Original Article

Energy Metabolism and the Burden of Multimorbidity in Older Adults: Results From the Baltimore Longitudinal Study of Aging

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Abstract

Excessively elevated resting metabolic rate (RMR) for persons of a certain age, sex, and body composition is a mortality risk factor. Whether elevated RMR constitutes an early marker of health deterioration in older adult has not been fully investigated. Using data from the Baltimore Longitudinal Study of Aging, we hypothesized that higher RMR (i) was cross-sectionally associated with higher multimorbidity and (ii) predicted higher multimorbidity in subsequent follow-ups. The analysis included 695 Baltimore Longitudinal Study of Aging participants, aged 60 or older at baseline, of whom 248 had follow-up data available 2 years later and 109 four years later. Multimorbidity was assessed as number of chronic diseases. RMR was measured by indirect calorimetry and was tested in regression analyses adjusted for covariates age, sex, and dual-energy x-ray absorptiometry–measured total body fat mass and lean mass. Baseline RMR and multimorbidity were positively associated, independent of covariates ($p = .002$). Moreover, in a three-wave bivariate autoregressive cross-lagged model adjusted for covariates, higher prior RMR predicted greater future multimorbidity above and beyond the cross-sectional and autoregressive associations ($p = .034$). RMR higher than expected, given age, sex, and body composition, predicts future higher multimorbidity in older adults and may be used as early biomarker of impending health deterioration. Replication and the development of normative data are required for clinical translation.

Key Words: Multimorbidity—Resting metabolic rate—Aging—Health status—Metabolism

Energy production and expenditure are essential for life. The idea that aging and health are linked to energy metabolism was introduced over a century ago, but the role of energy metabolism in human aging and chronic disease progression is still debated in the literature (1,2). Recent evidence indicates that energy requirements may be strongly affected by aging and disease, but the magnitude...
and longitudinal nature of the association between disease and energy utilization has not been well characterized.

Resting metabolic rate (RMR)—often defined as the energetic cost of living—is the energy required to maintain structural and functional homeostasis at physical rest, in fasting and thermoneutral conditions. RMR accounts for 60%–70% of daily energy expenditure and is typically assessed via indirect calorimetry (3). It is well known that RMR normalized by body size declines rapidly from birth up to the end of the third decade, and then continues to decline more slowly from adulthood until death, mostly but not completely as a consequence of the age-related loss of lean body mass (4–6).

From previous studies, the decline in RMR in mid-late life is known to be as a general aging phenomenon, and a lack of such decline may be a marker of health deterioration in older adults. In fact, if RMR is not normalized by body composition, lack of or retarded decline in RMR may also be due to maintenance of lean body mass, indicating good health status and/or healthy active lifestyle. However, when RMR is normalized by age, sex, and body composition, RMR higher than expected may be an independent risk factor for mortality. Previous research from Baltimore Longitudinal Study of Aging (BLSA) confirmed this by showing that long-lived individuals are able to preserve a low energy metabolism reflecting good health status (3). A plausible interpretation of the higher RMR associated with poor health status is that the extra energy may be due to pathological conditions causing a homeostatic dysregulation that increases minimum energy requirements. Consistent with this hypothesis, a recent cross-sectional study from the BLSA showed that individuals who are fully functional and free of major medical conditions have a lower RMR than those with diseases and functional impairments (7). In addition, Kim and colleagues (8) found that in nonagenarians, declining health (measured with a 43-item frailty index) is associated with increased energy demands in the form of higher RMR.

It is generally acknowledged that “elevated RMR” should be interpreted as RMR higher than expected for a certain age, sex, and body composition (9). Unfortunately, standard cutoff thresholds for elevated RMR levels that take into account the effect of age, sex, and body composition have not been developed. The aim of the present study was to assess whether RMR higher than expected after adjusting for age, sex, and body composition is associated with an increased risk of health deterioration, operationally defined as the number of coexistent chronic conditions (or multimorbidity), in participants of the BLSA aged 60 and older. In particular, we hypothesized that “elevated RMR” may be an early marker of impending health deterioration and disease susceptibility that leads to increasing multimorbidity, a dimension that is typically considered a fundamental aging phenotype.

