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Two novel models evaluating the determinants of resting metabolic rate in Indian children

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Abstract

Background Resting metabolic rate (*RMR*) quantifies the minimal energy required to sustain vital body functions and is a crucial component of childhood development. Mean *RMR* per unit body mass (*RMR*/*BM*) has very accurately been modelled in references for Caucasian adolescents.

Objectives Here we address the extent to which such a model can be adapted to explain *RMR*/*BM* in Indian children.

Subjects and Methods The multicenter study (MCS) is a cross-sectional dataset on 495 children (235 girls and 260 boys) aged 9 to 19 years with anthropometric, body composition, and *RMR* measurements. The RMR-ultrasonography study (RMR-USG) consists of anthropometric data, *RMR* , and liver and kidney volume measured through ultrasonography in nine girls and nine boys aged 6 to 8 years.

Results The mean *RMR*/*BM* in Indian children is significantly lower compared to their Caucasian counterparts, except in boys in the age group 9–13 years. We present two novel phenomenological models that describe the mean *RMR*/*BM* stratified by age in Indian children and adolescents. The first is a modified Wang model in which the relative masses of four major organs are assumed to be uniformly lowered for Indian children. Theoretical predictions of liver size are not uniformly borne out in a pilot validation study; however, the relative mass of the kidney is found to be significantly lower. The second model demonstrates that changes in body composition alone can also explain the Indian data.

Conclusion A modified Wang model in which the relative masses of four major organs are assumed to be uniformly lower in Indian children and differences in body composition can be used to estimate mean *RMR*/*BM* by age in Indian children; however, understanding the mechanistic basis of variation in *RMR*/*BM* remains an open problem.

Take-home message for students The resting metabolic rate per unit body mass (*RMR*/*BM*) in Indian children is significantly lower than that of their Caucasian counterparts, except in boys in the age groups 9–13 years. A preliminary investigation could not resolve whether lowered organ tissue masses or body compositional differences explain this lower *RMR*/*BM*.

Introduction

Malnutrition in developing countries, such as India, is often paradoxically characterized as the simultaneous prevalence of undernutrition and rising overweight and obesity in children and adolescents (NCD Risk Factor Collaboration, 2017; WHO, 2020). One approach to studying malnourishment is through assessing the energy intake and expenditure of a population. For instance, a 200 kcal per day difference in energy intake was sufficient to explain the excess weight of US children in 2003–2006 compared to 1976–1980 (Hall et al., 2013). Energy expenditure in particular is predominantly determined by the physiology of the individual and varies significantly, both within and across populations (Henry, 2005; Johnstone et al., 2005; Reneau et al., 2019). It is necessary to understand factors leading to variation in energy expenditure to create personalized interventions to tackle the double burden of malnutrition (WHO, 2020). We note that the World Health Organization's (WHO) recommendations for energy requirements (FAO/WHO/UNU, 2004) are based on studies that overestimate energy expenditure in the Indian population by 12% (Henry, 2005). Here we are interested in developing models that accurately describe the (resting) energy expenditure in Indian children.

A primary component of energy expenditure is the resting energy expenditure (*REE*), or the resting metabolic rate (*RMR*), which measures the energy required to maintain the vital body functions at rest. *RMR* is measured through direct or indirect calorimetry (Weir, 1949) under standard conditions, such as in the post-absorptive state, in wakefulness, in the absence of any physical activity and diseases, with minimal emotional disturbance, and in a thermoneutral environment (22–26°C). Phenomenological models developed on a sample population are frequently used to estimate *RMR*. A large number of regression models for *RMR* have been based on anthropometric and body composition factors for nearly a century (Aub and Du Bois, 1917; Bedale, 1923; Cunningham, 1980; FAO/WHO/UNU, 1985; Harris and Benedict, 1918; Henry, 2005; Katch et al., 1990; Kleiber, 1932; McMurray et al., 2014; Mifflin et al., 1990; Owen et al., 1987, 1986; Schofield, 1985). These models find that fat-free mass (*FFM*) is the single largest predictor of *RMR*, followed by fat mass (*FM*), age, and sex. However, *RMR* is found to be highly variable between individuals in a population (Henry, 2005; Johnstone et al., 2005). Overall, models based on body composition have been of limited success, as they are able to explain only about 60–80% variation in *RMR*.

An alternate strategy for modelling is to challenge the assumption that the body mass is metabolically homogeneous, as is inherent in predicting *RMR* from linear models of *FFM* or body mass. *FFM* or body mass is composed of organs and tissues of varying metabolic activity, which together contribute to whole-body *RMR*. Gallagher et al. (Gallagher et al., 1998) partition *RMR* as the sum of metabolic rates of a number of major organs and tissues constituting the body mass. The metabolic rates of individual organs were calculated as the product of measured organ mass and the metabolic rate per unit mass (specific metabolic rate) of each organ, which was estimated in vivo by Elia (Elia, 1992). The Gallagher model was able to explain 80–98% variation of *RMR* in several studies in adults (Bosy-Westphal et al., 2008, 2004; Müller et al., 2011; Wang, 2012; Wang et al., 2010, 2005, 2001). However, the Gallagher model was found to underpredict *RMR* in children (Hsu et al., 2003; Wang, 2012; Wang et al., 2010). Wang (Wang, 2012) modified the Gallagher model to study

how *RMR*/*BM* varies in children from birth to adulthood and described the mean *RMR*/*BM* ($R^2 = 0.99$) in a reference Caucasian dataset (Talbot, 1938). Here we ask if the Wang model can describe *RMR*/*BM* in an Indian population.

Studies on metabolic rates in Indian children are scarce (Cherian et al., 2018; Kajale et al., 2022; Patil and Bharadwaj, 2013; Swaminathan et al., 2013). Predictive equations developed for Caucasian populations (FAO/WHO/UNU, 1985; Harris and Benedict, 1918) have been reported to overpredict metabolic rates in Indian adults (Cherian et al., 2018; Henry, 2005; Soares et al., 1998), however, they continue to be used to predict *RMR* in Indian children (Esht et al., 2018; Indian Council of Medical Research (ICMR), 2010; Srivastava et al., 2017). Previous studies in Indian adults (Krishnan and Vareed, 1932; Kumar et al., 1961; Mason et al., 1963; Mason and Benedict, 1931; Mukherjee and Gupta, 1931; Niyogi et al., 1939; Rahman, 1936; Rajagopal, 1938) have shown that the measured *RMR* per unit body surface area in Indian population is 5–18% lower than the Harris-Benedict standards (Harris and Benedict, 1918). However, Soares et al. (Soares et al., 1998) reported no significant difference in *RMR* adjusted for in males and in *RMR* adjusted for and in females, in Indian and Australian populations between the ages of 18 and 30 years. Moreover, Soares et al. (Soares et al., 1998) observed a *higher RMR*/*FFM* in the Indian population than in the Australian population; the reason was speculated to be due to a higher proportion of organ mass within compared to muscle mass, but this has not been verified. There is a clear absence of literature on RMR in the current Indian population. We study the influential model of *RMR*/*BM* by Wang (Wang, 2012) in Caucasian children closely to understand the determinants of *RMR* in Indian children.

