Gender-Specific Associations in Age-Related Changes in Resting Energy Expenditure (REE) and MRI Measured Body Composition in Healthy Caucasians

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Abstract

Background: The effect of gender as well as gender-specific changes of fat free mass (FFM) and its metabolic active components (muscle mass and organ masses [OMs]) and fat mass (FM) on age-related changes in resting energy expenditure (REE) are not well defined. We hypothesized that there are gender differences in (1) the age-specific onset of changes in detailed body composition (2); the onset of changes in body composition–REE associations with age.

Methods: Using a cross-sectional magnetic resonance imaging database of 448 Caucasian participants (females and males) with comprehensive data on skeletal muscle (SM) mass, adipose tissue (AT), OMs, and REE.

Results: We observed gender-specific differences in the onset of age-related changes in metabolic active components and REE. Declines in body composition and REE started earlier in females than in males for SM (29.4 vs 39.6 years), AT (38.2 vs 49.9 years), OM (34.7 vs 45.7 years), and REE (31.9 vs 36.8 years). The age-related decrease of AT was significantly higher in females than in males (−5.69 kg/decade vs −0.59 kg/decade). In females adjusted REEmFFM&FM (resting energy expenditure measured adjusted for FFM and FM) and REEmSM/OM/AT (resting energy expenditure measured adjusted for skeletal muscle and organ mass and adipose tissue) decreased by −145 kJ/d/decade and −604.8 kJ/d/decade after the age of 35.2 respectively 34.3 years. SM was main determinant of REEm in females ($R^2 = .67$) and males ($R^2 = .66$) with remaining variance mainly explained by kidney mass ($R^2 = .07$) in females and liver mass ($R^2 = .09$) in males.

Conclusion: We concluded that gender affects the age-related changes in body composition as well as changes in body composition–REE relationship. This trial was registered at linicaltrials.gov as NCT01737034.

Keywords: Caucasian—Sex-specific—Age-specific—Body composition changes—Resting energy expenditure

Aging is associated with divergent changes in body composition, that is, fat free mass (FFM) decreases and fat mass (FM) increases. Skeletal muscle (SM) is the major organ of FFM. SM mass increases up to age 40 years followed by a subsequent decline (1). 15 years ago, Janssen and colleagues (1) were first to describe the age-related decline in SM mass as assessed by whole-body magnetic resonance imaging (MRI) in a multi-ethnic group of 468 healthy participants. In addition to SM mass aging is considerably associated with a decrease in mass and specific metabolic rates in metabolically active organs such as heart, liver, and kidneys (2,3). Contrary to muscle mass FM increases with age, which is associated with increases in visceral and intramuscular fat, subcutaneous adipose tissue (AT) decreases (4,5).

Because changes in body composition are related to specific body functions, for example resting energy expenditure (REE), these should be taken into account (6,7). Age-related decreases in REE are mainly explained by decrease in metabolically active organs masses.
or body cell mass (8, 9). SM is the major determinant of REE but part of the variance is explained by brain, heart, liver, and kidneys (10); in addition, FM also adds to the variance in REE (6). Besides age-related changes in organ and tissue masses their specific metabolic rates also decrease with age (10, 11).

The effect of gender on age-related changes in organ and tissue masses together with changes in REE has not been widely examined. REE decreases by 1% to 2% per decade in participants older than 20 years (12) also with negative consequences for health and function (13). However, longitudinal data on REE are very rare. Two longitudinal studies, the Baltimore Longitudinal Study (BLSA) and Health Ageing and Body Composition Study (Health ABC), indicated that a high resting metabolic rate was a risk factor of mortality (14) as well as multimorbidity (15, 16) in males. A further longitudinal study was the German Gießener Senioren Langzeitstudie (GISELA) study (17). In the GISELA study, the authors presented that the REE fall by 11.2 and 34.1 kJ/d per year in females and males, respectively; however, males had a higher age-related decline in resting and total energy expenditure than females (17). The data of the Health ABC study also showed gender-specific differences in the decreases of REE, changes in FFM were positively associated with changes in REE in males but not in females (18). In contrast, Roubenoff and colleagues (19) showed the opposite way around. None of these studies had used whole-body MRI. We now assess SM mass and high metabolic OMs (eg, brain, heart, liver, kidneys), total and regional AT as well as bone mineral content (BMC) assessed by dual energy X-ray absorptiometry (DXA).

We hypothesized that there are gender differences in (1) the age-specific onset of decreases in detailed body composition (2); the onset of changes in body composition–REE association with age.