Methods

Study Design and Setting

The BLSA is a study of human aging established in 1958 and conducted by the National Institute on Aging Intramural Research Program. A general description of the sample and enrollment procedures and criteria has been previously reported (10). Briefly, the BLSA continuously enrolls healthy volunteers aged 20 and older who are followed for life regardless of the development of diseases and conditions. Participants aged 60 or older are examined every 2 years at the National Institute on Aging Intramural Research Program Clinical Research Unit in Baltimore, Maryland, over 3 days of testing. Certified nurse practitioners and certified technicians administer all assessments following standardized protocols.

Participants

The sample for the current study consists of 695 participants aged 60 or older, who had a visit between February 2007 and May 2013, and underwent a comprehensive medical history interview, clinical examination, laboratory and cardiovascular testing, cognitive testing, and RMR assessment. Because the measure of RMR rate was introduced relatively recently in the BLSA (in 2007), a limited number of participants had follow-up data after 2 and 4 years (248 and 109 individuals, respectively), and they were all included in the longitudinal analysis.

Measurements

Multimorbidity

In recent years, the study of multimorbidity has gained considerable interest in the literature although no standard operational definition of multimorbidity has emerged. One of the most common approaches is to define multimorbidity as count of number of diseases (11). For this purpose, Fortin and coworkers (12) suggested including (at least) the 12 most prevalent chronic diseases with high impact or burden in a given population. Following these recommendations, we selected “a priori” a list of 15 candidate chronic conditions that could be reliably adjudicated based on the data available and known to have high prevalence and to be associated with high disability and mortality risk in older adults (described later). As in previous studies, we operationalized multimorbidity as number of diagnosed diseases (according to standard clinical criteria) in each participant at each time point (13).

Chronic diseases

The presence of 15 chronic conditions was ascertained at baseline and follow-ups. Most conditions (hypertension, diabetes, coronary artery disease, congestive heart failure, stroke, chronic obstructive pulmonary disease, cancer, Parkinson's disease, history of hip fracture, and lower extremities joint disease) were defined using standard criteria and algorithms similar to those used in the Women’s Health and Aging Study (14). In addition, anemia was defined as hemoglobin <12 g/dL in women and <13 g/dL in men (15); chronic kidney disease was defined as glomerular filtration rate estimated using the MRDR (Modification of Diet in Renal Disease) equation <60 mL/L (16); peripheral arterial disease was defined as ankle-brachial index measured by Doppler stethoscope < 0.9 (17); cognitive impairment was defined as Mini-Mental State Examination score <24, and depression was defined as a score of 16 or greater on the Center for Epidemiologic Studies-Depression scale (18,19).

The distribution of the 15 chronic conditions included in our definition of multimorbidity in the baseline population is shown in Supplementary Material 1.

Resting metabolic rate

RMR was assessed using indirect calorimetry (Cosmed K4b2, Rome, Italy) (20,21). In a previous study in the BLSA, we verified the accuracy of estimating energy consumption at rest and in walking conditions using Cosmed K4b2 compared with Medgraphics D-series gas-exchange system (Medgraphics, Medical Graphics Corporation, St. Paul, MN), a widely used breath-by-breath analyzer, as the reference standard. The results showed that Cosmed provides acceptable measures of RMR, and it can be used for this purpose without substantial bias and with acceptable precision (22).

RMR was assessed for 16 minutes first thing in the morning after an overnight stay in the clinic in a quiet, thermoneutral environment with the participant in a fasted, rested state. Any possible ingestion of common stimulants, including coffee and tea, was avoided. Before
testing, the analyzer was calibrated using a 3.0-L flow syringe and gases of known concentrations. The analyzer collects gas-exchange data on a breath-by-breath basis averaged over 30-second intervals to reduce variability. RMR in kilocalories per day was calculated from gas-exchange data using the Weir equation (1949) (23). The first 5 minutes of data were discarded to allow adaptation to the testing procedures, and the remaining 11 minutes were averaged to arrive at a single measure of RMR (24).

Body composition

Total body dual-energy x-ray absorptiometry (DEXA) was performed using the Prodigy Scanner (General Electric, Madison, WI) and analyzed with version 10.51.006 software. DEXA uses tissue absorption of x-ray beams to identify different components of the human body (bone mineral content, lean body mass, and fat mass) and to provide quantitative data on body composition (25–27). Absolute measures of total body fat mass and lean mass in kilograms were included as covariates in the present analysis. After removing shoes and disrobing, body weight was measured in kilograms with a calibrated scale to the nearest 0.1 kg. Body height was measured in centimeters by a stadiometer to the nearest 0.1 cm (28). Body mass index was calculated by dividing body weight in kilograms by the square of height in meters (kg/m²). From this information, percentage of fat mass and percentage of lean mass were also calculated as total fat mass and total lean mass in percent of body weight as well as the ratio of lean-to-fat mass (total body lean mass divided by total body fat mass).