In our study, a naive application of the Wang model clearly overestimates the mean *RMR*/*BM* observed in Indian children. We assess two major modifications of the model aimed at revealing the mechanistic basis of the lower *RMR*/*BM*. We first calibrate the relative masses of the four major organs to the observed RMR/BM, followed by a pilot study to validate organ mass predictions. Organ sizes were not found to be uniformly small, as predicted by model fits. Next, we vary the residual mass, to show that this can equivalently explain whole-body *RMR*/*BM*. In other words, our paper re-evaluates the role of the relative mass of four major organs and the metabolic contribution of residual mass in determining *RMR*/*BM* in an Indian population. We conclude that either model provides useful phenomenological descriptions of *RMR* varying with age in Indian children. However, identifying the physiological determinants of variation in *RMR* continues to be an elusive problem.

Methods

Datasets

The following datasets were used in the study:

Multicentre study (MCS) dataset

MCS is a dataset on 495 healthy school going children (235 girls) aged 9 to 19 years from multiple centres in India, which is a subset of data collected as a part of a previous study (Khadilkar et al., 2019). Anthropometric, body composition, and metabolic variables such as the height, weight, fat mass (*FM*), fat-free mass (*FFM*), and *RMR* of the subjects were measured.

A portable indirect calorimeter Fitmate GS (by COSMED srl, Italy) was used to measure *RMR*. Fitmate GS has previously been validated in healthy adults by Nieman et al. (Nieman et al., 2006) and Vandarakis et al. (Vandarakis et al., 2013). The machine was routinely calibrated according to manufacturer recommendations, and automatic oxygen sensor calibration was carried out before each measurement. Throughout the measurement, the child remained seated and was asked to relax while it was ensured that the child remained awake. The test was considered complete after achieving steady state. Body composition was assessed using Bioelectrical Impedance Analyzer (BIA; Tanita Model BC-420MA), and the child was asked to void before the measurement (Chiplonkar et al., 2017; Kyle et al., 2004). The physical characteristics of the subjects are given in Table 1.

Written consent was obtained from the parents of the children and from subjects above 18 years, and assent was obtained from children above 7 years. De-identified data were used for all the analyses. Ethics permission for conducting this multicenter study was granted by the Ethics Committee, Jehangir Clinical Development Centre Pune (dated 21st June 2016). A waiver for secondary data analysis was issued by the Ethics Committee for Human Research at the Indian Institute of Science Education and Research Pune (IECHR/Admin/2019/002).

RMR-USG dataset

In this study, we measured anthropometry, *RMR*, and organ mass (liver and kidney) of nine healthy girls and boys in the age group 6 to 8 years, recruited from a school in Western India. The age group 6 to 8 years was selected so that variation in *RMR* due to pubertal growth spurt could be avoided. Written consent was obtained from the children's parents. De-identified data were used for all the analyses. *RMR* is measured using indirect calorimetry (Fitmate GS, COSMED srl, Italy) under the standard conditions (see above). The liver and kidney volume in the subjects were measured using ultrasonography (Voluson P8 BT 16, GE Healthcare). The liver volume was examined in the supine position and kidney volume in lateral decubitus position. The measurements were taken during deep inspiration. The measured organ volume was converted to mass as density × volume. The density of liver and kidney in the Indian population is assumed to be 1.16 (Chandramohan et al., 2012) and 1.05 (kg/cm$^{3)}$ respectively (ICRP, 2009; Menzel et al., 2009). A summary of the RMR-USG dataset is given in Table 2. The MCS and RMR-USG studies were carried out as per relevant guidelines and regulations.

Relative organ mass (M_i/BM) data

A prominent dataset for reference physiological variables in North American population compiled by Altman and Dittmer (Altman and Dittmer, 1962) was used for organ weights from birth to maturity. To the best of our knowledge, this was the only dataset that provided liver, brain, heart, and kidney weights of children in age groups one year apart, from birth to adulthood. The reference relative mass (M_i/BM) of liver, kidney, heart, and brain is illustrated in Figure 1 and 2.

Model

A mechanistic model for RMR/BM in children and adolescents according to Wang (Wang, 2012) can be written as

$$\frac{RMR}{BM} = R_c \sum K_i \frac{M_i}{BM}, \qquad (1)$$

where R_c is the relative cellularity, K_i is the specific metabolic rate of an organ (i for brain, heart, kidney, liver, and the residual mass) and M_i/BM is the relative mass of the organ 'i' with respect to the body mass (BM). Residual mass is obtained by subtracting the sum of the mass of four organs from the body mass. These physiological parameters in Eq. 1 are described in detail as follows:

Relative cellularity (R_c)

The ratio of body cell mass (BCM) to fat-free mass (FFM) is defined as the whole-body cellularity, which quantifies the metabolically active portion of FFM . Whole-body cellularity is thought to change in the course of life and is assumed to be smaller in children than young adults (Wang et al., 2010, 2005). Hence, the factor "relative cellularity" (R_c), which is defined as the ratio of BCM/FFM in children to that of adults, is incorporated in Eq. 1. Here, BCM is assumed to be proportional to the total body potassium (TBK) and the change in BCM/FFM in children is estimated through TBK/FFM. In the reference Caucasian adults (Snyder et al., 1975), TBK/FFM (mmol/kg) is reported to be 68.1 for men and 64.2 for women

Table 1 Median and interquartile region (IQR; as (Q1, Q3)) of the observed physical characteristics of the subjects in the MCS dataset. The sample size (n) is given for each variable. BMI: body mass index. Boys and girls were compared using Wilcoxon rank sum test and the p-values are also given in the table.