Methods

Participants

The study population used for body composition analysis consisted of 448 healthy Caucasians (224 females and 224 males). In 267 participants (150 females and 117 males) REE and OMs were measured. Body composition analysis was performed at the “Reference Center for Body Composition” (Institute of Human Nutrition and Food Science of the Christian-Albrechts University Kiel, Kiel, Germany) with specific competence in comprehensive methods of body composition analysis. The study was conducted according to the guidelines laid down in the “Declaration of Helsinki” and was approved by the local ethical committee of the Christian-Albrechts-University zu Kiel. Written informed consent was obtained from all participants before participation.

Anthropometric Measurements

Body height was measured to the nearest 0.5 cm with participants wearing no shoes (Seca Stadiometer; Vogel & Halke, Hamburg, Germany). Weight was assessed to the nearest 0.01 kg with an electronic scale (Tanita, Tokyo, Japan).

Magnetic Resonance Imaging

SM mass, total, subcutaneous and visceral AT (SAT and VAT) were measured using whole-body multislice MRI. Scans were obtained with a 1.5T scanner (Magnetom Vision Siemens, Erlangen, Germany) as previously described (20). Participants were placed on the platform with their arms extended above their heads. The volumes of four internal organs (brain, heart, liver, and kidney) were also measured by MRI as described earlier (21). SM, AT, and organ areas were manually analyzed using the SliceOmatic software (version 4.3; Tomovision, Montreal, Canada). Intra-observer coefficient of variation was 1.8 % for total SM, 1.8% for brain, 0.07% for liver, 1.7% for heart, and 1.0% for kidney. MRI estimated SM volumes were converted to mass using a density of 1.04 kg/L and AT was converted using a density of 0.92 kg/L (22). SM index (SMI) was created by dividing the SM by squared height (m²).

Dual Energy X-Ray Absorptiometry

DXA whole-body measurement was performed (QDR4500A, Hologic Inc., Bedford, MA). Participants lay in supine position during the 10-minute scan. Manufacturers software (version V8.26a:3) was used for analysis of bone mineral content (BMC; lean body mass (LBM), and FM. FFM was calculated from LBM plus BMC and skeletal bone mass (BMD) was calculated as BMC/ΔDXA × 1.85 (22).

Measured Resting Energy Expenditure

REE was measured by indirect calorimetry (measured resting energy expenditure [REEm]) using an open-circuit ventilated-hood system (Vmax Spectra 29n, SensorMedics BV, Viasys Healthcare, Bilthoven, the Netherlands; software V-max version 12.1A). REEm was measured in the early morning after an overnight fast, a detailed description of the measurement was reported elsewhere (23). The coefficient of variation for repeated measures of REEm was 5.0% (24). REEm was adjusted for FFM and FM (resting energy expenditure measured adjusted for FFM and FM [REEmFFMFM]) or SM, OM, and AT (resting energy expenditure measured adjusted for skeletal muscle and organ mass and adipose tissue [REEmSMOMAT] according to the residual method.

Calculation of REE

Calculation of REE (REEc) was based on the sum of eight high metabolic body compartments multiplied by the corresponding specific tissue metabolic rate reported by Elia and colleagues (23). For skeletal bone density (BMD) a specific metabolic rate of 9.63 kJ/(kg × d) was assumed (26):

\[ REE_c (kJ/d) = (1008 \ kJ \times \text{brain mass (kg)}) + (840 \ kJ \times \text{liver mass (kg)}) + (1048 \ kJ \times \text{heart mass (kg)}) + (1458 \ kJ \times \text{kidney mass (kg)}) + (53 \ kJ \times \text{skeletal muscle mass (kg)}) + (19 \ kJ \times \text{adipose tissue (kg)}) + (9.63 \ kJ \times \text{skeletal bone mass (kg)}) + (45 \times \text{residual mass (kg)}) \]

Statistical Analysis

Statistical analysis was performed using SPSS statistical software (SPSS 21.0, Inc., Chicago, IL). All data are given as means ± SD. Differences between females and males were tested by an independent t test and between age groups using analysis of variance with Bonferroni correction. Differences between paired parameters were tested by a paired sample t test, Pearson correlations were used to determine the relationship between age and different body composition parameters. Figures were drawn using Excel 2010. The turning points of age with nonlinear functions were calculated in body composition parameters, OM and REE. Linear regression analyses were performed after turning points and the significance of the gender-specific decreases was tested by generalized linear model. The difference of REEm and REEc (Δ REEm–REEc) was plotted against age, as described by Bland and
Altman (27). Multivariate linear regression analysis was performed using REEm, REEm\textsubscript{FEMALES} and A REEm–REEc as dependent variables. A p value <.05 was accepted as the limit of significance.

