Research Article

Energetics of Aging and Frailty: The FRADEA Study

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Abstract

Background: Resting metabolic rate (RMR) and total daily energy expenditure (TDEE) decrease with aging, but it is not known whether frailty modulates this association. We hypothesize that RMR and TDEE values are similar between younger and older nonfrail older adults, whereas they are lower in older prefrail and frail compared with younger adults.

Methods: A cross-sectional analysis of the FRADEA study, Albacete (Spain), including 402 participants (213 women) older than 70 years (mean age 76 years; range 70–91), was conducted. Estimated RMR (eRMR), oxygen consumption (VO₂), expired volume (Ve), and respiratory frequency (RF) were determined using indirect calorimetry; TDEE was determined with the Calcumed instrument; and fat-free mass was determined by bioimpedanciometry. General linear models were used for analysis.

Results: Mean TDEE was 1,889 (SD 470) kcal and eRMR was 1,071 (SD 323) kcal. Both TDEE (B = −24 kcal/day; 95% confidence interval: −35.4 to −14.2; p < .001) and eRMR (B = −15.8 kcal/day; 95% confidence interval: −23.1 to −8.5; p < .001) diminished linearly with age, with lower values in frail and prefrail participants. There was a strong trend between frailty and lower eRMR (F = 2.9; p = .058), with a modifying effect between age and frailty (F = 3.6; p = .020). eRMR in prefrail and frail participants were on average 160 and 114 kcal/day less than that in the nonfrail participants, respectively, and taken together, 154 kcal/day less (F = 5.4; p = .020). Frail and prefrail participants also presented lower Ve and VO₂ values that were partially compensated by an RF increase.

Conclusion: Frailty status modulates the energy requirements of aging. Frail and prefrail older adults present lower eRMR than nonfrail adults.

Keywords: Energy—Frail elderly—Resting Metabolic Rate

The study of energy availability and consumption across the life span may help to understand the aging process. Previous findings have described that, with older age, total energy expenditure decreases, energy availability declines, peak energy expenditure decreases, and energy needs for independent living increase (1–4). A decrease in total energy expenditure of 7.5% per decade for men and 6% per decade for women has been described (4). Between 55% and 60% of total available energy is lost between middle age and late life, which may explain the decline in physical activity commonly observed in older individuals (2). The consequence of this energetic availability reduction is that a high percentage of energy must be used to perform basic activities of daily living, and over time, this may contribute to functional loss, frailty, and disability in instrumental activities of daily living as the cost of the basic activities of daily living approaches 100% of peak energy availability (5,6).

Resting metabolic rate (RMR), the energy necessary for maintaining vital functions at rest, also called “the cost of living,” generally declines with age (7–9), only in part because of diminished lean mass (5,10) but mainly because of slowed organ metabolic rates (11). Although there is great variability in RMR values in older adults (12), a 5% reduction in RMR per decade in men and a 3% reduction in women have been reported (4). This decline in RMR with aging has been observed in sedentary men but may be attenuated in men who maintain exercise volume and/or energy intake throughout the life span (13).

It is well known that there is a great heterogeneity of health status with aging, and consequently, older adults are not a
homogeneous population. In recent years, frailty has demonstrated to be a valid construct of reduced physiologic function (14,15) that confers individuals a high risk of mortality and disability (16,17). RMR in old age may play a critical role in the pathogenesis of frailty, and high and low levels have been associated with this condition (12). However, the differential relationship between energy requirements and the aging process according to frailty status is not well known, although some authors have hypothesized that age-associated profile of RMR in frail individuals with chronic conditions may differ from that of RMR in nonfrail ones (18). The finding of a differential association could support the hypothesis that energetics and basal metabolism may play a role in the pathogenesis of frailty and a plausible explanation for a successful aging.