Variables	Boys		Girls		p-value
	n	Median (Q1, Q3)	n	Median (Q1, Q3)	
Age (years)	260	13.3 (11.7, 14.8)	235	13.0 (11.3, 14.5)	0.1
Weight (kg)	260	42 (32, 51)	235	40 (33, 49)	0.5
Height (cm)	260	152 (142, 164)	235	150 (143, 156)	0.007
BMI (kg/m^2)	260	17.5 (15.4, 20.5)	235	18.0 (15.8, 20.6)	0.3
RMR (kcal/day)	260	1172 (1030, 1333)	232	1043 (928, 1168)	< 0.001
RMR/BM (kcal/(kg day))	260	29 (25, 33)	232	26 (22, 31)	< 0.001
Fat mass (kg)	257	5 (3, 12)	234	10 (6, 14)	< 0.001
Fat-free mass (kg)	257	35 (28, 43)	234	31 (27, 35)	< 0.001

Table 2 Median and IQR of the physical characteristics in the RMR-USG dataset. Q1: 1st quartile or 25th percentile; Q3: 3rd quartile or 75th percentile.

Variables	Boys (n = 9)	Girls (n = 9)
	Median (Q1, Q3)	Median (Q1, Q3)
Age (years)	7.1 (6.3, 7.7)	7.6 (7.0, 7.9)
Weight (kg)	19 (17.7, 20.9)	18.3 (17.6, 19.1)
Height (cm)	120.0 (112.4, 126.8)	122.5 (114.5, 124.2)
BMI (kg/m^2)	13.8 (13.2, 15.1)	12.9 (11.9, 13.4)
RMR (kcal/day)	984 (904, 1113)	873 (726, 936)
RMR/BM (kcal/(kg day))	48.1 (43.2, 56.6)	47.7 (47.1, 50.4)
Liver mass (kg)	0.68 (0.56, 0.73)	0.52 (0.42, 55)
Kidney mass (kg)	0.091 (0.080, 0.094)	0.080 (0.076, 0.093)

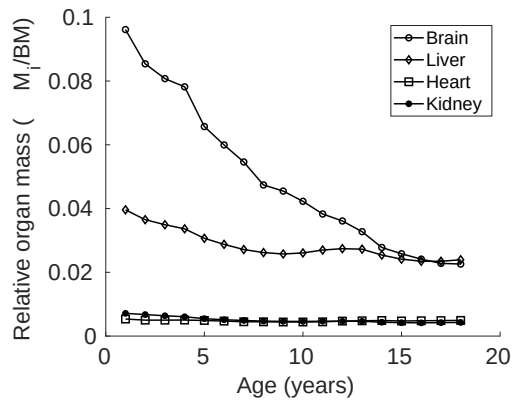

Figure 1 Relative organ mass (M_i/BM) of brain, liver, heart and kidney reported by Altman and Dittmer (Altman and Dittmer, 1962) in boys in the North American population.

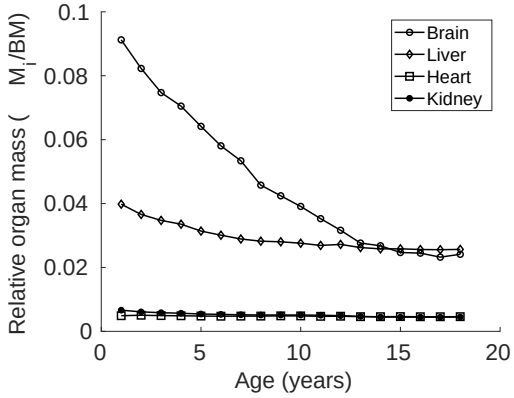

Figure 2 Relative organ mass (M_i/BM) of brain, liver, heart, and kidney reported by Altman and Dittmer (Altman and Dittmer, 1962) in girls in the North American population.

(Forbes, 1987). Thus, in children, R_c is approximated as $(TBK/FFM)/68.1$ in boys and $(TBK/FFM)/64.2$ in girls, in a given age group. Data on R_c from birth to adulthood were compiled by Wang (Wang, 2012), based on age-related changes in total body potassium (TBK) relative to FFM, from studies by Fomon et al. (Fomon et al., 1982).

Specific metabolic rate (K_i)

Specific metabolic rate (kcal/(kg day)) of an organ 'i' is the metabolic rate per unit mass of that organ, denoted as K_i. The specific metabolic rate (K_i) of organs in adults was measured in vivo by Elia (Elia, 1992). Elia estimated the oxygen consumption of organs in vivo by measuring the difference in arterio-venous oxygen concentration across tissue and the blood flow rate. The K_i (kcal/(kg day)) values are reported as 200 for liver, 240 for the brain, 440 for heart and kidneys, 13 for skeletal muscle mass, 4 for fat mass, and 12 for residual mass in adults. K_i values are thought to be higher in children (Chugani et al., 1987; Wang et al., 2005). Hence, the adult K_i values estimated in vivo by Elia (Elia, 1992) are adjusted in the Wang model with an age depending factor 'relative K_i' (Wang, 2012), which is the ratio of K_i values in children to that of adults. Relative K_i values are assumed from surrogate physiological parameters such as brain oxygen consumption (Chugani et al., 1987), heartbeat rates, and other physiological parameters.

Modified model of RMR/BM in Indian children.

Eq.1 suggests that relative mass of organs (and tissues) and their specific metabolic rates are the two major factors that determine the RMR/BM in children and adolescents. In this study, we look at two particular sources of variation influencing the whole-body RMR/BM. First of all, we consider the variation in the relative mass of major organs, assuming the specific metabolic rates of organs are constant (Elia, 1992). Secondly, we consider the composition of residual mass and its effect on the metabolic rate of relative residual mass and in turn on RMR/BM. We propose two models for RMR/BM in Indian children as follows:

Model 1: adjusting the relative mass of high metabolic rate organs

We modified Eq. 1 by adjusting the relative organ mass of four major organs (liver, kidney, brain, and heart) by a fraction δ_i.

We define δ_i as the ratio of relative organ mass (M_i/BM) in the Indian population to the M_i/BM in the Caucasian population. Assuming M_i/BM of major organs (liver, brain, kidney, heart) are adjusted by the same fraction δ, Eq. 1 can be written for the Indian population as

$$\begin{aligned}\frac{RMR_{\delta}}{BM} &= \Big(\delta\Big(K_{liver}\frac{M_{liver}}{BM} + K_{heart}\frac{M_{heart}}{BM} \\ &+ \mathrm{K_{brain}}\frac{\mathrm{M_{brain}}}{\mathrm{BM}} + \mathrm{K_{kidney}}\frac{\mathrm{M_{kidney}}}{\mathrm{BM}}\Big) \\ &+ K_{\mathrm{residual\ mass}}\frac{\mathrm{M'_{residual\ mass}}}{\mathrm{BM}}\Big)R_c\,, \qquad (2)\end{aligned}$$

where

$$\begin{aligned}\frac{\mathrm{M'_{residual}}\,mass}{BM} &= 1-\delta\Big(\frac{M_{liver}}{BM} + \frac{M_{heart}}{BM} \\ &+ \frac{M_{brain}}{BM} + \frac{M_{kidney}}{BM}\Big) \qquad (3)\end{aligned}$$

$\frac{M'_{residual\,mass}}{BM}$ is the residual mass after adjusting the relative mass of major organs by a factor δ, whereas R_c is the relative cellularity, and K_i is the specific metabolic rate of an organ.

