Mathematical ratios lead to spurious conclusions regarding age- and sex-related differences in resting metabolic rate[1–3]

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ABSTRACT Resting metabolic rate (RMR) data have been normalized by dividing RMR by fat-free mass (FFM) (ie, ratio method), or by using a regression-based approach. We compared both data-normalization procedures on age- and sex-related differences in RMR. The ratio method showed no differences in adjusted RMR between older men (0.084 ± 0.004 $kJ \cdot FFM^{-1} \cdot min^{-1}$) and younger men (0.082 ± 0.003 $kJ \cdot FFM^{-1} \cdot min^{-1}$), whereas analysis of covariance showed a lower ($P < 0.01$) adjusted RMR in older men (4.81 ± 0.04 kJ/min) than in younger men (5.14 ± 0.04 kJ/min). In another example, the ratio method showed that women had a higher ($P < 0.05$) adjusted RMR (0.10 ± 0.004 kJ/min) than did men (0.08 ± 0.003 kJ/min), whereas analysis of covariance showed a lower ($P < 0.01$) adjusted RMR in women (4.45 ± 0.03 kJ/min) than in men (4.62 ± 0.03 kJ/min). The ratio method provides misleading conclusions regarding sex- and age-related differences in RMR when compared with a regression-based approach. *Am J Clin Nutr* 1995;61:482–5

KEY WORDS Metabolic rate, normalization, ratio, regression analysis

Introduction

Resting metabolic rate (RMR) is quantitatively the largest component of daily energy expenditure in humans, constituting 60–70% of daily energy output in a person of average physical activity level (1). Because of its large contribution to daily energy expenditure and its important role in the regulation of body weight and body composition, the assessment of RMR has become routine practice in clinical research laboratories and hospital settings.

RMR is dependent on body size and body composition. Fat-free mass (FFM), although imperfect in its estimation of metabolically active tissue, is generally considered the most accurate predictor of RMR (2–5), and is frequently used as the normalizing variable in energy metabolism experiments. Thus, to compare individuals differing in body size and composition, it is necessary to remove its confounding influence, or to normalize metabolic rate for differences in FFM.

There has been great debate regarding the appropriate statistical approach to normalize body size– and body composition–dependent variables in literature about animals and humans (6–15). Recent investigations, however, with the availability of body-composition methodology, have normalized RMR data by using two methods: *1)* divide RMR by the quantity of FFM (ie, ratio method), or *2)* that adjust RMR for the linear relationship between RMR and FFM by using a regression-based approach. The ratio method has been criticized because it does not take into account the nonzero *y* intercept and thus does not fully remove the effect of body weight or FFM from RMR data (11–15). The mathematical bias, therefore, may introduce spurious conclusions when individuals that vary in body size and composition are compared. Tanner (13), and more recently our laboratory (12), have shown that the ratio approach provides misleading results when used to normalize peak oxygen consumption (peak $\dot{V}O_2$), another body size–dependent variable, because of a nonzero *y* intercept between FFM (or body weight) and peak $\dot{V}O_2$.

Despite these recent and historical warnings regarding the use of the ratio method to normalize body size–dependent variables, its use is still widely evident in the literature concerning energy metabolism. It is possible that investigators believe that both statistical approaches provide similar information, or are unaware of the impact of the data-normalization procedures on data interpretation. Because a systematic comparison between the ratio method and the regression-based approach has not been undertaken in a large sample size by using body-composition methodology, we conducted the present study to underscore the importance of standardizing data-normalization procedures.

Thus, our primary objective was to directly compare data-normalization procedures (ratio method vs regression-based approach) and their impact on interpretation of age- and sex-related differences in RMR.

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Subjects and methods

Subjects

We used data from our ongoing studies of aging and energy expenditure. In the present analysis 426 healthy men (age 17–90 y) and 293 healthy women (age 18–88 y) were examined (total $n = 719$). Volunteers were recruited from advertisements and radio announcements. A subsample of this cohort was previously published (4, 5). Subjects were excluded from participation in the study for the following reasons: *1)* clinical evidence of coronary heart disease (eg, ST-segment depression >1 mm at rest or exercise) or cardiomyopathy, *2)* resting blood pressure >160/100 mm Hg, *3)* medication use that could affect cardiovascular function or metabolic rate, *4)* medical history of diabetes, *5)* instability of body weight during the preceding year (a change of >2 kg), *6)* exercise-limiting noncardiac disease (arthritis, peripheral vascular disease, cerebral vascular disease, etc), and *7)* history of oophorectomy. No women at interview were receiving estrogen replacement therapy. All premenopausal women were tested between days 5 and 12 during the follicular phase to standardize measurements during the same phase of the menstrual cycle. The experimental procedures were approved by the Committee on Human Research for the Medical Sciences. Written informed consent was obtained from each subject before investigation.