Methods
Participants and Study Setting
Our study presents cross-sectional data from the first wave (2007–2009) of the FRADEA study, a population-based concurrent cohort study that is actually under follow-up process. The rationale, design, methodology, selection of participants, and baseline characteristics have been previously described (19). Briefly, 1,172 participants were randomly selected in 2007 from the population aged 70 years or older from the census of health card holders from the city of Albacete (n = 18,137), of whom 993 (84.7%) agreed and 179 (15.3%) refused to participate. Random selection was implemented using a 15:1 ratio and was stratified by sex and age. The baseline interview was carried out in person at the geriatric facilities of the Hospital Perpetuo Socorro in Albacete by four trained nurses, between November 2007 and November 2009, and the participants performed functional testing the same day. From the original 993 participants included, 450 accepted to undergo calorimetry of which 402 participants had complete data for analysis.

Energy Requirements Measurement
RMR was assessed using indirect calorimetry in a quiet, thermoneutral (23°C) environment in the morning before eating or drinking. We asked participants to fast at least 12 hours and to avoid all nonessential activities at least 24 hours before the test. Abstention of caffeine, nicotine, and other stimulants was encouraged in the previous 12 hours. All measurements were collected between 8:30 and 9:30 AM. Participants were placed in a comfortable position in a semirecumbent chair and asked to rest for 15 minutes while breathing normally into a mask attached to the FitMate portable metabolic analyzer (Cosmed SRL, Rome, Italy) for habituation. They were reminded to stay “as quiet as possible.” Participants were then asked to continue breathing into the mask for another 20 minutes after the first 15-minute habituation (12,13,18,20). Trained research staff recorded any deviations from protocol.

The FitMate system does not contain either a carbon dioxide analyzer or a real-time ambient temperature sensor, and to determine a person’s caloric equivalent based on a person’s substrate utilization profile for each liter of oxygen consumed, a fixed 0.85 respiratory exchange ratio was used as the default setting. Ambient temperature was also manually entered at the start of testing. Test–retest intraclass correlations of .95–.99, p ≤ .0001 have been described for all FitMate parameters tested, compared with a previously validated COSMED QUARK CPET research-based calorimetry system. Ve, RMR, VO2, and heart rate were not significantly different between the two systems. These results suggest that the FitMate is a reliable canopy dilution system for RMR measurements in healthy adults (20). Moreover, FitMate has been validated through a wide range of ages (21). However, as there is no evidence that substrate utilization is unaffected by frailty status, by using a standardized respiratory exchange ratio (0.85), we could be missing or creating potential differences. For this reason, we decided to report “estimated RMR” (eRMR), instead of pure RMR, as the outcome variable across the analysis.

At test completion, oxygen consumption (VO2), expiratory volume (Ve), respiratory frequency (RF), expired oxygen fraction (FeO2), and eRMR were determined. We also calculated the eRMR/weight and eRMR/fat-free mass (FFM) ratios, in order to know basal metabolism adjusted for weight and lean mass.

Total daily energy expenditure (TDEE) was measured with the Calcumed instrument (http://www.fisterra.com/herramientas/calcedum/). This questionnaire assesses the number of daily hours of sleep, very light, light, moderate, and high physical activity, sex, age, and body mass index (BMI) and calculates the consumed TDEE (kcal). Later, we calculated the TDEE/weight and TDEE/FFM ratios in order to know the total energy adjusted for weight and lean mass.

Main Independent Variable: Frailty Criteria
During the baseline visit, the frailty criteria proposed by Fried (22) were used, with one small modification in the physical activity criteria. This item was calculated with the Calcumed instrument instead of the Minnesota Leisure Time Physical Activity Questionnaire that was used by Fried, using the same original adjusted cutoff points described, less than 383 kcal/week of physical activity for men and less than 270 kcal/week for women. Weight loss was considered when loss was 4.6 kg or greater or loss was 5% or more of body weight in the past year. Weakness was identified by grip strength lower than the 20th percentile adjusted for sex and BMI using a Jamar digital hand dynamometer, with the criteria specified by Fried: Men BMI ≤ 24 = ≤ 29 kg, BMI 24.1–26 = ≤ 30 kg, BMI 26.1–28 = ≤ 30 kg, and BMI > 28 = ≤ 32 kg. Women BMI ≤ 23 = ≤ 17 kg, BMI 23.1–26 = ≤ 17.3 kg, BMI 26.1–29 = ≤ 18 kg, and BMI > 29 = ≤ 21 kg. Low energy level and exhaustion were identified by two questions from the Center for Epidemiologic Studies-Depression (CES-D) scale, also used by Fried. Walking speed was assessed in a 4-m distance at normal pace. Slow walking speed was considered when participants presented values under the lowest quintile as adjusted for sex and height, using the same cutoff points described by Fried: Men height ≤ 173 cm = ≥ 7 s and height > 173 cm = ≥ 6 s; Women height ≤ 159 cm = ≥ 7 s and height > 159 cm = ≥ 6 s. To calculate the criteria for frailty as a variable, participants had to have at least three valid values of the five criteria. Participants were classified as frail when three or more of the characteristics were present and prefrail when one or two were present.