Model 2: adjusting the metabolic contribution from relative residual mass

In Model 2, RMR/BM in Eq. 1 is modified under the assumption that the metabolic contribution from residual mass in the Indian population is lower by factor δ' compared to the Caucasian population. Thus, the alternate model for RMR/BM can be written as

$$\begin{aligned}\frac{RMR_{\delta'}}{BM} &= \Big(K_{liver}\frac{M_{liver}}{BM} + K_{heart}\frac{M_{heart}}{BM} \\ &+ K_{brain}\frac{M_{brain}}{BM} + K_{kidney}\frac{M_{kidney}}{BM} \\ &+ \delta' K_{residualmass}\frac{M_{residualmass}}{BM}\Big)R_c, \qquad (4)\end{aligned}$$

where

$$\begin{aligned}\frac{M_{residualmass}}{BM} &= 1-\Big(\frac{M_{liver}}{BM} + \frac{M_{heart}}{BM} \\ &+ \frac{M_{brain}}{BM} + \frac{M_{kidney}}{BM}\Big). \qquad (5)\end{aligned}$$

R_c is the relative cellularity, K_i is the specific metabolic rate, and M_i/BM is the relative mass of the respective organs.

Statistical analysis

All descriptive data are reported as the mean ± standard deviation (SD). The measured and the theoretical values were compared using the paired t-test with the significance level set at $\alpha = 0.05$. The relative organ mass between the two populations was compared through a non-parametric Wilcoxon signed-rank test, with the significance level set at $\alpha = 0.05$. All the analyses were carried out using MATLAB R2019b (The MathWorks Inc., 2019) and R version 3.6.2 (R Core Team, 2019).

Results

The measured RMR per unit body mass (kcal/(kg day)) in Indian children is denoted as RMR_M/BM. RMR_T/BM represents the theoretical expectation calculated from the Wang model (Eq. 1) with the reference organ weights data reported by Altman and Dittmer (Altman and Dittmer, 1962). Similarly, RMR/BM calculated from Model 1 (Eq. 2) is denoted as RMR_{δ}/BM and from Model 2 (Eq. 4) as $RMR_{\delta'}/BM$. Subjects are grouped one year apart in the analysis. We employ the following notation: Children above the age of 10 but below the age of 11 years are denoted for brevity as age group 10, and so on.

RMR/BM in Indian children is significantly lower than in Caucasian children

We studied RMR/BM in Indian children using a mechanistic model by Wang (Wang,

2012) (Eq. 1) which partitions total body mass into four major organs and residual mass.

The mean RMR_M/BM measured in the MCS cohort, stratified by age, was compared with the theoretical RMR_T/BM from Eq. 1 calculated with the relative mass of the four major organs reported for the Caucasian population (Altman and Dittmer, 1962). In Figure 3 and 4, the solid curve shows the mean measured RMR_M/BM ($\mu \pm SD$); the dotted curve is the theoretical RMR_T/BM (Wang model) and is representative of the mean RMR/BM in Caucasian children (Talbot, 1938; Wang, 2012). In boys, the measured RMR_M/BM is significantly lower than the theoretical RMR_T/BM in the age groups 11, 13, 14, 15 and 16years ($p < 0.05$); but not at 10 and 12 years ($p = 0.70.09$, respectively). In girls, RMR_M/BM is significantly lower than RMR_T/BM in all the age groups from 10 years to 16 years: < 0.05 for 10 years and < 0.001 for 11 to 16 years.

We thus observe a significantly lower mean RMR/BM in Indian adolescents (232 girls and 260 boys) compared to the reference Caucasian adolescents (Talbot, 1938), except in boys aged 9 to 11 years and 12 to 13 years.

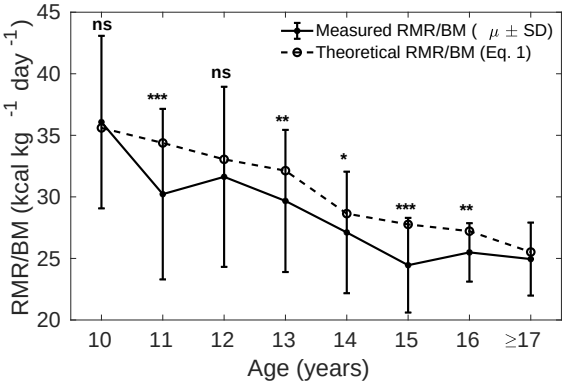

Figure 3 The solid curve shows the mean (± SD) RMR_M/BM measured in each age group, and the dotted line shows the mean theoretical RMR_T/BM based on Eq. 1 for the Caucasian population in boys. ns: not significant, *: $p < 0.05$, **: $p < 0.01$ and ***: $p < 0.001$. The groups of 9- and 10-year-olds were combined for the statistical tests. The analysis was not done when the number of samples was less than 10 (for age 17 years and above).

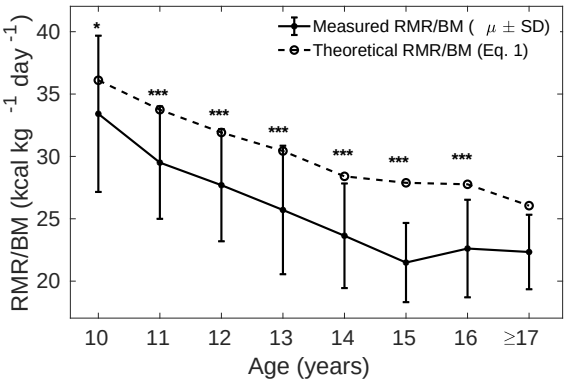

Figure 4 The solid curve shows the mean (± SD) RMR_M/BM measured in each age group, and the dotted line shows the mean theoretical RMR_T/BM based on Eq. 1 for the Caucasian population in girls. ns: not significant, *: $p < 0.05$, **: $p < 0.01$ and ***: $p < 0.001$. The groups 9- and 10-year-olds were combined for the statistical tests. The analysis was not done when the number of samples was less than 10 (for age 17 years and above).

