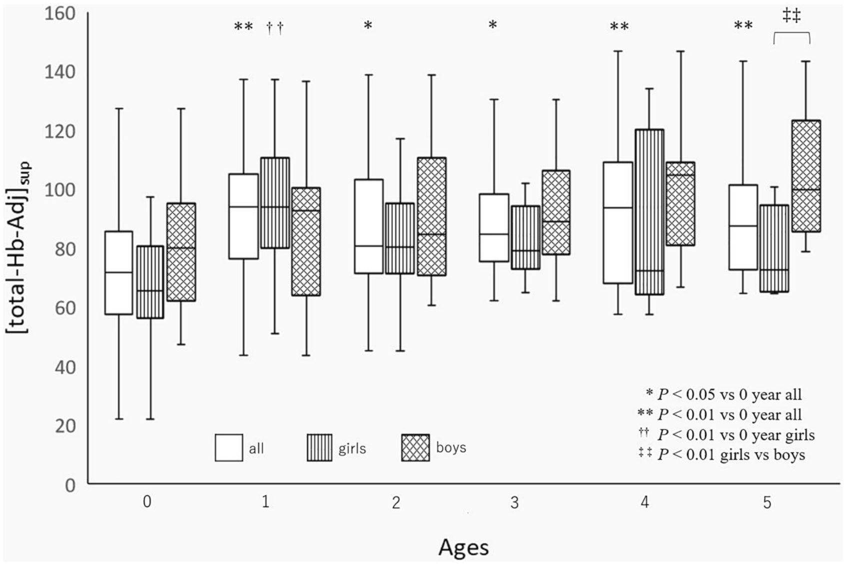

FIGURE 2 Comparison of [total-Hb-Adj]$_{sup}$ by age and sex. Data are expressed as mean (first and third quartiles). The Kruskal–Wallis test is conducted to compare [total-Hb-Adj]$_{sup}$. $^{*}p < 0.05$ versus 0 year all, $^{**}p < 0.01$ versus 0 year all, $^{††}p < 0.01$ versus 0 year girls, $^{‡‡}p < 0.01$ versus girls and boys of the same age. [total-Hb-Adj]$_{sup}$: total hemoglobin concentration in the supraclavicular region adjusted according to the subcutaneous adipose tissue thickness

TABLE 2 Independent association of predictor analysis for the total hemoglobin concentration in the supraclavicular region adjusted according to the subcutaneous adipose tissue thickness ([total-Hb-Adj]$_{sup}$), a parameter for the brown adipose tissue density, and related parameters

	Spearman correlation coefficient		Logistic regression analysis			
			95% CI for E Exp(B)			
[total-Hb-Adj]$_{sup}$ (BAT-d)	*R*	*p*	Exp(B)	Lower	Upper	*p*
Sex	−0.214**	<0.001	0.494	0.291	0.837	0.009**
Age	0.230**	<0.001	1.147	0.971	1.354	0.107
Fertilization season (Nov to Apr/May to Oct)	−0.130*	0.044	0.685	0.404	1.161	0.160

Note: The Spearman rank correlation coefficient was used to analyze the relationship between each parameter. Logistic regression analysis was conducted to assess the factors influencing [total-Hb-Adj]$_{sup}$. Sex: 0 = boys, 1 = girls; fertilization season: 1 = Nov to Apr, 2 = May to Oct. The distance between transmission and detection with near-infrared time-resolved spectroscopy in the supraclavicular area was 1.5 cm for participants aged <1 year and 2.0 cm for participants aged ≥1 year.

Abbreviations: BAT-d, BAT vascular density; CI, confidence interval.

$^{*}p < 0.05$ and $^{**}p < 0.01$.

3.3 | Predictor analysis for [Total-Hb-Adj]$_{sup}$ using sex, age, and fertilization season

According to the results of univariate analysis, sex, age, and fertilization season ($p < 0.05$) were significant. Logistic regression analysis showed that sex remained a significant predictor of [total-Hb-Adj]$_{sup}$ ($p = 0.049$) (Table 2).

3.4 | Predictor analysis for the Kaup index and SAT$_{del+int}$ using sex, age, fertilization season, and [Total-Hb-Adj]$_{sup}$

According to the results of univariate analysis, the Kaup index was significantly associated with sex, age, and [total-Hb-Adj]$_{sup}$ regardless of the fertilization season. Univariate analysis also showed that SAT$_{del+int}$ was significantly associated with sex, age, fertilization season, and [total-Hb-Adj]$_{sup}$. Moreover, according to the results of logistic regression analysis, age ($p < 0.001$ for both the Kaup index and SAT$_{del+int}$) and [total-Hb-Adj]$_{sup}$ ($p = 0.037$ for the Kaup index and $p < 0.001$ for the SAT$_{del+int}$) remained significant predictors of both the Kaup index and SAT$_{del+int}$. Younger children had a significantly higher Kaup index and SAT$_{del+int}$ than older children. Children who had higher [total-Hb-Adj]$_{sup}$ had a significantly lower Kaup index and SAT$_{del+int}$ (Tables 3 and 4, respectively).