Study Covariables
At the baseline visit, age, sex, and disability in basic activities of daily living using the Barthel index were determined, and the percentage of participants with disability in bathing, grooming, toileting, dressing, and eating was calculated. Age was categorized in 5-year periods (70–74, 75–79, 80–84, and ≥85 years). Chronic diseases and the number of usually consumed drugs were identified by their medical records. Diseases were coded according to the International Classification of Diseases-10.
and thereafter classified within large homogeneous groups for later analysis. The Charlson comorbidity index was used to analyze comorbidity, and chronic obstructive pulmonary disease and ever smoker status were recorded. Weight (kg), height (cm), BMI (kg/m²), and waist circumference (cm) were also measured. Risk of malnutrition was determined with the short-form Mini Nutritional Assessment (SF-MNA). Body composition was analyzed by bioimpedanciometry with a BC-418 Segmental Body Composition Tanita instrument (Tanita, Tokyo, Japan), and fat mass (kg and %) and FFM (kg) were determined. Patients were assessed for dehydration or edema before bioimpedance acquisition and were excluded if any of these conditions were present. Gait speed at usual pace in 4 m (m/s), grip strength with a JAMAR digital dynamometer (kg), and peak flow (best of three attempts) with a peak flow meter (L/min) were assessed to measure the muscular strength indirectly \(^{(23,24)}\). Quality of life was measured with the SF-12 instrument.

**Ethical Aspects**

Our investigation complies with the standards of the Helsinki declaration concerning investigation with human participants. The study was approved by the Albacete health region Independent Ethics Committee and the Complejo Hospitalario Universitario de Albacete Ethics Committee. All participants signed an informed consent form prior to inclusion in the study.

**Statistical Analysis**

A descriptive analysis of the characteristics of the sample using proportions or means with the standard deviation, according to the nature of the variables, was performed. We also analyzed the association between the potential confounders and frailty status using chi-square and t tests. The associations between control variables and calorimetric data were analyzed by simple linear regression method. Scatter plots were constructed and the linear fit was drawn to analyze the association between age and energetic parameters according to frailty status.

Given the asymmetry in the distribution of eRMR, age, and frailty, we conducted a general linear model statistical analysis to estimate the marginal impact that a one-degree increase in the level of frailty and age would have on the total eRMR. Model 1 included age categorized in 5-year periods and frailty in two different approaches, frail and prefrail together against nonfrail and frail, prefrail, and nonfrail in three categories. Model 2 also included sex, FFM, and Charlson index as covariables. GLMs specify the conditional mean function directly, and they are essentially generalizations of nonlinear least squares. GLMs allow getting predictions directly on the eRMR (no retransformation), they also allow for heterocedasticity through the choice of distributional family, and they also provide consistent estimates. With this statistical tests, estimates on entire sample-zeros pose no problem for fitting models. We used a complete factorial model with sum of square type III, and simple contrast analysis for frailty and age using first category as reference. A profile graphic was obtained to determine the marginal means of each age category by frailty status.

All data were stored and analyzed using the SPSS 17.0 program.