Other variables included in supplemental analyses

Other variables were also included as potential correlates with RMR in additional analyses presented in Supplementary Materials. Cardiorespiratory fitness was assessed using a single, symptom-limited graded maximal treadmill exercise test following a modified Balke protocol with measurement of VO₂ (29). Men walked at a constant 3.5 miles/h (~5.6 km/h) and women at a constant 3.0 miles/h (~4.8 km/h) on a motor-driven treadmill. Treadmill grade was increased by 3% every 2 minutes until self-determined exhaustion. Expired gas volumes were measured using either Tissot tanks or a Parkinson–Cowan gas meter (Waitsfield, VA). Expired O₂ and CO₂ concentrations were measured using either dedicated O₂ and CO₂ analyzers or a medical mass spectrometer (Perkin-Elmer MGA-1110, Boston, MA). Oxygen consumption was measured continuously and calculated every 30 seconds throughout the exercise. The highest value was termed peak VO₂, or VO₂ max, expressed as milliliters O₂ per kilogram per minute. Physical activity information was assessed via self-report using an interviewer-administered standardized physical activity questionnaire, which has relatively high construct validity in well-educated health-conscious persons, which characterizes most BLSA participants (30,31). In particular, participants were categorized according to presence versus absence of vigorous physical activity over the past 2 weeks. Smoking status was ascertained by a questionnaire, and study participants were classified as active smokers versus past or never smokers. Waist circumference, defined as the minimal abdominal circumference between the lower edge of the rib cage and the iliac crests, was measured according to a highly standardized procedure and was used as proxy measure of central obesity. Number of medications was assessed as self-reported using a standardized interview. Season of the year (winter: December–February; spring: March–May; summer: June–August; autumn: September–November) was included as a categorical variable to account for possible seasonal effects on RMR.

Statistical Analyses

The characteristics of the baseline population (N = 695) are reported in Table 1 as means ± SD or proportions. Multiple linear regression models were performed to test the cross-sectional association between RMR and multimorbidity, independent of age, sex, and body composition (Table 2). Additional regression analyses were also performed to explore other potential correlates with RMR levels in the baseline population (Supplementary Materials 2 and 3). Furthermore, using data from participants who attended the 2-year follow-up visit (N = 248) and the 4-year follow-up visit (N = 109), the temporal relationship between RMR and number of diseases was tested by fitting a three-wave bivariate autoregressive cross-lagged model (Figure 1 and Table 2). This type of model allows estimation of the longitudinal influences of one variable on another, and vice versa, while also controlling for autoregressive associations and covariates (32). Two different pathways of associations are simultaneously evaluated: cross-lagged and autoregressive. The cross-lagged analyses are of primary interest for the present study, as they represent the association between RMR at time t and number of diseases at time t + 1 as well as the reciprocal association between number of diseases at time t and RMR at time t + 1. Autoregressive pathways estimate the association between RMR at time t and RMR at time t + 1 as well as the association between number of diseases at time t and number of diseases at time t + 1. Autoregressive and cross-lagged associations are assumed to be the same across time. Concurrent correlation between RMR and number of diseases at baseline is also estimated. Covariates, entered as predictors of both RMR and number of diseases, are baseline age, sex, and baseline DEXA-measured total body fat mass and lean mass. Thus, any significant association between RMR at time t and number of diseases at time t + 1 will be above and beyond the variance accounted for by the association between number of diseases at time t and RMR at time t + 1 and autoregressive associations, after adjusting for covariates.

Statistical analyses were performed using SAS statistical package, version 9.3 (SAS Institute Inc., Cary, NC) and Mplus 7.11 (Muthen & Muthen).

Results

Characteristics of Baseline Population

The baseline population includes 695 participants, aged 60–95 years old (mean ± SD: 72.3 ± 8.5), of whom 343 (49.3%) were women. Average values of RMR (1453 ± 438 kcal/d or 0.78 ± 0.20 kcal/kg) were consistent with those reported in other studies for the same age group (9). The average number of chronic conditions was 2.7 ± 1.6. Specifically, 170 participants (24.5%) had one disease, 296 (42.6%) had two or three diseases, and 144 (20.7%) had four or more diseases. Participants with higher numbers of chronic conditions were significantly older, had higher body mass index, had a greater percentage of total body fat mass and a lower percentage of total body lean mass, and had a lower ratio of total body lean mass to total body fat mass (Table 1).