Results
Participants Characteristics on Body Composition
Body composition and REE characteristics of the study population (n = 448) with 224 females and 224 males varying in age (18–78 years) and body mass index (16.8–47.7 kg/m\textsuperscript{2}) are presented in Table 1 and Supplementary Table 2. No significant differences between males and females were found in age, but males were significantly heavier, taller, and had a higher body mass index, SM (total and regional), but lower AT than females (p < .05). These differences remained after controlling SM for height (SMI). Females had lower VAT and VAT/SAT ratios than males (p < .05). There were no gender differences in BMC\textsubscript{LUM}.

Regarding different ages, in both genders younger participants (age 18–29 years) were heavier, taller and had a higher body mass index, SM, but lower AT compared with older participants (>60 years) (p < .05). The differences in SM remained after controlling for height (SMI). In comparison with younger females and males older participants had a significant lower SMI, higher AT, and VAT/SAT ratio (p < .05). There were no significant age differences in BMC\textsubscript{LUM}. Elderly female participants (>60 years) had significant lower liver and kidney mass, but higher brain mass than younger females (p < .05). No significant differences were found for heart and residual mass. Elderly male participants had significantly (p < .05) higher heart and kidney masses compared with younger males. Residual mass of young male participants was significantly (p < .05) lower when compared with elderly participants. When compared with young adults REEm was lower in older males and females (p > .05). This was also true after adjusting REEm for SM, OM, and AT. Males had a higher REEM when compared with females (Supplementary Table 1).

Age-associated nonlinear declines in body composition, OM, and REE are shown in Supplementary Figures 1–4.

Data presented in Supplementary Table 2 showed age-associated decrease rates in body composition, OM and REE per decade according to gender-specific different turning points of age. In males, age-associated decreases in body composition, OM, and REE started more than 10 years earlier when compared with females. In females, the decreases in LBM or muscle mass started in the fourth decade of age, while the decline began in the fifth decade of age in men. An age-associated decrease of OM started in fourth age decade in females but around one decade later in males. There were significant gender differences in declines of AT and SAT (p < .05).

Multivariate Regression Analysis
Multivariate stepwise regression analyses were performed to explain REEm (Model 1), REEm\textsubscript{FEMALES} (Model 2), and A REEm–REEc (Model 3) as dependent variables. In all models, gender (all participants), age, OM, SM, skeletal bone mass, residual mass, and AT (not in Model 2) were included as independent variables. The results of multiple regression analysis are presented in Table 2.

SM was the main determinant of REEm in all participants, females, and males. The remaining variance of REEm in all participants as well as in females and males was explained by different OM, AT, and age.

Model 1 was also calculated in females and males older than 31.9 and 36.8 years respectively. SM was the main determinant of REEm in females and males. In females and males the remaining variance of REEm was partly determined by OM, AT, and (age).

### Table 1. Participants’ Characteristics on Body Composition Parameters (n = 448)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–29</td>
<td>68 (44)</td>
<td>66 (44)</td>
<td>134 (88)</td>
</tr>
<tr>
<td>30–39</td>
<td>67 (46)</td>
<td>66 (46)</td>
<td>133 (88)</td>
</tr>
<tr>
<td>40–49</td>
<td>69 (49)</td>
<td>80 (51)</td>
<td>149 (98)</td>
</tr>
<tr>
<td>All</td>
<td>224 (149)</td>
<td>216 (149)</td>
<td>440 (298)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Height (cm)</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>175–200</td>
<td>76.1±20.6</td>
<td>73.4±20.6</td>
<td>149.5±20.6</td>
</tr>
<tr>
<td>160–174</td>
<td>69.6±38.1</td>
<td>67.2±38.1</td>
<td>136.8±38.1</td>
</tr>
<tr>
<td>All</td>
<td>60.4±38.1</td>
<td>59.6±38.1</td>
<td>119.9±38.1</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>60–89</td>
<td>64.3±9.2</td>
<td>57.1±9.2</td>
<td>121.4±9.2</td>
</tr>
<tr>
<td>90–119</td>
<td>52.1±11.3</td>
<td>45.2±11.3</td>
<td>97.3±11.3</td>
</tr>
<tr>
<td>All</td>
<td>50.5±11.3</td>
<td>45.7±11.3</td>
<td>96.2±11.3</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI (kg/m\textsuperscript{2})</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>16–18</td>
<td>26.5±6.7</td>
<td>26.5±6.7</td>
<td>53.0±6.7</td>
</tr>
<tr>
<td>18–20</td>
<td>26.5±6.7</td>
<td>26.5±6.7</td>
<td>53.1±6.7</td>
</tr>
<tr>
<td>All</td>
<td>26.5±6.7</td>
<td>26.5±6.7</td>
<td>53.1±6.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SAT (kg)</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.1±1.1</td>
<td>8.1±1.1</td>
<td>16.1±1.1</td>
<td></td>
</tr>
<tr>
<td>8.1±1.1</td>
<td>8.1±1.1</td>
<td>16.1±1.1</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>8.1±1.1</td>
<td>8.1±1.1</td>
<td>16.1±1.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VAT (kg)</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.4±2.3</td>
<td>11.4±2.3</td>
<td>22.8±2.3</td>
<td></td>
</tr>
<tr>
<td>11.4±2.3</td>
<td>11.4±2.3</td>
<td>22.8±2.3</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>11.4±2.3</td>
<td>11.4±2.3</td>
<td>22.8±2.3</td>
</tr>
</tbody>
</table>

