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

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ABSTRACT

Resting metabolic rate (RMR) quantifies the minimal energy required to sustain vital body functions and is a crucial component of childhood development. While inter-individual variations in RMR have been studied for over a century they are poorly understood. Wang (Am. J. Hum., 2012) has modelled mean RMR per unit body mass (RMR/BM) in children grouped into age classes one year apart; this model is able to explain the variation in RMR/BM very accurately in a reference Caucasian dataset based on the relative masses of four major organs (liver, kidney, brain, heart) and the residual mass. However, it is not clear if it applies to other ethnicities, especially when the variation in the RMR is observed to be large in a population. Here we address the extent to which such a model can be adapted to explain RMR/BM in Indian children. Here we present two novel phenomenological models that describe the mean RMR/BM stratified by age in Indian children and adolescents, using data from the Multi-Centre Study (MCS) and RMR-USG. MCS is a cross-sectional dataset on 495 (235 girls) children aged 9 to 19 years with anthropometric, body composition and RMR measurements. 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. The mean RMR/BM in Indian children is observed to be significantly lower compared to their Caucasian counterparts, except in boys in the age groups 9 to 11 years and 12 to 13 years. 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 size are not uniformly borne out in a pilot validation study, however, the relative mass of the kidney is indeed found to be significantly lower. We then present another version of the Wang model to demonstrate that changes in body composition alone can also explain the Indian data. Either model can be thus used phenomenologically to estimate mean RMR/BM by age in Indian children; however, understanding the mechanistic basis of variation in RMR/BM remains an open problem.

1 Introduction

India faces the double burden of malnutrition with the highest prevalence of undernutrition and a rising prevalence of overweight and obese children and adolescents¹,². Malnourishment can be studied through the energy intake and energy expenditure of the 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 1976-1980³. In contrast to energy intake, energy expenditure is predominantly determined by the physiology of the individual and varies significantly in a population⁴,⁵. It is necessary to understand the factors leading to this variation in energy expenditure to create personalised interventions to tackle the double burden of malnourishment. 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 calorimetry⁶ under standard conditions such as in the post-absorptive state, in wakefulness, in the absence of any physical activity and diseases, 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 century⁴,⁷–¹⁸. These models find that fat free mass (FFM) is the single largest predictor of RMR, followed by fat mass (FM), age, and gender. However, RMR is found to be highly variable between individuals in a population⁴,⁵. Overall models based on body composition have been of limited success, as they are able to explain only about 60 – 80% variation in RMR.

Studies on metabolic rates in Indian children are scarce¹⁹,²⁰. Predictive equations developed for Caucasian populations¹⁰,²¹ have been reported to overpredict metabolic rates in Indian adults²², however, they continue to be used to predict RMR in Indian children²³–²⁵. Previous studies in Indian adults²⁶–³³ have shown that the measured RMR per unit body surface area in Indian population is 5-18% lower than the Harris-Benedict¹⁰ standards. On the other hand, Soares²² has reported no significant
difference in RMR adjusted for FFM in males and RMR adjusted for FFM and FM in females, between 18 to 30 years old Indian and Australian population. Moreover, Soares had observed a higher RMR/FFM in Indian population than the Australian population; and the reason was speculated to be due to a higher proportion of organ mass within FFM compared to muscle mass, but this has not been verified. There is a clear absence of literature on RMR in current Indian population.

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. 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. The Gallagher model was able to explain 80-98% variation of RMR in several studies in adults. However, the Wang model was found to under-predict RMR in children. Wang modified the Gallagher model to study how RMR/BM varies in children from birth to adulthood, and described the mean RMR/BM in a reference Caucasian dataset. Here we ask if the Wang model can describe RMR/BM in an Indian population?

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 is useful as 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.

2 Results
The measured RMR per unit body mass (kcal kg⁻¹ day⁻¹) 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. Similarly, RMR/BM calculated from Model 1 (Eq. 2) is denoted as $RMR_{G}/BM$ and from Model 2 (Eq. 4) as $RMR_{G}/BM$. Subjects are grouped one year apart in the analysis. We employ the following notation: Children above the age of 10 years but less than 11 are denoted for brevity as age group 10, and so on.