3.5 | Comparison of [Total-Hb-Adj]$_{sup}$ by the Kaup index between the three groups

The [total-Hb-Adj]$_{sup}$ values were 94.8 ± 9.55 μM in the group with underweight, 88.3 ± 22.0 μM in the group without obesity, and

TABLE 3 Independent association of age, sex, fertilization season, and the total hemoglobin concentration in the supraclavicular region adjusted according to the subcutaneous adipose tissue thickness ($[\text{total-Hb-Adj}]_{sup}$), a parameter for the brown adipose tissue density, with the Kaup index

	Spearman correlation coefficient		Logistic regression analysis			
				95% CI for Exp(B)		
Kaup index	*R*	*p*	Exp(B)	Lower	Upper	*p*
Sex	0.183*	0.027	1.345	0.758	2.386	0.311
Age	−0.440**	<0.001	0.595	0.486	0.716	<0.001**
Fertilization season (Nov to Apr/May to Oct)	0.125	0.053	0.944	0.533	1.672	0.844
$[\text{total-Hb-Adj}]_{sup}$ (μM)	−0.295**	<0.001	0.986	0.972	0.999	0.037*

Note: The Spearman rank correlation coefficient was used to analyze the relationship between each parameter. Logistic regression analysis was conducted to assess the factors influencing the Kaup index. The Kaup index used median in logistic regression analysis; 0 = <16.28, 1 = >16.28. Kaup index: body weight [g]/height or length [cm]/height or length [cm] × 10, sex: 0 = boys, 1 = girls. The distance between transmission and detection with near-infrared time-resolved spectroscopy in the supraclavicular region was 1.5 cm for participants aged <1 year, and 2.0 cm for participants aged ≥1 year.

Abbreviation: CI, confidence interval.

*$p < 0.05$ and **$p < 0.01$.

TABLE 4 Independent association of age, sex, fertilization season, and total hemoglobin concentration in the supraclavicular region adjusted according to the subcutaneous adipose tissue thickness ($[\text{total-Hb-Adj}]_{sup}$), a parameter for the brown adipose tissue density, with the subcutaneous adipose tissue thickness in the deltoid and interscapular regions ($SAT_{delt+int}$)

	Spearman correlation coefficient		Logistic regression analysis			
				95% CI for Exp(B)		
$SAT_{delt+int}$ (cm)	*R*	*p*	Exp(B)	Lower	Upper	*p*
Sex	0.267**	<0.001	1.683	0.917	3.089	0.093
Age	−0.570**	<0.001	0.576	0.467	0.710	<0.001**
Fertilization season (Nov to Apr/May to Oct)	0.131*	0.043	0.833	0.451	1.538	0.559
$[\text{total-Hb-Adj}]_{sup}$ (μM)	−0.459**	<0.001	0.960	0.944	0.976	<0.001**

Note: The Spearman rank correlation coefficient was used to analyze the relationship between each parameter. Logistic regression analysis was conducted to assess the factors influencing $SAT_{delt+int}$. $SAT_{delt+int}$ used median in logistic regression analysis; 0 = <0.65 cm, 1 = >0.65 cm. Sex: 0 = boys, 1 = girls. The distance between transmission and detection with near-infrared time-resolved spectroscopy in the supraclavicular region was 1.5 cm for participants aged <1 year, and 2.0 cm for participants aged ≥1 year.

Abbreviation: CI, confidence interval.

*$p < 0.05$ and **$p < 0.01$.

78.7 ± 24.0 μM in the group with obesity. The group with obesity had the lowest $[\text{total-Hb-Adj}]_{sup}$ compared with the groups without obesity ($p = 0.011$) and with underweight ($p = 0.014$) (Figure 3).