Note: Data given as mean ± SD. n = number of participants. AT = adipose tissue; OM = organ mass; SAT = subcutaneous adipose tissue; SM = skeletal muscle mass; SMI = skeletal muscle mass index; VAT = visceral adipose tissue; BMI = body mass index; REEM = resting energy expenditure; REEm = resting energy expenditure; REEm\textsubscript{FEMALES} = resting energy expenditure in females; REEm\textsubscript{MALES} = resting energy expenditure in males; REEm–REEc = resting energy expenditure–resting energy expenditure.

Symbol p values are in italics.

Significant differences at α = .05 (Bonferroni corrected).

Notes: Data given as mean ± SD. n = number of participants. AT = adipose tissue; OM = organ mass; SAT = subcutaneous adipose tissue; SM = skeletal muscle mass; SMI = skeletal muscle mass index; VAT = visceral adipose tissue; BMI = body mass index; REEM = resting energy expenditure; REEm = resting energy expenditure; REEm\textsubscript{FEMALES} = resting energy expenditure in females; REEm\textsubscript{MALES} = resting energy expenditure in males; REEm–REEc = resting energy expenditure–resting energy expenditure.

Significant differences at α = .05 (Bonferroni corrected).

p ≤.05 analysis of variance (ANOVA).

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Table 2. Multiple Regression Analysis With REEm, REEm_{FFM&FM} and Δ REEm–REEc as Dependent Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>REEm</th>
<th>REEm_{FFM&amp;FM}</th>
<th>Δ REEm–REEc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Ages</td>
<td>All Participants</td>
<td>Females</td>
</tr>
<tr>
<td></td>
<td>R²</td>
<td>p</td>
<td>SEE</td>
</tr>
<tr>
<td>SM</td>
<td>0.744</td>
<td>0.000</td>
<td>468.5</td>
</tr>
<tr>
<td>Liver</td>
<td>0.065</td>
<td>0.000</td>
<td>468.5</td>
</tr>
<tr>
<td>AT</td>
<td>0.022</td>
<td>0.000</td>
<td>468.5</td>
</tr>
<tr>
<td>Brain</td>
<td>0.009</td>
<td>0.000</td>
<td>468.5</td>
</tr>
<tr>
<td>Residual mass</td>
<td>0.007</td>
<td>0.000</td>
<td>468.5</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.001</td>
<td>0.000</td>
<td>468.5</td>
</tr>
</tbody>
</table>

Notes: AT = adipose tissue; REEm = resting energy expenditure measured; REEm_{FFM&FM} = resting energy expenditure measured adjusted for fat free mass and fat mass; Δ REEm–REEc = resting energy expenditure measured minus resting energy expenditure calculated; SEE = standard error of estimate; SM = skeletal muscle mass.

The data of all subjects are in italics.
In Model 2 the main determinants of REEm$_{\text{FMR/FM}}$ were gender in all participants, kidney mass in females, and brain mass in males. According to gender-specific turning points of age (females 35.2 years) variance in REEm$_{\text{FMR/FM}}$ was in particular explained by kidney mass in females.