2.1 RMR/BM in Indian children is significantly lower than Caucasian children
We studied RMR/BM in Indian children using a mechanistic model due to Wang (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. In Figure 1a and 1b 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. 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 16 years ($P < 0.05$); but not at 10 and 12 years ($P = 0.7$ and 0.09, respectively). In girls, $RMR_{M}/BM$ is significantly lower than $RMR_{T}/BM$ in all the age groups from 10 years to 16 years; $P < 0.05$ for 10 years and $P < 0.001$ 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, except in boys aged 9 to 11 years and 12 to 13 years.

2.2 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 $\delta$ (see Section 4.2.1 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 $\delta$ (Model 1). We optimised $\delta$ by minimising the mean squared error (MSE) between the measured and the model (Eq. 2), for $\delta$ varying from 0 to 1. The optimal $\delta$ values corresponding to the least MSE was found to be $\delta = 0.90$ in boys and $\delta = 0.77$ in girls.

Model 1 (Eq. 2) evaluated with optimal $\delta$ was then compared with the measured $RMR_{M}/BM$, as shown in Figure 2. The dotted curve shows the mean $RMR_{G}/BM$ calculated from Eq. 2 with $\delta = 0.90$ in boys (Figure 2a) and $\delta = 0.77$ in girls (Figure 2b). The solid curve shows the measured $RMR_{M}/BM (\mu \pm SD)$. 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 lower by a factor 0.90 in boys and 0.77 in girls compared to reference relative organ mass in the Caucasian population.

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

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 year in the RMR-USG children to validate the Model 1 predictions. The ratio of relative liver and relative kidney mass (\( \frac{M_i}{BM} \)) measured in the RMR-USG dataset compared to the corresponding \( \frac{M_i}{BM} \) in the Caucasian counterparts are denoted as \( \delta_{\text{liver}} \) and \( \delta_{\text{kidney}} \), respectively. Figure 3 shows the \( \delta_{\text{liver}} \) and \( \delta_{\text{kidney}} \) observed in the RMR-USG dataset. The mean (±SD) observed \( \delta_{\text{liver}} \) is 1.19 ± 0.28 in boys and 1.0 ± 0.16 in girls, and \( \delta_{\text{kidney}} \) is 0.90 ± 0.097 in boys and 0.87 ± 0.10 in girls.

The \( \delta_{\text{kidney}} \) observed in the RMR-USG dataset is significantly lower (P=0.009 in boys and P=0.009 in girls; one-sided 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 \( \delta_{\text{liver}} \) (boys P=0.45 and girls P=0.91).

It is noteworthy that the \( \delta_{\text{kidney}} \) predicted by Eq. 2 was close to the observed \( \delta_{\text{kidney}} \). \( \delta_{\text{kidney}} \) was observed to be 0.90 ± 0.097 compared to the prediction 0.9 in boys; in girls \( \delta_{\text{kidney}} \) was observed to be 0.87 ± 0.10 compared to the predicted 0.77. However, the \( \delta_{\text{liver}} \) in both girls and boys is higher than the optimal \( \delta \) predicted by Eq. 2.

2.4 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 the 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. 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 \( \delta' \) which adjusts the metabolic rate of relative residual mass in the Indian population. An optimal \( \delta' \) was obtained by minimising the mean squared error between the measured \( RMR_i/BM \) and the \( RMR_i/BM \) calculated by Eq. 4 in the MCS dataset, for \( \delta' \) ranging from 0 to 1. The \( \delta' \) corresponding to the least MSE is found to be 0.85 in boys and 0.65 in girls.

In Figure 4, the dotted curve shows the \( RMR_i/BM \) calculated from Model 2, with \( \delta' = 0.85 \) in boys and \( \delta' = 0.65 \) in girls (Figure 4b); and the solid curve shows the measured RMR/BM (μ ± SD) in MCS dataset. In boys (Figure 4a), the dotted curve is not significantly different from the mean measured \( RMR_i/BM \) 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).

\( \delta' \) 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 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.

3 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, weight, fat and fat-free mass. One such prominent model is the Katch-McArdle equation which computes RMR as due to fat-free mass: \( RMR = 370 + (21.6FFM) \). 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 \( R^2 = 0.99 \). On the other hand, 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\textsuperscript{41}, 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$^{-1}$). It seems unlikely that larger sample sizes would substantially improve the accuracy of the model.