4 | DISCUSSION

NIR_{TRS} was used to evaluate the $[\text{total-Hb-Adj}]_{sup}$, a parameter of BAT-d, in 240 healthy Japanese infants and children aged 1 month to 5 years. Sex remained a significant predictor of $[\text{total-Hb-Adj}]_{sup}$; $[\text{total-Hb-Adj}]_{sup}$ of boys was higher than that of girls. Thus, to our knowledge, this is the first study to observe sex-related differences in BAT-d in healthy children aged 1 month to 5 years. Moreover, age and $[\text{total-Hb-Adj}]_{sup}$ were significant predictors of body adiposity evaluated using the Kaup index and $SAT_{del+int}$. Younger children had a significantly higher Kaup index and $SAT_{del+int}$ than older children. Children who had higher BAT-d had a significantly lower Kaup index and $SAT_{del+int}$. Finally, the group with obesity had the lowest BAT-d.

Although BAT is expected to be higher in newborns and in the early stages of infancy, our study showed that BAT-d was lowest in participants aged <1 year. The major BAT depots in human infants are located within the interscapular and supraclavicular/neck regions, and around the heart and kidney regions.[1] According to autopsy data, BAT in the interscapular region is consistently present in the first decade and gradually disappears at up to

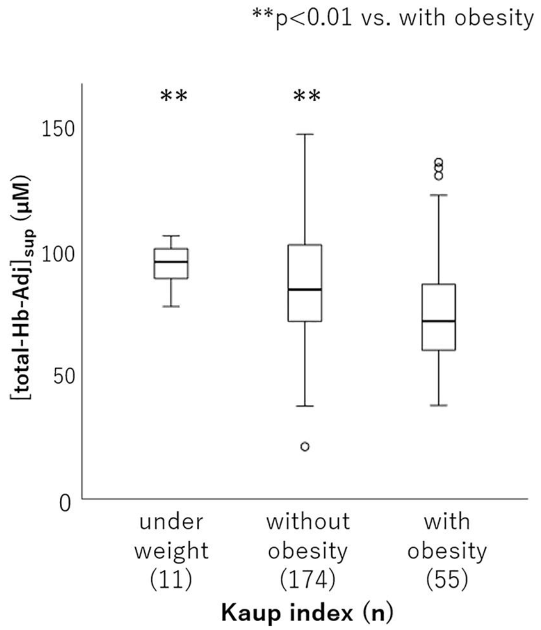

FIGURE 3 Comparison of [total-Hb-Adj]$_{sup}$ between the groups with underweight, obesity, and without obesity. Participants are divided into groups according to the Kaup index; <14, underweight; 15 to 17, without obesity,>18, obesity. Data are expressed as mean (first and third quartiles). The Kruskal–Wallis test is conducted to compare [total-Hb-Adj]$_{sup}$ between the three groups. **p < 0.01 versus the group with obesity. [total-Hb-Adj]$_{sup}$: total hemoglobin concentration in the supraclavicular region adjusted according to the subcutaneous adipose tissue thickness

30 years of age.[7] Thus, the reason for blunted BAT-d in participants aged <1 year in this study might be attributed to the assessment of BAT-d in the supraclavicular region only, which led to an underestimation of BAT-d.

This study showed that the BAT-d of boys was significantly higher than that of girls. BAT volume, primarily in the supraclavicular and neck regions, is significantly greater in pre-pubertal boys than girls aged 4 to 20 years and is closely related to muscle volume.[26,27] The supraclavicular region temperature is higher in boys aged 9 to 12 years after cold exposure, which is an indication of greater BAT activity.[28] In contrast to data on children, data on adult humans are inconsistent. BAT activity was found to be higher in women than in men,[29–34] particularly young women.[31] However, no sex differences were found in BAT activity using ^{18}FDG-PET/CT with cold exposure.[35,36] Furthermore, BAT activity was also found to be higher in young men than in young women.[9,37] BAT-d seems to be greater in boys than in girls aged 1 month to 12 years, but it is inconsistent in adult humans owing to different methodologies, experimental protocols (i.e., with or without cold exposure), and populations tested. Further studies are necessary to assess sex differences in terms of BAT characteristics across a wide age range. Multiple regression analysis revealed that only sex remained a significant predictor of BAT-d.

BAT in adult humans is negatively correlated with adiposity, such as BMI and body fat percentage.[37] A previous study indicated that in early newborns aged 0 and 6 months, no significant association was found between BAT volume and percentage of body fat; however, the existence of BAT leads to a smaller increase in body fat percentage over the first 6 months of postnatal life.[3] A study using magnetic resonance imaging for children aged 9 to 19 years indicated a negative correlation between BAT volume and BMI.[4] Fifty-five children aged 6 to 11 years were assessed using infrared thermography, measuring the temperature of the supraclavicular region at baseline and after cold exposure. BMI was a significant predictor of the baseline temperature of the supraclavicular region and of increasing temperature after cold exposure.[14] In this study, body adiposity (SAT$_{del+int}$) was also negatively associated with BAT-d, despite the differences in the measurements of BAT and participants' ages from previous studies. Thus, this might validate the assessment of BAT-d by NIR$_{TRS}$.