**Results**

Table 1 presents the baseline characteristics of the complete sample and their frailty status, and Table 2 provides the association between control variables and calorimetric parameters. Age was inversely associated with eRMR, women had lower eRMR than men, and participants with COPD had also lower eRMR than their counterparts. eRMR was also associated with FFM, fat mass (in kg but not in %), nutritional status, gait speed, and grip strength. Age was inversely associated with Ve and directly associated with FeO\(_2\). Women presented lower values of Ve and FeO\(_2\) and higher values of RF and VO\(_2\). Furthermore, after adjustment for FFM, women presented higher eRMR/FFM than men (24.7 kcal/day/kg vs 20.4 kcal/day/kg; \(p < .001\)).

**Figure 1** represents the associations between age and eRMR, eRMR/weight, and eRMR/FFM (panels A, C, and E, respectively) and the associations between age and TDEE, TDEE/weight, and TDEE/FFM (panels B, D, and F, respectively). Table 3 presents the numeric data of these associations. TDEE diminished linearly with age, with lower values in frail and prefrail participants compared with nonfrail ones, although significance was only reached in prefrail and frail participants. However, eRMR only decreased with increasing age in prefrail participants, with a slight increase in nonfrail ones. We propose that this discrepancy could be explained as a result of a successful and active aging with greater basal metabolic demands. After adjusting for weight and FFM, only prefrail older adults showed a significant decrease in eRMR (panels C and E).

**Figure 2** presents the relationship between calorimetric parameters and aging, according to frailty status. FeO\(_2\) did not change significantly with aging, with similar values in the three frailty groups (panel D). Interestingly, as participants aged, Ve and RF decreased in frail and prefrail participants, and VO\(_2\) decreased in prefrail ones but increased in nonfrail ones (panels A–C), probably reflecting a maintenance of muscular respiratory efficiency and a higher basal metabolic status. This is confirmed by a significant relationship between grip strength and FFM with Ve and RF (Table 2), and also with gait speed and peak flow, indirect measures of muscle performance (Table 2). Further, frail and prefrail participants at younger ages maintained eRMR, VO\(_2\), and Ve by increasing their RF without increasing their FeO\(_2\) (Figure 2A). However, at older ages, frail and prefrail participants had decreased FR, Ve, and eRMR values.

Table 4 and Figure 3 show the results obtained from the general linear model to determine how much frailty is a modifier in the relationship between age and eRMR. Adjusted for sex, FFM, and comorbidity, frailty was associated with lower eRMR \((F = 2.9; p = .058)\), but age was not \((F = 0.1; p = .984)\), and there was an important modifying effect between age and frailty \((F = 3.6; p = .002)\). Prefrail and frail participants together were also associated with lower eRMR \((F = 5.4; p = .020)\), with an important modifying effect \((F = 5.1; p = .002)\). eRMR in prefrail and frail participants were on an average 160 and 114 kcal/day less than that in the nonfrail participants, respectively, and taken together, 154 kcal/day less.

**Discussion**

Our study confirms previous data that TDEE and eRMR are lower in older compared with younger older adults \((1–12,18)\) but adds to previous findings that this decline is modulated by frailty status. Although eRMR and TDEE do not differ between older and younger nonfrail older adults, their values are lower in older compared with younger prefrail and frail ones. This finding could be in agreement with a recent research describing that variations in metabolism per se are not causally linked with the process of aging and that other factors such as fatness could mediate the negative link between RMR and life span \((25)\). Fat mass has been associated with frailty in older adults through a multifactorial pathway. Sedentarism, sarcopenic obesity, proinflammatory cytokines and adipokines production, insulin resistance, decreased growth hormone and IGF-1, and
low testosterone levels have been described as contributors of muscle wasting (26). Although our data confirm the association between the percentage of fat mass and frailty, we did not find a clear relationship with eRMR. The differential characteristics of our sample compared with those of the previous studies (older, more frail, higher BMI, lower FFM) could explain this discrepancy (18).