Next, we ask 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 organ 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 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\textsuperscript{49} and the observation of fewer nephrons in low birth weight babies\textsuperscript{50}. On the other hand, failure to observe a significant difference in relative liver weight could suggest a lower $K_{\text{liver}}$ instead, which is consistent with lower $K_i$ values reported in South Asian females\textsuperscript{51}. This challenges the applicability of specific metabolic rates estimated, in particular, in Elia\textsuperscript{35}, across racially and ethnically diverse populations. 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\textsuperscript{14,7-18,52}. 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\textsuperscript{53}. 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\textsuperscript{54}. Climate and temperature difference during RMR measurements also add to this variability.

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\textsuperscript{55} 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\textsuperscript{1}. 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.

4 Methods

4.1 Model

A mechanistic model for RMR/BM in children and adolescents due to Wang\textsuperscript{45} can be written as

$$\frac{RMR}{BM} = R_c \sum K_i M_i^{BM},$$

(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:

**4.1 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$^{39,40}$. 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 $TBK/FFM$ (see Section 4.3.4).

**4.1.2 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 $K_i$. $K_i$ values are thought to be higher in children$^{39,56}$. Hence the adult $K_i$ values estimated in vivo by Elia$^{35}$ are adjusted in the Wang model with an age depending factor ‘relative $K_i$’$^{45}$, which is the ratio of $K_i$ values in children to that of adults. Relative $K_i$ values are assumed from surrogate physiological parameters$^{45}$ (see Section 4.3.5).

**4.2 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, we consider the variation in the relative mass of major organs, assuming the specific metabolic rates of organs are constant$^{35}$. 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:

**4.2.1 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 $\delta$. We define $\delta$ 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 $\delta$, Eq. 1 can be written for the Indian population as

$$RMR_\delta/BM = \left( \delta \left( K_{liver} \frac{M_{liver}}{BM} + K_{heart} \frac{M_{heart}}{BM} + K_{brain} \frac{M_{brain}}{BM} + K_{kidney} \frac{M_{kidney}}{BM} \right) + K_{residual mass} \frac{M_{residual mass}}{BM} \right) R_c,$$

where

$$M_{residual mass} = 1 - \delta \left( \frac{M_{liver}}{BM} + \frac{M_{heart}}{BM} + \frac{M_{brain}}{BM} + \frac{M_{kidney}}{BM} \right),$$

$M_{residual mass}$ is the residual mass after adjusting the relative mass of major organs by a factor $\delta$. $R_c$ is the relative cellularity, and $K_i$ is the specific metabolic rate of an organ.

**4.2.2 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 $\delta'$ compared to the Caucasian population. Thus, the alternate model for RMR/BM can be written as

$$RMR_{\delta'}/BM = \left( K_{liver} \frac{M_{liver}}{BM} + K_{heart} \frac{M_{heart}}{BM} + K_{brain} \frac{M_{brain}}{BM} + K_{kidney} \frac{M_{kidney}}{BM} + \delta' K_{residual mass} \frac{M_{residual mass}}{BM} \right) R_c,$$

where

$$M_{residual mass} = 1 - \left( \frac{M_{liver}}{BM} + \frac{M_{heart}}{BM} + \frac{M_{brain}}{BM} + \frac{M_{kidney}}{BM} \right),$$

$R_c$ is the relative cellularity, $K_i$ is the specific metabolic rate and $M_i/BM$ is the relative mass of respective organs.
4.3 Datasets
The following datasets were used in the study:

4.3.1 Multi-Centre 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 study57. 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. Indirect calorimetry (Fitmate GS, COSMED Srl - Italy) was used to measure RMR. Throughout the measurement, the child remained seated, and he/she was asked to relax, and 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 measurement48,58. The physical characteristics of the subjects are given in Table. 1. Written consent was obtained from parents of the children and subjects above 18 years, and assent was obtained from children above 7 years. Deidentified data were used for all the analyses. The study was approved by the institutional ethics committees at HCJMRI Pune and IISER Pune, respectively.

4.3.2 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 to minimise the variation caused due to the pubertal growth in the later years. Written consent was obtained from parents of the children. Deidentified 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 \( \times \) volume. The density of liver and kidney in the Indian population is assumed to be 1.162 and 1.05 (\(kg/cm^3\)) respectively59. A summary of RMR-USG dataset is given in Table 2.

4.3.3 Relative organ mass \((M_i/BM)\) data
A prominent dataset for reference physiological variables in North American population compiled by Altman and Dittmer47 was used for the liver, brain, heart and kidney weights from birth to maturity. The reference relative mass \((M_i/BM)\) of liver, kidney, heart and brain is illustrated in Figure 5.