In this study, body adiposity (SAT$_{del+int}$) was associated with BAT-d regardless of the fertilization season, which contrasted with a previous study that reported that the presence of BAT and fertilization season are linked to body adiposity (BMI) in adult humans.[38] Thus, the effect of fertilization season on body adiposity through BAT is speculated to be prominent later in life via epigenetic programming of the sperm, such that the offspring enhances BAT activity and adaptation to nutritional status or fluctuations in environmental temperature.[38] However, multiple regression analysis revealed that age and [total-Hb-Adj]$_{sup}$, not fertilization season, were significant predictors of SAT$_{del+int}$. Younger children had a significantly higher SAT$_{del+int}$ than older children. Children who had higher BAT-d had a significantly lower SAT$_{del+int}$. For the first time, our study collectively and noninvasively showed that BAT-d was negatively correlated with both the Kaup index and SAT$_{del+int}$ in children aged 1 month to 5 years, identifying this age range as the missing piece. A previous study examining 131 children and adolescents aged <1 year to 18 years, and 23 adults, reported that BAT and uncoupling protein 1-positive adipocytes were detected in 10.3% of the 87 children with underweight (0.3–10.7 years old) and one child with overweight; however, no BAT was detected in children or adults with obesity.[8] Thus, BAT is negatively correlated with body adiposity over a wide age range, even from early infancy, and might influence human obesity to a much greater extent than expected. Last, although the casual relationship is not known, most research speculated that BAT might affect body adiposity or vice versa, considering the results observed in animal studies. The consistent observation of the relationship between BAT activity or density and fat amount in a wide range of ages, even infants, might indicate that fat or a certain unknown factor related to white adipose tissue might play a significant role in attenuating the activation of BAT.

The SAT in the supraclavicular region will have an impact on the results of [total-Hb]$_{sup}$. Thus, SAT in the supraclavicular region was measured, and the [total-Hb]$_{sup}$ was adjusted according to the underlying SAT.[24] For these reasons, the effect of SAT was eliminated.

This study had several limitations. Firstly, the location of [total-Hb-Adj]$_{sup}$ measurements was a limitation because the [total-Hb-Adj]$_{sup}$ of infants aged <1 year was significantly lower than that of older children. Thus, although the supraclavicular region is one of the largest locations where BAT depots are located, the results of this study might not be representative of the whole-body BAT-d in infants and children. Secondly, although NIR_{TRS} methods have been tested in adults, such NIR_{TRS} methods have not yet been validated in infants and children. However, it is challenging to measure ^{18}FDG-PET/CT in infants and children due to radiation exposure and cold exposure.

In conclusion, sex-related differences were found in the parameters of BAT-d in healthy children aged ≤5 years. Sex remained a significant predictor of $[\text{total-Hb-Adj}]_{sup}$, that is, the $[\text{total-Hb-Adj}]_{sup}$ of boys was higher than that of girls. Age and $[\text{total-Hb-Adj}]_{sup}$ were significant predictors of body adiposity. Furthermore, the group with obesity had the lowest $[\text{total-Hb-Adj}]_{sup}$, even in those aged ≤5 years. Thus, as a parameter of BAT-d, $[\text{total-Hb-Adj}]_{sup}$ is negatively correlated with body adiposity over a wide age range, even in early infancy.

BAT might affect human obesity to a much greater extent than expected. To prevent or treat obesity in infancy and early childhood, the level of BAT-d should be considered when using a dietary intervention. For example, children with obesity who have a low level of BAT-d might exhibit lower thermogenesis and, as a result, may respond to recommendations to reduce their energy intake and increase their level of energy expenditure though increased levels of physical activity.

ACKNOWLEDGMENTS

We acknowledge a Grant-in-Aid Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (19H04061, 19K20123). We also would like to thank the study participants.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: Takafumi Hamaoka and Yuko Kurosawa; investigation: Sayuri Hamaoka-Fuse, Ryotaro Kime, Tasuki Endo, and Riki Tanaka; formal analysis: Shiho Amagasa; writing original draft and funding acquisition: Miyuki Kuroiwa. All authors have read and approved the final manuscript. The corresponding author has had full access to the data in the study and accepts final responsibility for the decision to submit for publication.

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How to cite this article: Kuroiwa M, Hamaoka-Fuse S, Amagasa S, et al. Impact of brown adipose tissue vascular density on body adiposity in healthy Japanese infants and children. *Obes Sci Pract*. 2022;8(2):190-198. https://doi.org/10.1002/osp4.559