Protocol

All volunteers were admitted to the Clinical Research Center the afternoon before their metabolic testing between 1400 and 1600. Subjects were fed a standardized 4.2-MJ mixed meal (15% protein, 30% fat, and 55% carbohydrate) at ≈1730 and thereafter were given practice with the ventilated hood to reduce any concern or apprehension with testing conditions. After a 12-h overnight fast during which volunteers slept in the Clinical Research Center, the following tests were performed the next morning in sequence: RMR measurement and underwater weighing for body-composition determination.

Resting metabolic rate

RMR was established for each subject by using indirect calorimetry for 45 min with the ventilated-hood technique. Body fat was estimated from body density as measured by underwater weighing, with simultaneous measurement of residual lung volume by the helium dilution method using the formula of Siri (16). FFM was estimated as total body weight minus fat weight.

Statistical analysis

Differences between groups were assessed by unpaired *t* tests. The relationship between RMR and FFM was determined by using linear-regression analysis. Mean differences in RMR between men and women and between younger and older individuals were compared by using the ratio method with FFM as the divisor and with analysis of covariance. Analysis of covariance allows for the removal of the linear effect of the covariate (FFM) on RMR without making the assumption of a zero intercept. To illustrate the potential differences in the ratio method and analysis of covariance when individuals with different body compositions are compared, we compared differences in adjusted RMR between younger and older men and between men and women exhibiting a broad age range according to the two methods. All values are expressed as mean ± SE.

Results

Physical characteristics of the younger and older men are shown in **Table 1**. As expected, older men were shorter, had lower quantities of FFM, and greater fat mass than younger individuals. We examined the correlations between RMR and FFM in younger and older men. As expected, FFM was the highest correlate ($r = 0.74$, $P < 0.01$) of RMR in younger men. The equation is as follows:

$$[\text{RMR (kJ/min} = 1.70 + 0.054\ (\text{FFM, kg})]$$

In older men, FFM was also correlated with RMR ($r = 0.43$, $P < 0.01$). The equation is as follows:

$$[\text{RMR (kJ/min)} = 2.37 + 0.038\ (\text{FFM, kg})]$$

In each case, our data show that the relationship between RMR and FFM has a *y* intercept ($\bar{x}$ ± SEE) that is significantly different from zero ($P < 0.01$) in younger (1.70 ± 0.23 kJ/min) and older men (2.37 ± 0.39 kJ/min).

We then examined age-related differences in RMR using the ratio method ($\text{RMR} \cdot \text{FFM}^{-1} \cdot \text{min}^{-1}$) and analysis of covariance. **Table 2** shows that different conclusions can be drawn depending on the data-normalization method used. As expected, absolute measured RMR was lower in older men than in younger men because of the lower quantity of FFM in older men. With the ratio method, no differences in RMR were found between younger and older men. On the other hand, after adjustment for differences in FFM by using analysis of covariance, a lower adjusted RMR was found in older men. Thus, with the ratio method one would erroneously conclude that differences in FFM totally explain the lower RMR in older men compared with younger men.

Figure 1 shows the lines of best fit of the relationship between RMR and FFM in younger men and older men. In brief, the displacement of the regression line upward in younger men indicates that RMR, per kilogram of FFM, is higher in younger than in older men, which is contrary to the conclusion derived from the ratio method.

To further highlight the misleading information derived from the ratio method, we examined sex-related differences in RMR. The physical characteristics of a large cohort of men and women are shown in **Table 3**. As expected, standing height, body mass, and FFM were significantly greater in men than in

TABLE 1
Physical characteristics of younger and older men[1]

Characteristic	Younger men (n = 192)	Older men (n = 145)
Age (y)	25.6 ± 0.46	69.0 ± 0.46[2]
Height (cm)	178 ± 0.48	174 ± 0.56[2]
Body mass (kg)	78.0 ± 0.84	76.7 ± 0.75
Fat-free mass (kg)	67.7 ± 0.61	59.2 ± 0.53[2]
Fat mass (kg)	10.3 ± 0.52	17.5 ± 0.58[2]

[1] $\bar{x}$ ± SE.
[2] Significantly different from younger men, $P < 0.01$.