Cross-sectional Analysis

Association between RMR and multimorbidity

At baseline, crude mean values of RMR were higher with increasing number of chronic diseases (Table 1). Independent of age and sex, RMR and number of chronic diseases were highly significantly and positively associated (p < .001, Model I, Table 2), even after adjusting for height and DEXA-measured total body fat mass and lean mass (p = .002, Model II, Table 2).
Table 1. Characteristics of the Baseline Population According to Number of Chronic Diseases (N = 695)

<table>
<thead>
<tr>
<th>No Chronic Disease (N = 85)</th>
<th>One Chronic Disease (N = 170)</th>
<th>Two or Three Chronic Diseases (N = 296)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean ± SD</td>
<td>69.20 (± 2.77)</td>
<td>71.34 (± 8.38)</td>
</tr>
<tr>
<td>Sex (men), %</td>
<td>49.4</td>
<td>46.6</td>
</tr>
<tr>
<td>RMR (kcal/d), mean ± SD</td>
<td>1395.5 (± 360.0)</td>
<td>1419.0 (± 399.3)</td>
</tr>
<tr>
<td>BMI (kg/m²), mean ± SD</td>
<td>26.58 (± 4.10)</td>
<td>26.57 (± 4.16)</td>
</tr>
<tr>
<td>Total body fat mass (kg), mean ± SD</td>
<td>35.1 (± 7.7)</td>
<td>34.1 (± 7.6)</td>
</tr>
<tr>
<td>Percentage of total body fat mass, mean ± SD</td>
<td>47.9 (± 9.7)</td>
<td>46.2 (± 8.5)</td>
</tr>
<tr>
<td>Total body lean mass (kg), mean ± SD</td>
<td>62.0 (± 8.8)</td>
<td>62.2 (± 8.8)</td>
</tr>
<tr>
<td>Percentage of total body lean mass, mean ± SD</td>
<td>47.9 (± 9.7)</td>
<td>46.2 (± 8.5)</td>
</tr>
<tr>
<td>Ratio of total body lean mass to total body fat mass, mean ± SD</td>
<td>2.13 (± 0.5)</td>
<td>2.10 (± 0.5)</td>
</tr>
</tbody>
</table>

Note: BMI = body mass index; RMR = resting metabolic rate.

Table 2. Multiple Linear Regressions Testing the Cross-sectional Relationship of Number of Diseases With Resting Metabolic Rate (RMR), Adjusting for Age and Sex (Model I) and Age, Sex, and Body Composition (Model II), in the Baseline Population (N = 695)

<table>
<thead>
<tr>
<th></th>
<th>Model I</th>
<th>Model II</th>
</tr>
</thead>
<tbody>
<tr>
<td>β (SE)</td>
<td>p Value</td>
<td>β (SE)</td>
</tr>
<tr>
<td>Age, y</td>
<td>-16.47 (1.76)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Sex (men)</td>
<td>415.7 (19.81)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Number of diseases</td>
<td>34.45 (9.06)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Total body fat mass (kg)</td>
<td>4.03 (1.42)</td>
<td>.005</td>
</tr>
<tr>
<td>Total body lean mass (kg)</td>
<td>1.81 (0.96)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Height, cm</td>
<td>6.67 (2.40)</td>
<td>.005</td>
</tr>
</tbody>
</table>

Exclusion of potential confounders

In addition, age- and sex-adjusted univariate analyses were also performed to explore other potential correlates (cardiovascular fitness, physical activity, smoking status, medications, waist circumference, and seasonal patterns) with RMR levels in the baseline population (Supplementary Material 2). We found that only waist circumference was significantly correlated with RMR levels in our population (ρ < .001). Smoking status only approached statistical significance (ρ < .01), whereas all other potential confounders were not significantly associated with RMR. Based on these findings, we included waist circumference and smoking status as additional covariates in the multivariate analysis having RMR as the dependent variable. The original results did not substantially change, and the association between multimorbidity and RMR was confirmed (Supplementary Material 3).