In our sample, direct (grip strength) and indirect (gait speed and peak flow) measures of strength were higher in nonfrail participants compared with those in the frail and prefrail ones, with also higher FFM values. Strength is one of the hallmarks of frailty and was identified as the cornerstone of the physiopathological frailty cycle by Fried (22). In our study, grip strength, gait speed, and FFM were positively associated with eRMR through an increase in Ve and a decrease in RF. Probably, frail and prefrail participants compensate the loss of strength by increasing their RF. This increase in respiratory rate in prefrail and frail participants could be an adaptive response to lower muscular or metabolic efficiency in the initial phases of frailty development, aimed at maintaining basal energetics. This adaptive response would be impossible to sustain and a decrease in RF. Probably, frail and prefrail participants compensate the loss of strength by increasing their RF. This increase in respiratory rate in prefrail and frail participants could be an adaptive response to lower muscular or metabolic efficiency in the initial phases of frailty development, aimed at maintaining basal energetics. This adaptive response would be impossible to sustain in older adults with frailty progression, leading to a lower global energy efficiency (22).

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The decrease in RMR with aging is caused only in part by diminished lean mass (5,10) but mainly because of slowed organ metabolic rates (11). It has been described that skeletal muscle accounts for about 60% (18). In our study, grip strength, gait speed, and FFM were positively associated with eRMR through an increase in Ve and a decrease in RF. Probably, frail and prefrail participants compensate the loss of strength by increasing their RF. This increase in respiratory rate in prefrail and frail participants could be an adaptive response to lower muscular or metabolic efficiency in the initial phases of frailty development, aimed at maintaining basal energetics. This adaptive response would be impossible to sustain in older adults with frailty progression, leading to a lower global energetic status. A change in contractile-coupling efficiency has been the conventional explanation for differences in muscular efficiency in older adults (27), although recently, it has been described that mitochondrial-coupling dysfunction is the basis of the decline in muscular efficiency with age, identifying mitochondria as the target for intervention to reverse this problem in this population (28).

The decrease in RMR with aging is caused only in part by diminished lean mass (5,10) but mainly because of slowed organ metabolic rates (11). It has been described that skeletal muscle accounts for about 60% (18), and that the combination of two aging-related factors (decline in both the mass and the cellular fraction of organs and tissues) may account for the lower RMR observed in older adults (29). This is in agreement with the frailty definition of a decline in the functional reserve of multiple body systems and could explain the modifying effect of frailty on the relationship between aging and RMR (22).
Table 2. Association Between Control Variables and Calorimetric Data