TABLE 2
Comparison of resting metabolic rate (RMR) in younger and older men by using the ratio method and analysis of covariance[1]

Method	Younger men (n = 192)	Older men (n = 145)
Measured RMR (kJ/min)	5.29 ± 0.04	4.60 ± 0.05[2]
Ratio method (kJ · $FFM^{-1}min^{-1}$)	0.082 ± 0.003	0.084 ± 0.004
RMR adjusted for FFM by using covariance method (kJ/min)	5.14 ± 0.04	4.81 ± 0.04[3]

[1] $\bar{x}$ ± SE.
[2,3] Significantly different from younger men: [2] $P < 0.01$, [3] $P < 0.05$.

women. FFM was the highest correlate of RMR in women (r = 0.73, $P < 0.01$). The equation is as follows:

$$[\text{RMR (kJ/min)} = 1.35 + 0.054\ (\text{FFM, kg})]$$

FFM was also related to RMR in men (r = 0.69, $P < 0.01$). The equation is as follows:

$$[\text{RMR (kJ/min)} = 1.51 + 0.054\ (\text{FFM, kg})]$$

In each case, our data show that the relationship between RMR and FFM has a y intercept ($\bar{x}$ ± SEE) that is significantly different from zero ($P < 0.01$) in women (1.35 ± 0.14 kJ/min) and men (1.51 ± 0.18 kJ/min).

Table 4 shows the sex differences in RMR when the ratio method and analysis of covariance were used. Measured RMR was higher in men than in women. The ratio method showed that women had a higher adjusted RMR than men. On the other hand, after adjustment for FFM by using analysis of covariance, a lower adjusted RMR was found in women.

Figure 2 shows the lines of best fit of the relationship between RMR and FFM in men and women. The displacement of the regression line upward in men relative to women supports the notion that RMR, per kilogram of FFM, is slightly

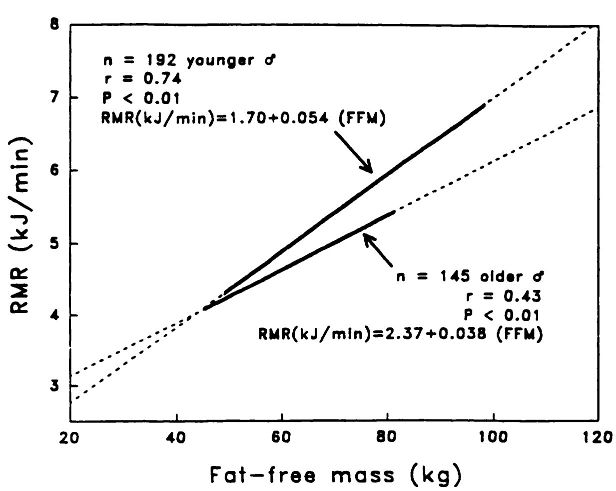

FIGURE 1. Relationship between resting metabolic rate (RMR) and fat-free mass (FFM) in younger and older men. The solid line represents the relationship between RMR and FFM within the range of FFM examined, whereas the dotted line represents an extrapolation of the regression line.

TABLE 3
Physical characteristics of men and women[1]

Characteristic	Men (n = 426)	Women (n = 293)
Age (y)	45.5 ± 0.96	50.2 ± 0.87[2]
Height (cm)	177 ± 0.34	163 ± 0.31[2]
Body mass (kg)	77.7 ± 0.52	62.2 ± 0.43[2]
Fat-free mass (kg)	64.1 ± 0.40	45.1 ± 0.28[2]
Fat mass (kg)	13.6 ± 0.37	17.1 ± 0.36[2]

[1] $\bar{x}$ ± SE.
[2] Significantly different from men, $P < 0.01$.

higher in men than in women, which is the opposite result obtained by the ratio method.

Discussion

We examined the influence of two data-normalization methods on the interpretation of RMR data. The ratio method, which divides RMR by FFM, was compared with a regression-based approach, which adjusts RMR for the linear relationship between RMR and FFM. Both normalization methods are frequently used interchangeably in studies of human metabolism to compare RMR in individuals that vary in body size and composition.

The mathematical bias introduced by the ratio method has previously been outlined (10–15). In brief, the ratio method assumes the model RMR (kJ/min) = b [FFM, (kg)], where b is the slope and the y intercept is assumed to equal zero. Biological variables, such as RMR, however, rarely regress to a zero intercept (13). Thus, when the ratio method is applied to variables in which the relationship has a nonzero intercept, it does not adequately remove the effect of the normalizing variable from the dependent variable. In other words, seemingly minor departures from a zero intercept can have major consequences on the ratio's ability to control for the denominator. Despite the statistical bias introduced by the expression of RMR per kilogram of FFM (ie, the ratio method), its use is still common in studies of human metabolism, possibly because of its convenience.