Longitudinal analysis

The longitudinal relationship between RMR and multimorbidity was tested by fitting a three-wave autoregressive cross-lagged model (Figure 1) at three time points: baseline visit (N = 695), 2-year follow-up visit (N = 248), and 4-year follow-up visit (N = 109). Covariates were baseline age, sex, and baseline DEXA-measured total body fat mass and lean mass. Consistent with the cross-sectional analysis, baseline values of RMR were highly correlated with the baseline number of diseases (ρ = .005). Moreover, for both RMR and number of chronic diseases, the autoregressive pathways were statistically significant, indicating that previous RMR predicted future RMR (ρ < .001) and, likewise, previous number of diseases predicted future number of diseases (ρ < .001). Cross-lagged associations revealed that higher values of RMR at previous assessment were significantly associated with a greater future number of diseases (ρ = .034). In contrast, previous number of diseases was not associated with follow-up RMR (Table 3).

Discussion

The present study investigates the cross-sectional and longitudinal relationships between RMR and multimorbidity in older adults. Our results showed that, independent of age, sex, and body composition, higher RMR was cross-sectionally associated with a higher number of chronic diseases. In addition, in longitudinal analyses, we found that prior higher values of RMR predicted a greater number of diseases in the future, suggesting that elevated RMR may be an early marker of impending future development of multimorbidity in the...
elderly adults. In particular, the longitudinal model shows that in individuals with the same age, sex, and body composition, having an RMR 100 kcal/d higher is associated with developing 1.5 more diseases over the next 2 years.

Previous longitudinal studies have shown that RMR declines with aging, in part but not completely as a consequence of changes in body composition, in particular, the decline in fat-free mass (5,33). The decline in RMR with aging may be interpreted as a progressive reduction in the energy required by an organism losing complexity and attempting to compensate for progressive decline in aerobic capacity. These age-related compensatory mechanisms are counterbalanced by the emergence of chronic medical conditions such as chronic infections, autoimmune diseases, cardiovascular diseases, and cancer that cause an increase in energy consumption, which may even result in weight loss and cachexia (34,35).

Previous findings from the BLSA showed that higher RMR is a risk factor for mortality and that healthy and fully functional individuals present lower levels of RMR compared with those with diseases or disability (3,7). Few studies, relatively small studies that explored the relationship between RMR and frailty, have reported partially conflicting findings. In particular, Weiss and colleagues (36) found both high and low RMR in frail women older than 80. On the other hand, a recent study in the oldest old showed that declining health, measured with a 43-item frailty index, was associated with increased energy demands in the form of higher RMR. These findings suggest that the increased RMR is likely the derivative of greater demands on maintenance of an aging organism whose tissue and integrated functions are degrading (8). This mechanism may be particularly important in the context of aging because preclinical studies and gene expression studies have shown that mitochondrial dysfunction is a major phenotype of aging, and increased energetic cost due to multimorbidity may be superimposed upon an already limited energetic reserve (37).

Table 3. Results From Three-Wave Autoregressive Cross-lagged Model Testing the Longitudinal Relationship Between Resting Metabolic Rate (RMR, kcal/d) and Number of Diseases, Independent of Baseline Age, Sex, and Baseline Dual-Energy x-Ray Absorptiometry–Measured Total Body Fat Mass and Lean Mass

<table>
<thead>
<tr>
<th>RMR → RMR</th>
<th>Number of Diseases → Number of Diseases</th>
<th>Number of Diseases → RMR</th>
<th>RMR → Number of Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>β (SE)</td>
<td>0.42 (0.04)</td>
<td>0.92 (0.02)</td>
<td>−0.04 (0.11)</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.739</td>
</tr>
</tbody>
</table>

Note: Model fit information: RMSEA (root mean square error of approximation) = 0.065; CFI (comparative fit index) = 0.938.