<table>
<thead>
<tr>
<th></th>
<th>VO$_2$ (mL/kg/min)</th>
<th>Ve (mL/min)</th>
<th>RF (min)</th>
<th>FeO$_2$ (%)</th>
<th>eRMR (kcal/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>70–74 (n = 176)</td>
<td>−0.013 (−0.028 to −0.002)</td>
<td>−56.7 (−92.6 to −20.8)†</td>
<td>0.05 (−0.04 to 0.14)</td>
<td>0.014 (0.003 to 0.026)*</td>
<td>−15.8 (−23.1 to −8.5)***</td>
</tr>
<tr>
<td>75–79 (n = 136)</td>
<td>2.23 (0.64)</td>
<td>5.3</td>
<td>16.4</td>
<td>17.0</td>
<td>1,135 (320)</td>
</tr>
<tr>
<td>80–84 (n = 77)</td>
<td>2.09 (0.68)</td>
<td>5.1</td>
<td>16.5</td>
<td>17.2</td>
<td>1,047 (334)</td>
</tr>
<tr>
<td>≥85 (n = 13)</td>
<td>2.17 (0.58)</td>
<td>4.8</td>
<td>17.1</td>
<td>17.1</td>
<td>995 (310)</td>
</tr>
<tr>
<td><strong>Sex (male/female)</strong></td>
<td>2.09/2.23 (0.14; −0.02 to −0.28)*</td>
<td>5.495/4.808 (6.87; 381 to 992)***</td>
<td>15.8/17.3 (1.5; 0.8 to 2.2)***</td>
<td>17.2/16.9 (0.3; 0.2–0.4)***</td>
<td>1,103/1,042 (61; −3 to 124)***</td>
</tr>
<tr>
<td><strong>Barthel index</strong></td>
<td>−0.015 (−0.020 to −0.010)***</td>
<td>−11.7 (−33.9 to 10.5)***</td>
<td>−0.08 (−0.14 to −0.03)***</td>
<td>0.000 (−0.008 to 0.007)</td>
<td>−2.1 (−6.7 to 2.4)</td>
</tr>
<tr>
<td><strong>BMI (kg/m$^2$)</strong></td>
<td>−0.032 (−0.046 to −0.019)***</td>
<td>35.0 (10.8 to 68.8)*</td>
<td>0.10 (0.02 to 0.19)*</td>
<td>−0.022 (−0.032 to −0.011)***</td>
<td>14.4 (7.5 to 21.3)***</td>
</tr>
<tr>
<td><strong>Waist circumference</strong></td>
<td>−0.010 (−0.015 to −0.005)***</td>
<td>26.8 (14.9 to 38.8)***</td>
<td>0.03 (−0.01 to 0.05)</td>
<td>−0.002 (−0.006 to 0.002)</td>
<td>6.9 (4.4 to 9.3)***</td>
</tr>
<tr>
<td><strong>FFM (kg)</strong></td>
<td>−0.032 (−0.046 to −0.019)***</td>
<td>54.0 (36.2 to 71.7)**</td>
<td>0.10 (0.05 to 0.15)***</td>
<td>−0.014 (−0.021 to −0.007)***</td>
<td>2.0 (−2.4 to 6.4)</td>
</tr>
<tr>
<td><strong>Fat mass (%)</strong></td>
<td>−0.017 (−0.028 to −0.007)*</td>
<td>−14.0 (−35.5 to 7.5)</td>
<td>0.00 (−0.03 to 0.03)</td>
<td>−0.002 (−0.006 to 0.002)</td>
<td>9.4 (5.7 to 13.1)***</td>
</tr>
<tr>
<td><strong>MNA-SF</strong></td>
<td>−0.013 (−0.047 to 0.021)</td>
<td>112.0 (29.9 to 194.0)**</td>
<td>−0.20 (−0.41 to −0.00)</td>
<td>0.014 (0.013 to 0.041)</td>
<td>20.4 (3.5 to 37.3)*</td>
</tr>
<tr>
<td><strong>Charlson index</strong></td>
<td>−0.039 (−0.086 to 0.009)</td>
<td>6.1 (−110.5 to 122.8)</td>
<td>0.39 (0.11 to 0.67)**</td>
<td>0.041 (0.004 to 0.079)†</td>
<td>−11.9 (−35.8 to 12.1)</td>
</tr>
<tr>
<td><strong>COPD (no/yes)</strong></td>
<td>2.21/1.78 (0.42; 0.21 to 0.64)***</td>
<td>5.115/3.86 (193; −811 to 426)***</td>
<td>16.7/15.7 (1.0; −0.3 to 2.2)***</td>
<td>17.0/17.6 (0.5; 0.4 to 0.7)***</td>
<td>1,083/960 (123; 17.4 to 227.9)***</td>
</tr>
<tr>
<td><strong>Number of drugs</strong></td>
<td>−0.015 (−0.035 to 0.005)</td>
<td>−50.7 (−100.0 to 17.9)***</td>
<td>0.25 (0.13 to 0.37)***</td>
<td>0.010 (−0.026 to 0.006)</td>
<td>−8.4 (−1.8 to 1.7)</td>
</tr>
<tr>
<td><strong>Smoker (no/yes)</strong></td>
<td>2.21/2.08 (0.13; −0.01 to 0.27)</td>
<td>4.935/5.352 (597; 249 to 994)***</td>
<td>16.9/16.1 (0.7; −0.1 to 1.5)***</td>
<td>17.0/17.3 (0.3; 0.2 to 0.4)***</td>
<td>1.05/1.097 (39; −109 to 32)</td>
</tr>
<tr>
<td><strong>Grip strength (kg)</strong></td>
<td>−0.004 (−0.010 to 0.003)</td>
<td>31.9 (17.7 to 46.0)***</td>
<td>−0.08 (−0.11 to −0.04)***</td>
<td>0.005 (0.001 to 0.010)</td>
<td>4.8 (1.9 to 7.7)***</td>
</tr>
<tr>
<td><strong>Peak flow (m/s)</strong></td>
<td>0.000 (0.000 to 0.000)</td>
<td>180 (38.0 to 325.3)***</td>
<td>−0.88 (−1.22 to −0.53)***</td>
<td>0.032 (−0.014 to 0.080)</td>
<td>26.7 (−3.0 to 56.4)</td>
</tr>
</tbody>
</table>