A modified Wang model of RMR/BM for Indian children

Measured RMR_M/BM in the MCS dataset is significantly lower than the mean RMR_T/BM in the Caucasian population. In accordance with Eq. 1, RMR_T/BM is determined by the relative mass of four major organs, with smaller (larger) M_i/BM leading to smaller (larger) RMR_T/BM. Thus, we hypothesise that the lower mean RMR/BM between the Indian and the Caucasian children is due to a lower mean relative mass of the four major organs in the Indian population.

We define δ_i (see Section 2.3.1 below) as the ratio of relative organ mass (M_i/BM) in the Indian population to the M_i/BM in the Caucasian population. Eq. 1 is modified to Eq. 2 by adjusting the mass of major organs by a fraction δ (Model 1). We optimised δ by minimising the mean squared error (MSE) between the measured and the model (Eq. 2), for δ varying from 0 to 1. The optimal δ values corresponding to the least MSE was

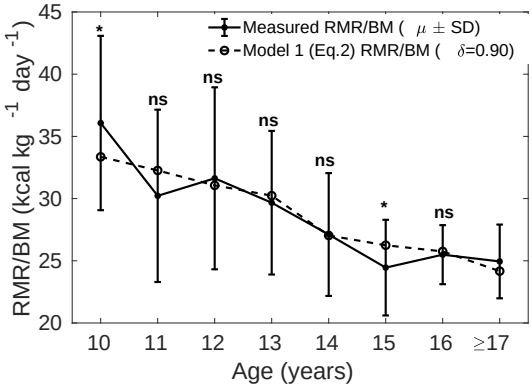

Figure 5 The dotted curve is the adjusted RMR/BM calculated from Eq. 2 assuming that the relative mass (M_i/BM) of all the organs (liver, brain, kidney, heart) are smaller by a fraction of 0.90 in boys compared to that of Caucasian population (1962), that is with $\delta = 0.90$ in Eq. 2. The solid curve shows the mean measured RMR_M/BM in MCS dataset. ns: not significant, *: p<0.05, **: p<0.01 and ***: p<0.001 (Compare Figure 3).

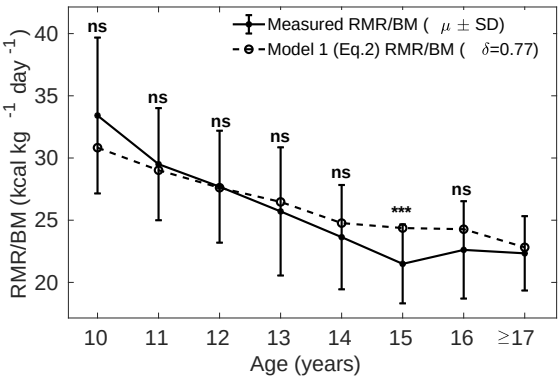

Figure 6 The dotted curve is the adjusted RMR/BM calculated from Eq. 2 assuming that the relative mass (M_i/BM) of all the organs (liver, brain, kidney, heart) are smaller by a fraction of 0.77 in girls compared to that of Caucasian population (1962), that is with $\delta = 0.77$ in Eq. 2. The solid curve shows the mean measured RMR_M/BM in MCS dataset. ns: not significant, *: p < 0.05, **: p < 0.01 and ***: p < 0.001 (Compare Figure 4).

found to be $\delta = 0.90$ in boys and $\delta = 0.77$ in girls.

Model 1 (Eq. 2) evaluated with optimal δ was then compared with the measured RMR_M/BM, as shown in Figures 5 and 6. The dotted curve shows the mean RMR_δ/BM calculated from Eq. 2 with $\delta = 0.90$ in boys (Figure 5) and $\delta = 0.77$ in girls (Figure 6). The solid curve shows the measured RMR_M/B (μ±SD). We verify that the model is not significantly different from the measured values, except in the age groups 10 and 15 years in boys and 15 years in girls.

Our modified Wang model (Eq. 2) is thus better suited to predicting RMR/BM in Indian children compared to the naive Wang model (Eq. 1). Physiologically this implies that the relative organ masses in the Indian population ought to be lower by the factor 0.90 in boys and 0.77 in girls compared to reference relative organ mass in the Caucasian population (Altman and Dittmer, 1962).

Relative kidney mass in 6 to 8 years old Indian children is significantly lower, but relative liver mass is not.

Model 1 (Eq. 2) predicts that the relative mass of major organs in the Indian population is lower by 10% in boys and 23% in girls compared to the Caucasian population. We measured the liver and kidney masses in 9 girls and 9 boys aged 6 to 8 years from the group of RMR-USG children to validate the Model 1 predictions. The ratio of relative liver and relative kidney mass (M_i/BM) measured in the RMR-USG dataset compared to the corresponding M_i/BM in the Caucasian counterparts (Altman and Dittmer, 1962) are denoted as δ_{liver} and δ_{kidney}, respectively. Figure 7 shows the δ_{liver} and δ_{kidney} observed in the RMR-USG dataset. The median ($Q1, Q3$) observed δ_{liver} is 1.32 (1.02, 1.40) in boys and 0.92 (0.90, 1.08) in girls, while δ_{kidney} is 0.90 (0.83, 0.96) in boys and 0.83 (0.80, 0.91) in girls.

The δ_{kidney} observed in the RMR-USG dataset is significantly lower ($p = 0.009$ in boys and $p = 0.009$ in girls; one-sided

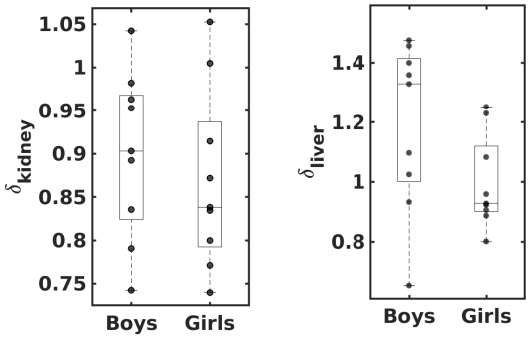

Figure 7 δ_{kidney} and δ_{liver} observed in Indian children (9 girls and 9 boys), where δ_i denotes the ratio of the relative mass of the organ 'i' measured in RMR-USG dataset to that of their Caucasian counterparts (Altman and Dittmer, 1962). The lower and upper whiskers indicate the minimum and the maximum values; and the lower edge, middle line and the upper edge of the box indicate the 25th percentile, median and the 75th percentile values, respectively. The dots show the observed individual δ values.

Wilcoxon signed-rank test). Consistent with Eq. 2 predictions, the relative kidney mass measured in Indian children is found to be lower than that of reference Caucasian children in the respective age groups. However, we failed to find any significant difference in the observed δ_{liver} (boys $p = 0.5$ and girls $p = 0.9$).