In Model 3 $\Delta$ REEm–REEc was used as dependent variable. Heart mass explained the highest amount of variance in $\Delta$ REEm–REEc in females and males together. In females, the variance in $\Delta$ REEm–REEc was explained mainly by heart and in males by kidney mass.

**Discussion**

There are gender differences in (1) the age-associated onset of changes in detailed body composition and (2) the onset of changes in body composition–REE associations with age. The first essential finding is that age is associated with a gender-specific decline of SM, AT, and OM (Supplementary Figures 1–3). In females, the turning points of age are considerably earlier in life than in males. Our data support the previous findings of Janssen and colleagues (1) of an age-associated decrease in SM mass measured by MRI. However, Janssen and colleagues (1) identified a decrease in total SM mass in men and women at an age of 45 years. By contrast, we found gender differences in the age-associated onset of changes in detailed body composition with an earlier SM decrease in females (29.4 years) and males (39.6 years). This was also true for LBM which is in line with the findings of Gallagher and colleagues (28). Gallagher and colleagues (28) showed a linear relationship between LBM and age (20–70 years), the decline per decade was different between females and males (10.8% vs 14.7%). The latter finding is in contrast with our data, that similar decline rates were seen in females and males. Our findings are in line with earlier findings. In a previous study, Kyle and colleagues (29) demonstrated that the decline in FFM is accelerated in older males and females. He and colleagues (2) showed that OM as part of FFM has a gender independent negative relationship with age. Chumlea and colleagues (30) presented an FM peak up to an age of 60 years, which is in contrast to our data with an age peak between 40 and 50 years. However, gender-specific changes in SAT and VAT have been observed in our study too, with an earlier onset of a significant decrease in SAT in females, whereas VAT increases more rapidly in males. This is in accordance to the findings of Kotani and colleagues (31) that VAT increases about 0.39% per year in males and about 0.15% per year in premenopausal females (31). The gender-specific and age-associated changes of SM and AT could be partly explained by gender- and age-associated endocrine alterations for example, changes in plasma levels of testosterone, estrogen, or myokinins. In males, circulating testosterone declines at a rate of about 1% per year after 40 years (32,33) along with the onset of SM mass decrease. There are also considerable differences in testosterone levels between younger and elderly females (34,35). Besides, testosterone estrogen is lost after menopause by 80% per year in females (36) inducing a decline in SM. The role of leptin or adiponectin as cause or consequence of reduced SM is still unclear, but leptin has already been identified as a marker of SM mass reduction (37).

In the present study, high metabolic rate of OM also showed gender differences in their association with age. OMs were nonlinearly related to age (Supplementary Figure 3), which is in contrast to previous findings analyzing OM derived from autopsy data (38). Garby and colleagues (38) in autopsy data as well as He and colleagues (2) in MRI data showed an inverse linear relationship between age and OM (brain, liver, kidneys, spleen, and heart). However, He and colleagues (2) argued that the sample size was too small to detect nonlinear relationships. Garby and colleagues (38) described that females had lower brain and heart mass when compared with males.

In summary, the present study revealed new gender-specific and nonlinear associations between OM and age.

These aforementioned findings of our study lead to our second essential finding. There is a gender-specific age-associated decline in the body composition–REE relationship (Supplementary Figure 4). SM and OM mainly explained the variance in REE (10,39) and also explained gender- and age-associated changes of REE (7,40). Changes in REE started earlier in life in females than in males. REEm showed a decline of 310 kJ/d (males) to 470 kJ/d (females) per decade, which is in line with longitudinal changes in REEm in the GISELA study (17). REEm decreased in females and males by 158 vs 326 kJ/d per decade, after considering changes in FFM and FM the decreases were 81 and 307 kJ/d per decade (17).

The observed gender-specific, age-related changes in REE support the assumption of Roberts and colleagues (41) that gender affects onset and decline of REE. Changes of specific metabolic rates of organs and tissues are an additional explanation. In a previous article (11) we could calculate that specific metabolic rates of organs and tissues changed with aging. However, gender differences were not tested. In our presented data the differences between REEm and REEc increased with age. This was also observed in the GISELA study (17). These differences were gender-specific and explained by different organs (liver females) and tissues (AT males). These findings lead to the assumption that there are gender differences in the specific metabolic rates of these organs.

In conclusion, gender affects age-associated changes in body composition as well as the body composition–REE relationship.

**Supplementary Material**

Please visit the article online at [http://gerontologist.oxfordjournals.org/](http://gerontologist.oxfordjournals.org/) to view supplementary material.

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**Conflict of Interest**

All authors reported no conflict of interest.

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