Notes: All data represent B (95% CI) by simple linear regression models, except for age in 5-year intervals and sex that are means (SD) by analysis of variance and Student’s t test, respectively.

BMI = body mass index; COPD = chronic obstructive pulmonary disease; CI = confidence interval; eRMR = estimated resting metabolic rate; FeO$_2$ = expired oxygen fraction; FFM = fat-free mass; MNA-SF = Mini Nutritional Assessment Short Form; RF = respiratory frequency; Ve = expired volume; VO$_2$ = oxygen consumption

*p < .05. **p < .01. ***p < .001.
They proposed the hypothesis that there could be more than one point of entry into the frailty spiral. One characterized by a disease-related hypermetabolic state, leading to a high RMR, and the other by an accelerated age-associated decline in metabolic state, leading to a low RMR (12). In our study, we did not find such a dichotomy or U-shaped relationship between frailty and eRMR but found a linear one instead. This could be explained by several reasons as follows: (i) the range of age of our sample was wider than that of the WHAS-II study, possibly avoiding survival biases; (ii) our sample was larger and composed of both men and women; (iii) and our sample was mainly composed of independent older adults with low comorbidity. This last characteristic would give more importance to the second pathway suggested by Weiss, that is an accelerated age-associated decline in metabolic state leading to frailty.

It has been recently described that individuals who are fully functional and free of major medical conditions (“IDEAL”...

Figure 1. Resting and activity energy consumption according to age and frailty.

A

B

C

D

E

F

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individuals) have lower RMR than those affected by disease and functional impairments (“non-IDEAL” individuals) (30) and that higher RMR is associated with an increased burden of multimorbidity (31). The first result could seem opposite to ours, although frailty and “IDEAL” criteria do not represent the same population. For instance, “IDEAL” participants from the Baltimore study were younger and with higher functional status than frail participants from our sample. Moreover, RMR was higher in the Baltimore study (1,512 kcal/day) than in the FRADEA study (1,071 kcal/day), probably reflecting a younger, less frail, and disabled population. We can’t also exclude a measurement difference, because our calorimeter used fixed RQ, and the two results may not be directly comparable. However, conclusions could not be contradictory. Our study only describes that frailty is a modifier in the complex relationship between age and energetics, relationship that is also modified from young to old ages by medical conditions and functional status. In our study, we were not able to find any association between comorbidity and RMR, neither in the bivariant analysis nor in the adjusted GLMs, and Charlson index was only associated with a higher RF and FeO₂. Fabbri and colleagues (31) measured the number of chronic diseases, and we collected the Charlson index, and although they are closely related, we can’t assume that both measures are the same.