It is noteworthy that the δ_{kidney} predicted by Eq. 2 was close to the observed δ_{kidney}: δ_{kidney} was 0.90 (0.83, 0.96) compared to the prediction 0.9 in boys; in girls δ_{kidney} was 0.83 (0.80, 0.91) compared to the predicted 0.77. However, the δ_{liver} in both girls and boys was higher than the optimal δ predicted by Eq 2.

Alternate model of RMR/BM in Indian children based on residual mass

Residual mass (the mass remaining after subtracting liver, brain, heart, and kidney mass from total body mass) constitutes a much larger part of the body mass compared to the sum of masses of four major organs. The residual mass is composed mainly of skeletal muscle mass and fat mass, along with lungs, spleen, gastrointestinal tract, connective tissue etc. Broadly speaking, skeletal muscle mass and fat mass are the more malleable components of the body compared to the sizes of the major organs. Moreover, the fat and muscle mass per cent in Indian children is characteristically different from the Western population (Chiplonkar et al., 2017). This can potentially account for the wide variation in RMR between children. To examine this possibility, we next studied an alternate model of RMR/BM (Model 2) which takes into account the variation in the metabolically active constituents of residual mass.

We modified Eq. 1 to Eq. 4 (Model 2) by incorporating a factor δ' which adjusts the metabolic rate of relative residual mass in the Indian population. An optimal δ' was obtained by minimizing the mean squared error between the measured RMR_M/BM and the $RMR_{\delta'}/BM$ calculated by Eq. 4 in the MCS dataset, for δ' ranging from 0 to 1. The δ' corresponding to the least MSE is found to be 0.85 in boys and 0.65 in girls.

In Figure 8 and 9, the dotted curve shows the $RMR_{\delta'}/BM$ calculated from Model 2, with $\delta' = 0.85$ in boys and $\delta' = 0.65$ in girls (Figure 9); the solid curve shows the measured RMR/BM ($\mu \pm SD$) in the MCS dataset. In boys (Figure 8), the dotted curve is not significantly different from the mean measured RMR_M/BM in the MCS dataset (solid curve), except in the age groups 11 and 15 years ($p = 0.03$ and 0.02, respectively). Similarly, in girls the solid curve is not significantly different from the dotted curve, except in the age group 15 years ($p = 0.001$).

δ' can be interpreted physiologically as the effect of body composition differences on RMR/BM. Thus Model 2 raises the hypothesis that the metabolic contribution from the relative residual mass is reduced in the

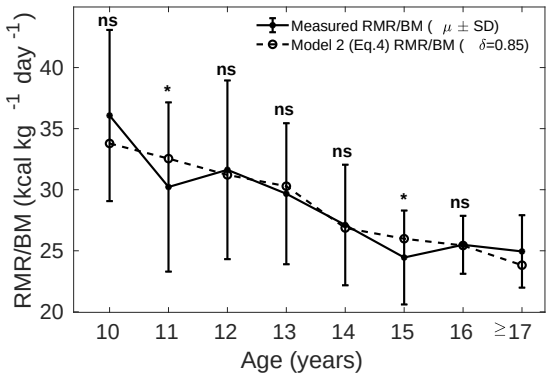

Figure 8 Measured RMR_M/BM (μ ± SD) is shown as the solid curve, and the dotted curve shows the RMR/BM calculated from Eq. 4 with $\delta' = 0.85$ in boys and reference relative organ mass for the Caucasian population (1962).

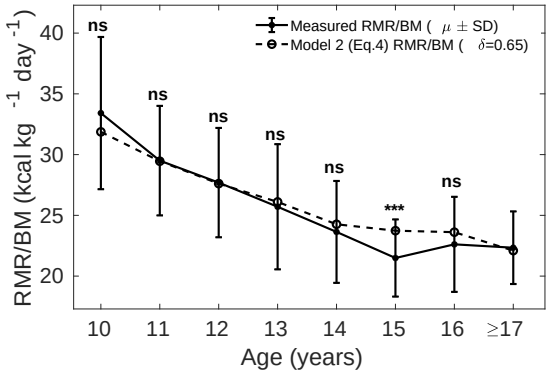

Figure 9 Measured RMR_M/BM (μ ± SD) is shown as the solid curve, and the dotted curve shows the RMR/BM calculated from Eq. 4 with $\delta' = 0.65$ in girls and reference relative organ mass for the Caucasian population (1962).

Indian children, lower by 15% in boys and 35% in girls, if the relative mass of major organs is assumed to be similar in the two populations. This indicates that variation in body composition could play a considerable role in determining *RMR* in Indian children.

Discussion

Resting metabolic rate (*RMR*) is a significant factor in determining energy balance, which in turn critically influences the energy available for growth from birth to adulthood. The mean RMR per unit body mass (RMR/BM) is not uniform across populations; Indian children have significantly lower RMR/BM compared to their Caucasian counterparts. Not only are these population differences not understood from a physiological standpoint, but inter-individual variations are also poorly explained. Several models have been proposed over the years to try to explain *RMR* through various anthropometric variables such as height and weight as well as fat or fat-free mass. One such prominent model is the Katch-McArdle equation (Katch et al., 1990), which computes *RMR* as due to fat-free mass: $RMR = 370 + (21.6\, FFM)$. However, such models have been reported to explain only about 60–80% of the intraspecific variation. An alternate strategy is to explain the *mean* RMR of children clustered into one-year age groups. A very successful model in this class is the Wang model, which achieves an $R^2 = 0.99$. However, it is unclear if the Wang model is readily applicable to other populations. In particular, the Caucasian dataset modelled in the Wang study shows little variation in the age-stratified data, whereas a much wider variability is expected, in general, in Indian children. In this study, we attempt to modify the Wang class of models for application to Indian children. It is worth pointing out that using linear regression models based on body composition, such as the Katch-McArdle equation, we could only explain about 70% variation in the mean RMR/BM in an age group. We also explored several other regression models based on body composition and anthropometry, but they each explained only 30–60% of the inter-individual variation in RMR observed in Indian children (analysis not shown).

In this work we construct two models of RMR/BM in Indian children based on the

Wang model (Wang, 2012), which describe the mean *RMR*/*BM* stratified by age phenomenologically. In Model 1, we assume lower organ masses are responsible for the lower observed *RMR*; in Model 2, residual masses are calibrated to the observed *RMR*. The coefficients of determination (R^2) in explaining the mean measured *RMR*/*BM* for Model 1 and Model 2 are 0.84 and 0.85 in boys and 0.95 and 0.97 in girls, respectively. The lower accuracy of these models in describing the *RMR*/*BM* in Indian children compared to the Caucasian children ($R^2 = 0.99$) is consistent with high variation in the observed *RMR* (ranging from 612 to 2370 kcal/day). It seems unlikely that larger sample sizes would substantially improve the accuracy of the model.