4.3.4 Relative cellularity
The relative cellularity \((R_c)\) is reported as a ratio of the parameter value in children relative to that in a reference young adult60. In the reference Caucasian adults,60 \(TBK/FFM\) (mmol/kg) is reported to be 68.1 for men and 64.2 for women61. 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 group41,62,63. Data on \(R_c\) from birth to adulthood were compiled by Wang41 based on age-related changes in total body potassium (TBK) relative to FFM, from studies by Fomon et al.62 and Pierson63.

4.3.5 Specific metabolic rates of organs \((K_i)\).
The specific metabolic rate \((K_i)\) of organs in adults was measured in vivo by Elia35. 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\(^{-1}\)day\(^{-1}\)) 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 measured in adults are adjusted for children based on surrogate physiological measurements. The relative \(K_i\) in children was assumed from brain oxygen consumption56, heartbeat rates, and other physiological parameters41.

4.4 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 population was compared through non-parametric Wilcoxon signed-rank test, with the significance level set at \(\alpha = 0.05\). All the analyses were carried out using MATLAB R2019b and R version 3.6.2.

Data Availability
The RMR, age, gender, and body weight (the MCS dataset) is attached as the supplementary data.
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Acknowledgements
We thank all the children and parents for their consent to share the data and participate in this study. SA was supported by the Council of Scientific and Industrial Research, Govt. of India.

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

Additional information
Competing interests The authors declare no competing interests.
Figures and Tables

| Variables        | Boys (n=90) | Girls (n=90) |
|------------------|------------|-------------|
|                  | Mean ± SD  | Range       | Mean ± SD  | Range       |
| Age (years)      | 7.1 ± 0.8  | 6.3 - 8.1   | 7.6 ± 0.8  | 6.5 - 8.7   |
| Weight (kg)      | 20.2 ± 3.2 | 17.5 - 26.5 | 18.3 ± 2.3 | 15.0 - 22.4 |
| Height (cm)      | 119.0 ± 7.6| 109.5 - 128.4| 119.7 ± 8.0| 104.9 - 131.9|
| BMI (kg m⁻²)     | 14.2 ± 1.3 | 12.7 - 16.3 | 12.8 ± 0.9 | 11.5 - 14.2 |
| RMR (kcal day⁻¹) | 1004 ± 189 | 771 - 1366  | 835 ± 187  | 552 - 1128  |
| RMR/BM (kcal kg⁻¹ day⁻¹) | 50.5 ± 11.0 | 37.1 - 70.4 | 45.8 ± 9.1 | 28.9 - 58.2 |
| Liver mass (kg)  | 0.66 ± 0.14| 0.47 - 0.92 | 0.53 ± 0.12| 0.40 - 0.78 |
| Kidney mass (kg) | 0.09 ± 0.02| 0.07 - 0.12 | 0.08 ± 0.01| 0.06 - 0.10 |

Table 1. Mean ± standard deviation and the observed range of physical characteristics of subjects in the RMR-USG dataset. The sample size (n) is given for each variable. BMI: body mass index.

Table 2. Mean ± standard deviation and the observed range of physical characteristics of subjects in the MCS dataset.
**Figure 1.** The solid curve shows the mean (±SD) RMR/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 (1a) and girls (1b). ns: not significant, *: $P < 0.05$, **: $P < 0.01$ and ***: $P < 0.001$. 9 and 10 years groups were combined for the statistical tests. The analysis is not done when the number of samples was less than 10 (17 years and above).

**Figure 2.** 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 and 0.90 in boys compared to that of Caucasian population, that is with $\delta = 0.90$ and 0.77 in Eq. 2 in boys and girls respectively. 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 Fig. 1)
Figure 3. $\delta_{\text{kidney}}$ and $\delta_{\text{liver}}$ observed in Indian children (9 girls and 9 boys), where $\delta$ denotes the ratio of the relative mass of the organ $i$ measured in RMR-USG dataset to that of their Caucasian counterparts\textsuperscript{47}. 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 indicates the 25th percentile, median and the 75th percentile values, respectively. The dots show the observed individual $\delta$ values.

Figure 4. Measured RMR/BM ($\mu \pm SD$) 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 $\delta' = 0.65$ in girls, and reference relative organ mass for the Caucasian population\textsuperscript{47}.
Figure 5. Relative organ mass ($M_i/BM$) of brain, liver, heart and kidney reported by Altman and Dittmer$^{47}$ in North American children.