Table 3. Association Between RMR and Total Daily Energy With Age

<table>
<thead>
<tr>
<th>Measure</th>
<th>Complete sample B (95% CI)</th>
<th>Nonfrail B (95% CI)</th>
<th>Prefrail B (95% CI)</th>
<th>Frail B (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>eRMR</td>
<td>-13.8 (-23.1 to -8.5)***</td>
<td>5.0 (-10.6 to 20.5)</td>
<td>-23.7 (-32.8 to -14.6)***</td>
<td>-15.6 (-37.4 to 6.2)</td>
</tr>
<tr>
<td>eRMR/weight</td>
<td>-0.09 (-0.19 to 0.01)</td>
<td>0.13 (-0.07 to 0.33)</td>
<td>-0.23 (-0.36 to -0.09)***</td>
<td>0.01 (-0.31 to 0.33)</td>
</tr>
<tr>
<td>eRMR/FFM</td>
<td>-0.14 (-0.30 to 0.01)</td>
<td>0.23 (-0.07 to 0.53)</td>
<td>-0.38 (-0.59 to -0.18)***</td>
<td>-0.05 (-0.55 to 0.45)</td>
</tr>
<tr>
<td>TDEE</td>
<td>-24.8 (-35.4 to -14.2)***</td>
<td>-13.8 (-34.1 to 6.5)</td>
<td>-17.0 (-30.2 to -3.8)*</td>
<td>-22.8 (-42.3 to -3.4)*</td>
</tr>
<tr>
<td>TDEE/weight</td>
<td>-0.13 (-0.24 to -0.01)*</td>
<td>-0.08 (-0.30 to 0.14)</td>
<td>-0.04 (-0.19 to 0.10)</td>
<td>-0.03 (-0.24 to 0.17)</td>
</tr>
<tr>
<td>TDEE/FFM</td>
<td>-0.18 (-0.34 to -0.02)*</td>
<td>-0.02 (-0.32 to 0.29)</td>
<td>-0.13 (-0.33 to 0.07)</td>
<td>-0.12 (-0.54 to 0.31)</td>
</tr>
</tbody>
</table>

Notes: CI = confidence interval; eRMR = estimated resting metabolic rate (kcal/day); FFM = fat-free mass (kg); TDEE = total daily energy expenditure (kcal). *p < .05. ***p < .01.

Figure 2. Calorimetric data and age in frail, prefail, and nonfrail participants.
Although causation can’t be inferred from our cross-sectional design, we could hypothesize that age-associated prefrailty and posterior frailty development are associated with an eRMR decline secondary to slowed organ metabolic rates at first stage, and subsequently to FFM loss. Although eRMR declines with aging in both prefrail and frail older adults, faster in the prefrail group (Figure 1A), in prefrail older adults eRMR per kg of FFM declines (Figure 1E), probably reflecting a maintenance of organ metabolic rates. Later, when participants evolve to frailty, eRMR per kg of FFM remains stable, suggesting an added loss of FFM. However, longitudinal studies are necessary to analyze whether frailty is a cause, a consequence, or only a confounder in this complex relationship.

As can be seen in Figure 2, FeO₃ did not change significantly with aging, with similar values in the three frailty groups (panel D). Interestingly, Ve, RF, and VO₂ decreased in frail and prefrail participants with aging but increased in nonfrail ones (panels A–C). Prefrail and frail participants had 1.7 and 2.2 more breaths per minute, respectively, than nonfrail participants. This could be a respiratory compensatory mechanism of prefrail and frail participants to compensate the initial age-associated decline in eRMR, VO₂, and Ve observed (Figures 2B and C), probably reflecting a maintenance of muscular respiratory efficiency and a higher basal metabolic status. This is confirmed by a significant relationship between grip strength and FFM with Ve and RF (Table 2), and also with gait speed and peak flow, indirect measures of muscle performance (Table 2).

Our study has some limitations. First, the FitMate is a calorimeter without CO₂ analyzer and uses a standardized respiratory exchange ratio (0.85) to calculate RMR. Although it has been validated against other calorimeters including a CO₂ analyzer, we have no evidence that substrate utilization is unaffected by frailty status. For this reason, we could be missing or creating potential differences, and consequently, decided to use the term “estimated Resting metabolic Rate” to clearly address this issue. Although the participants of the FRADEA study are a representative sample of Albacete older adults, only 450 accepted to undergo calorimetry, and only for 402 cases, complete data were available for analysis. Thus, we can’t assume that the sample of this article is representative of the population. Furthermore, the more active participants of the FRADEA study were the ones who accepted for calorimetry, probably suggesting an initial decline in organ metabolic rates. 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Conflict of Interest
The authors have no conflicts of interest.

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Figure 3. Estimated marginal means of estimated resting metabolic rate by age categories depending on frailty status (general linear model analysis). (A, B) Unadjusted. (C, D) Adjusted for sex, fat-free mass, and Charlson index.


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