Next, we asked if these models provide a physiological understanding of the lower *RMR*/*BM* observed in Indian children. If the lower *RMR*/*BM* is due to a lower relative mass of four major organs (liver, kidney, heart, brain) through a modified Wang model, Model 1 (Eq. 2) predicted that the relative masses of the four major organs should be lower by 10% in boys and 23% in girls. Our pilot study designed to test these predictions showed the relative kidney mass was significantly lower, but it failed to find any significant difference in the relative liver mass. It is interesting to note that a lower relative kidney mass in Indian children is consistent with the Barker hypothesis (Almond and Currie, 2011) and the observation of fewer nephrons in low birth weight babies (Wlodek et al., 2008). On the other hand, failure to observe a significant difference in relative liver weight could suggest a lower K_{liver} instead, which is consistent with lower K_i values reported in South Asian females (Shirley et al., 2019). One limitation of the current study is the assumption that brain and heart masses are likely to be relatively conserved within an age group; due to practical difficulties, these were not measured in our study.

To provide further contrast, we constructed Model 2, which analyses the influence of metabolically active constituents of residual mass on *RMR*/*BM*. Model 2 predicts that the metabolic rate of residual mass is lower by 15% in boys and 35% in girls in the Indian population compared to the Caucasian population. Model 2 re-emphasizes the importance of body composition in explaining variation in *RMR*. It is interesting that a century-long attempt to decipher the relationship between body composition and RMR has not been very successful (Aub and Du Bois, 1917; Bedale, 1923; Corrigan et al., 2020; Cunningham, 1980; FAO/WHO/UNU, 1985; Harris and Benedict, 1918; Henry, 2005; Katch et al., 1990; Kleiber, 1932; McMurray et al., 2014; Mifflin et al., 1990; Owen et al., 1987; Schofield, 1985). Thus, understanding the physiological underpinnings of Model 2 remains an open problem. Finally, we note that it is plausible that more complex formulations than basing RMR on either organ mass or residual mass are necessary. One attractive approach for future work is to employ data-driven machine learning strategies to discover these complex relations.

We remark on some refinements of our work that might be possible in future studies. In children, strict standard conditions for RMR measurement are difficult to achieve. The terms basal metabolic rate (*BMR*), resting metabolic rate (*RMR*) and resting energy expenditure (*REE*) are different measurements of the resting metabolism and are often used interchangeably; however, *RMR* and *REE* can be 3–10% higher than *BMR*, as they follow less stringent settings for the measurements (Psota and Chen, 2013). In our study, *RMR* in children was not measured following fasting conditions alone; hence, RMR measured in our study could be higher

than the basal metabolism; such differences could be up to 100 kcal/day (Haugen et al., 2003). However, indirect calorimeters have been reported to underestimate *REE* in some studies (Purcell et al., 2020). We argue that the distinct patterns in boys and girls are of prime interest, and these are less likely to be explained by measurement bias alone. Climate and temperature difference during *RMR* measurements also add to this variability.

The ratio *RMR*/*BM* was used to normalize the *RMR* with respect to *BM*. This ratio has been used by several studies, including (Rahmandad, 2014; Wang, 2012). However, other authors have critiqued this ratio due to the observation that a linear *RMR–BM* relationship extrapolates to a non-zero intercept (Poehlman and Toth, 1995; Tschöp et al., 2012). While it is not immediately clear if *RMR* should be normalized by *BM* , in our study, we follow the Wang (Wang, 2012) model closely. In other words, since our comparisons are with respect to the Wang model, the appropriate variable in our work is the normalized *RMR*/*BM*.

The significance of our study is that a lower *RMR*/*BM* in Indian children can significantly influence energy balance and amplify the effects of lower or higher energy intakes. Swinburn and colleagues (Swinburn et al., 2006) have reported that even a 10% change in total energy expenditure (*TEE*; consists of *RMR* as a component) could lead to a 4.5% difference in mean weight of children between two populations. The implications of lower *RMR*/*BM* in Indian children on the dynamics of growth and development will be studied in the future, in particular, using quantitative models of growth and weight changes (Hall et al., 2013). The present study has provided that basis through two phenomenological models, either of which can be used to estimate age-wise mean *RMR*/*BM* in Indian adolescents. While predicting individual *RMR*/*BM* is far from complete, the present models are likely to be referred to by clinicians and policymakers to infer energy expenditure benchmarks in Indian children. Such studies are critical to understanding the implications of a lower *RMR*/*BM* in growth, development, and life-course diseases.

Data Availability

The datasets analyzed during the current study are not publicly available in order to protect subject anonymity. Please contact the corresponding authors for reasonable requests to access raw data.

Author contributions statement

PG and AK conceived the study. AK and NK were involved in collecting the MCS dataset. ASK, AK, and NK were involved in collecting the RMR-USG dataset. PG and SA carried out the mathematical and statistical analysis and the analysis was reviewed by AK, NK, and ASK. PG and SA wrote the paper together with AK. All authors contributed to the manuscript.

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An early version of the manuscript is available as a preprint (Areekal et al., 2021).