On the other hand, a regression-based approach to normalize RMR data does not assume a zero y intercept, but instead adjusts RMR group and individual data according to the linear relationship between RMR and FFM [ie, RMR (kJ/min) = (b [FFM]) + c], which is derived in the investigator's

TABLE 4
Comparison of resting metabolic rate (RMR) in men and women by using the ratio method and analysis of covariance[1]

Method	Men (n = 426)	Women (n = 293)
Measured RMR (kJ/min)	5.02 ± 0.03	3.89 ± 0.03[2]
Ratio method (kJ · FFM^{-1} · min^{-1})	0.08 ± 0.003	0.10 ± 0.004[3]
RMR adjusted for FFM by using covariance method (kJ/min)	4.62 ± 0.03	4.45 ± 0.03[2]

[1] $\bar{x}$ ± SE.
[2,3] Significantly different from men: [2] $P < 0.01$, [3] $P < 0.05$.

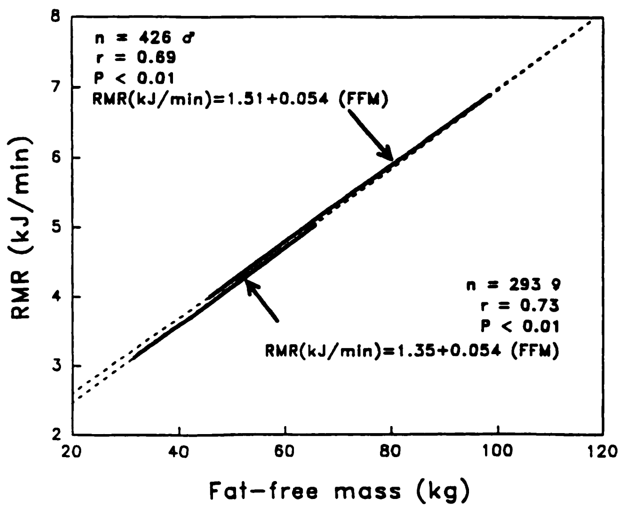

FIGURE 2. Relationship between resting metabolic rate (RMR) and fat-free mass (FFM) in men and women. The solid line represents the relationship between RMR and FFM within the range of FFM examined, whereas the dotted line represents an extrapolation of the regression line.

laboratory. Therefore, regression analysis will produce adjusted RMR values with the effect of the normalizing variable, ie, FFM, fully removed. Its application, although less convenient for the investigator, has recently been outlined (12). The question of interest in the present study is whether both normalization procedures provide similar or dissimilar information when normalizing RMR data.

To investigate this issue, we chose two examples: the comparison of RMR in younger and older men and between men and women. It is not our intent to focus on the physiological basis for age- and sex-related differences in RMR as these issues have previously been examined (17–20), but rather to use these questions as examples to compare normalization procedures.

In our first example, we compared RMR in a large sample of younger and older men. As expected, RMR was 13% lower in older men, primarily because this group had a lower quantity of FFM. When data were normalized by using the ratio method, age-related differences in RMR were abolished. On the other hand, a 6% lower adjusted RMR persisted in older men relative to younger men when the analysis of covariance procedures were used. In this example, the inadequacy of the ratio method to take into account the nonzero *y* intercept resulted in an overestimation of the adjusted RMR in individuals with a smaller quantity of FFM (ie, older men).

In our second example, RMR was compared between men and women. As expected, measured RMR was 23% lower in women than in men. When FFM was used as the divisor, women exhibited a higher RMR for their metabolic size than did men. On the other hand, the analysis of covariance procedures resulted in a 4% lower RMR in women. Thus, if the ratio method of data normalization were used in this case, one would have erroneously concluded that women have a higher normalized RMR than do men, when in fact the opposite is true. Collectively, it is clear that these statistical approaches to normalizing RMR data provide dissimilar information and an attempt should be made to standardize RMR data-normalization procedures for the study of human metabolism.

We recommend the following: *1)* determine the relationship between RMR and FFM in the investigator's laboratory, and *2)* if the *y* intercept is significantly different from zero, a regression-based approach to normalize RMR values is a more suitable approach to normalize data than is the ratio method. ■

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