To the best of our knowledge, this is the first study that explored the longitudinal relationship between RMR and multimorbidity in the elderly adults. Because of potential multidirectional associations, we performed the analysis by an autoregressive model and showed that although RMR predicted future higher multimorbidity, higher multimorbidity was not predictive of future RMR. Though in the context of an observational study, these findings provide some insight into the pathway that connects RMR with declining health. The rising RMR at an early stage of health deterioration may indicate that extra energetic resources are needed to cope with progressive loss of resiliency and respond efficiently and effectively to internal and environmental challenges. Ultimately, this process points to a clinical expansion in multimorbidity. The nature of the homeostatic dysregulation that “drains” energy is still unknown, but a reasonable candidate is the presence of a mild chronic proinflammatory state, which has been found to be strongly associated with the longitudinal expansion of multimorbidity in the elderly adults (13). In addition, the chronic elevation of metabolic rate, facilitating oxidative stress and mitochondria dysfunction, may contribute in a vicious circle to organ damage at the cellular level, resulting in further compromised health status. Interestingly, in some geriatric patients, a catabolic state and the resulting loss of weight may occur in a preclinical stage, years before patients develop a recognizable disease (38).

Due to the importance of fully understanding the dynamic interactions among basal metabolism, health status, and changes in body composition, further investigations, performed in a larger population with longer time of follow-up, are required. Simultaneously, testing longitudinal changes in RMR levels and body composition in relation...
to the expansion of multimorbidity may be useful to better clarify the potential role of body composition and its changes with aging and diseases in determining the association between higher RMR and greater later multimorbidity. This study has some limitations. First, the main aim of our analysis was to look at “elevated RMR” as potential predictor of overall multimorbidity as a biomarker of general disease susceptibility, a phenotype that is at the center of geriatric research. Therefore, we purposely did not focus on specific diseases. Second, the sample population is relatively small, especially for the longitudinal analysis. The limited number of participants with available data after 2 and 4 years is due to the fact that the measure of RMR was introduced relatively recently in the BLSA, in 2007. In fact, data for baseline population were collected between 2007 and 2013, with most participants not yet having longitudinal information. However, we included all longitudinal data available, with no exclusion criteria. Our findings should be validated in a larger study and possibly over longer follow-up. Third, we acknowledge that, because the BLSA continuously enrolls healthy volunteers followed for life, participation is very demanding and time consuming and those enrolled in the study tend to be highly educated and healthier than participants of the same age in the overall population. Fourth, it is possible that differential mortality according to RMR affected our findings. Indeed, 28 participants evaluated at baseline died between January 2007 and July 2013. However, a previous BLSA research showed that higher RMR is associated with higher mortality risk (3). In particular, persons who died had a blunted age-related RMR decline compared with those who survived, confirming that long-lived individuals are able to preserve a low energy metabolism reflecting good health status. The discrepancy in RMR between individuals who died and those who survived was interpreted due to pathological conditions causing a homeostatic dysregulation that substantially increase minimum energy requirements to maintain stability. Such interpretation is further confirmed by the findings of this study, namely that RMR is prospectively associated with multimorbidity. As a consequence, it is reasonable to hypothesize that those who died (and therefore experienced the worst possible decline in health status) had higher RMR at baseline. Thus, mortality is not a competing event, but it actually confirms and reinforces our results. Under this assumption, it is likely that our study underestimated the true strength of the relationship between RMR and multimorbidity. Fifth, as we mentioned earlier, a standard cutoff threshold for elevated RMR levels has not been developed. Therefore, in our study, the expression “elevated RMR” should be interpreted as “RMR elevated for a specific age, sex, and body composition” and defined at the individual level according to these characteristics (9). Normative data for RMR that take into account age, sex, and body composition should be estimated in future studies, performed in larger and more diverse populations, in order to translate our findings into clinically relevant information. Finally, in the three-wave autoregressive cross-lagged model, because of the small size of the sample and short time of follow-up, RMR measurements at the follow-ups at 2 and 4 years were adjusted only for baseline values of body composition (and not also for values of body composition at follow-up time). Indeed, as previously acknowledged, testing simultaneously the effect of longitudinal changes in RMR and body composition may be interesting and may be the topic of further investigation when more longitudinal data are collected.

In conclusion, our results, showing that higher RMR is a predictor of future higher development of multimorbidity in older persons, are consistent with previous findings that demonstrate the lack of decline in RMR with aging is a risk factor for rapid health status decline and shed some important light on the debate about the role of energy metabolism in human aging. In particular, RMR may hold important clinical significance as an early quantitative measure of subclinical disease burden that predicts future development of multiple chronic diseases in geriatric patients. Information on RMR may help to better target and monitor the effect of interventions and strategies aimed at preventing and treating the burden of multimorbidity in older adults.

Supplementary material
Supplementary content can be found at: http://biomedgerontology.oxfordjournals.org/

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Conflict of Interest
There are no conflicts of interest to report.

References