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Appendix

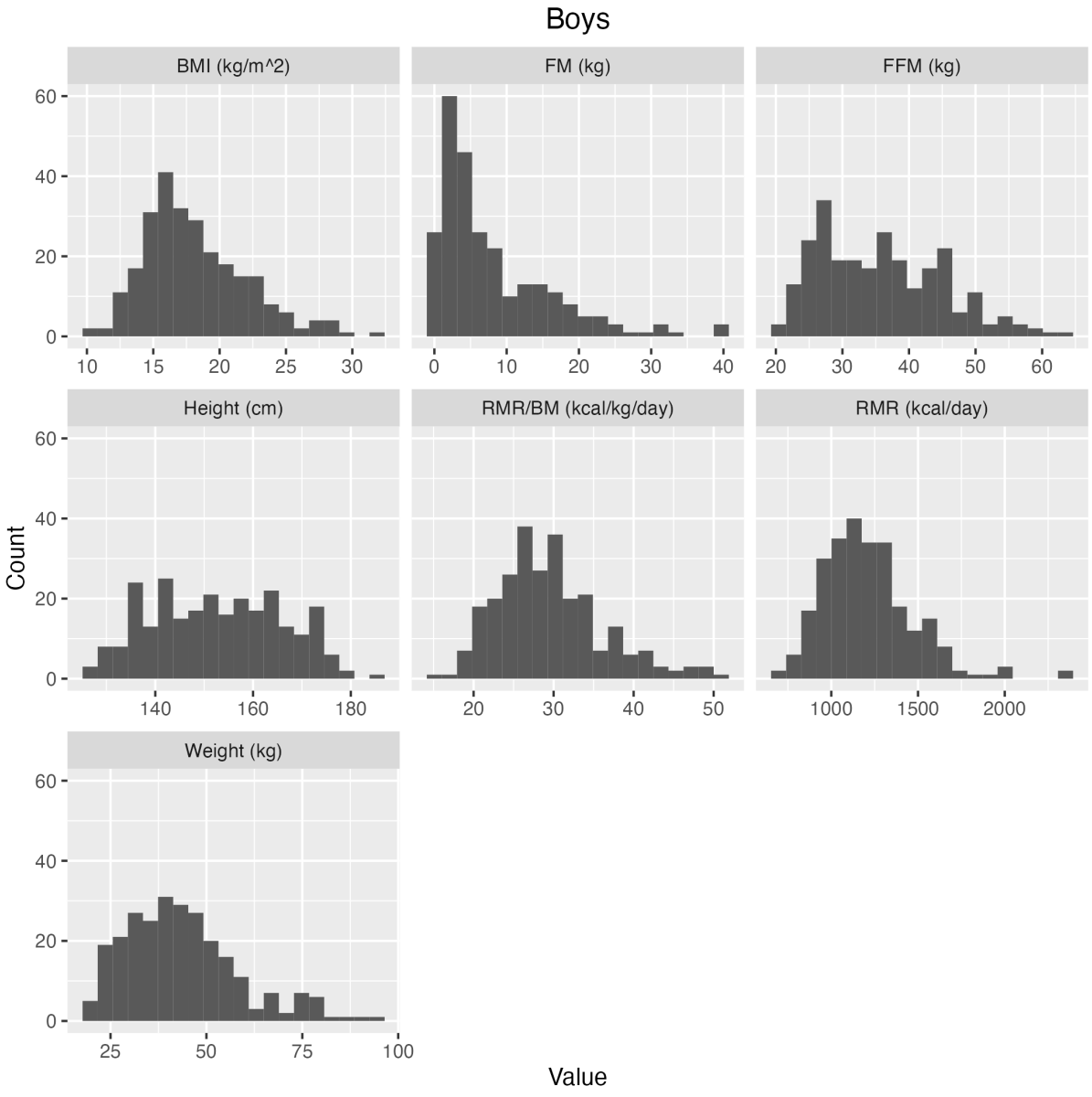

Figure S1 Histogram of the measured covariates in RMR-MCS dataset in boys.

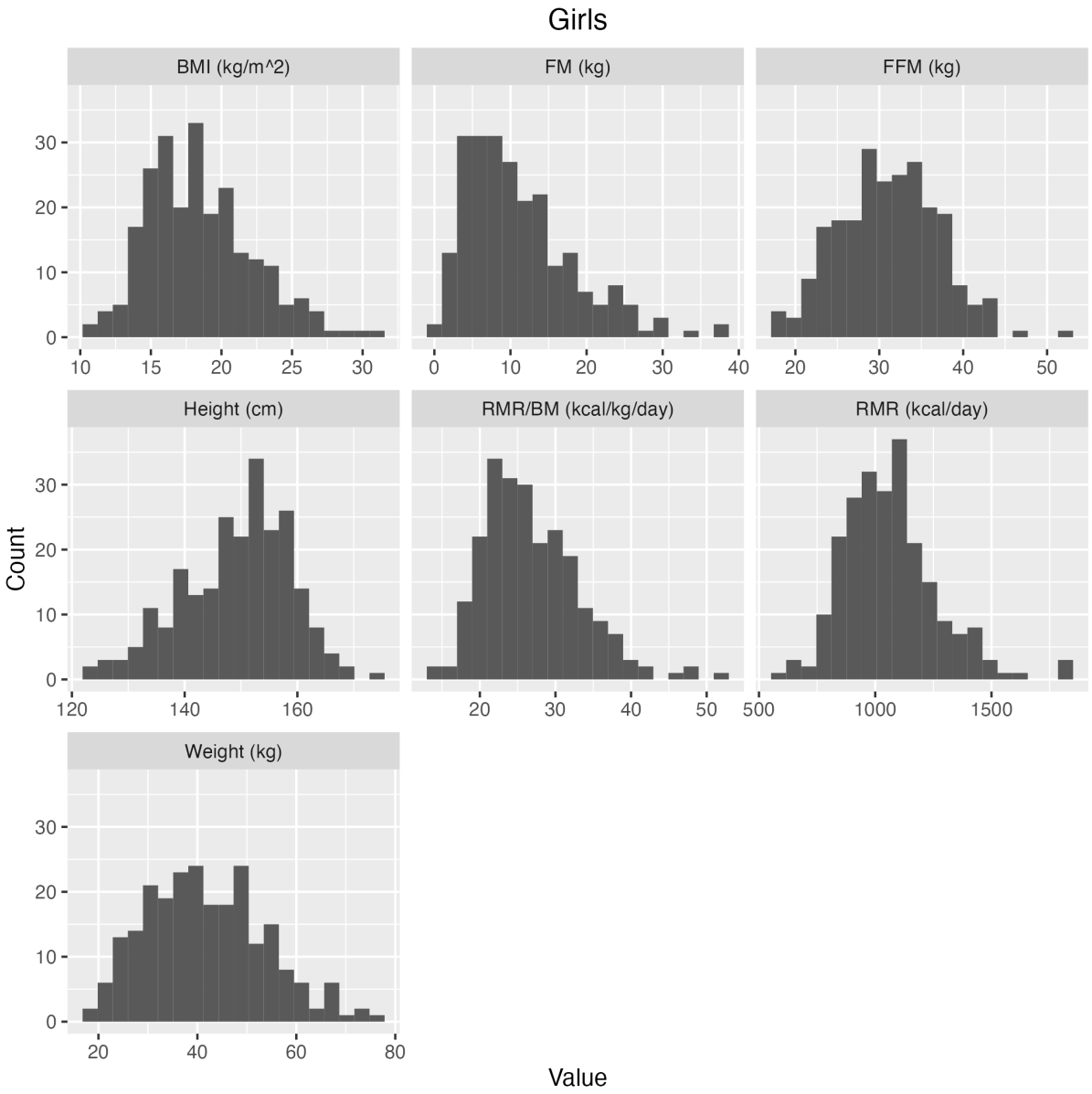

Figure S2 Histogram of the measured covariates in RMR-MCS dataset in girls.