Association Between Adiposity and Perceived Physical Fatigability in Mid- to Late Life

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Objective: This study aimed to compare and contrast the associations between measures of adiposity and fat distribution and perceived fatigability among well-functioning individuals in mid- to late life.

Methods: In 1,054 adults (70.4 ± 12.4 years, 52% female), adiposity was measured as BMI, percent fat (dual-energy x-ray absorptiometry), waist and hip circumferences, and waist to height ratio. In a subset of 383 participants, visceral fat was measured. Perceived fatigability was evaluated after a 5-minute treadmill walk (1.5 mph) using the Borg rating of perceived exertion (range, 6-20). Associations between adiposity measures and perceived fatigability were assessed using regression models adjusting for age, sex, race, smoking, and comorbidities.

Results: All adiposity measures, except subcutaneous fat, were positively associated with perceived fatigability after adjustment (P < 0.05 for all). Standardized coefficients indicated that BMI, hip circumference, and visceral fat had the strongest associations with fatigability. Associations between BMI and fatigability were present only among those above the threshold for overweight and strongest in those aged ≥ 65 years. Moreover, BMI was associated with fatigability only among participants with higher waist circumference.

Conclusions: Measures of adiposity, particularly central adiposity, are strongly associated with fatigability, suggesting that weight management may be an effective target for curbing fatigability and maintaining quality of life with aging.

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Introduction

In recent years, the obesity epidemic has expanded to become an emergent public health problem, particularly in middle and late adulthood (1). In 2016, the prevalence of obesity among adults aged 40 years and older in the United States reached a historical peak at more than 40% (2). The health consequences of obesity, including greater all-cause and cardiovascular mortality, increased risk of diabetes, hypertension, stroke, cancer, osteoarthritis, depression, and disability (3-7), and lower quality of life (8,9), are well established. Yet the association between excess weight and body fatness and fatigue, a common threat to quality of life that becomes more prevalent with age (10-13), is less clear.

Fatigue, or lack of energy or vitality, is a common symptom among older individuals and those living with obesity, which greatly affects quality of life and makes engaging in daily physical activities more challenging (10,14). Because of its subjective nature, fatigue is difficult to define and quantify and can be confounded by self-pacing and low activity (15), leaving the true magnitude of the association between obesity and fatigue undefined. The development and validation of the construct of perceived fatigability in the gerontological literature assess fatigue in relation to a standardized physical task, thus gauging the individual’s perception of physical fatigability (15,16). Recent evidence has suggested that perceived fatigability acts as an early marker of functional decline and is a stronger predictor of functional outcomes than traditional measures of fatigue, such as reported tiredness or low energy levels (16). Thus, a better understanding of perceived fatigability and the primary contributors to its development and progression may present new opportunities to reduce its detrimental effects on health and quality of life with aging.

Emerging evidence has indicated that greater adiposity, as measured by BMI and percent fat, is associated with higher physical fatigability (17), and that both greater adiposity and central obesity have a deleterious effect on physical functioning in mid- to late life (18-20). However, the underlying contributing factors, including type and location of adipose tissue (e.g., visceral vs. subcutaneous, central vs. extremity), to fatigability are unknown. Additionally, the measures of adiposity (e.g., BMI, body composition, subcutaneous fat) that are most strongly associated with fatigability have not been identified. Further clarification of the magnitude and strength of the association between adiposity...
and fatigability may assist with gauging risks of becoming physically inactive and developing mobility limitations in individuals with obesity and further strengthen the idea that weight loss may curb fatigability, improve functional performance, and prevent performance decline.

Thus, this study aims to compare and contrast the associations between different measures of adiposity and fat distribution and perceived fatigability among well-functioning individuals in mid- to late life participating in the Baltimore Longitudinal Study of Aging (BLSA). Given that recent evidence has suggested the location of fat tissue is relevant for cardiometabolic outcomes (21,22), we hypothesized that greater adiposity, particularly central adiposity, is associated with higher perceived fatigability even after accounting for differences in health status, operationalized as the number of medical diagnoses, and other potential confounders.

Methods

Study population

The BLSA is a continuously enrolled cohort designed to study normative aging initiated in 1958 (23). Participants are volunteers who are free of major chronic conditions and cognitive or physical limitations at the time of enrollment and are followed for life. Participants are reevaluated every 1, 2, or 4 years depending on age, with older participants seen more frequently. At each assessment, participants are admitted for 3 days to the National Institute on Aging Intramural Research Program’s Clinical Research Unit, where they undergo comprehensive health, cognitive, and functional assessments. The Internal Review Board of the National Institute for Environmental Health Sciences approved the study protocol, and participants provided written informed consent.

For the current analysis, 1,167 participants aged ≥40 years with measures of body mass and composition who visited the Clinical Research Unit between August 2007 and December 2015 were initially considered. We restricted our analysis to participants without mobility limitations; therefore, those reporting any difficulty walking a one-quarter mile (n=84) or who had a usual walking speed slower than 0.6 m/s (n=9) were excluded from the analysis. Participants who were underweight (BMI < 18.5, n=8) or had missing information on chronic conditions or smoking history (n=8) were also excluded. The final analytic sample consisted of 1,054 well-functioning middle-aged and older adults (51.6% women, mean age = 70.4 [SD 12.4] years). A subset of participants (n=383, 48.8% women, mean age 66.5 [SD 13.3] years) also had measures of abdominal (e.g., visceral vs. subcutaneous) fat collected by computed tomography (CT). Participants who had CT data available were, on average, slightly younger than those without CT data (72.7 vs. 66.5 years, P<0.001 for t test), but there were no differences in the sex distribution, percent body fat, or Borg Rating of Perceived Exertion (RPE) scores (for χ² and t tests, P=0.167, 0.510, 0.659, respectively).

Measures of adiposity and fat distribution

General adiposity: BMI and percent fat. Height (meters) and weight (kilograms) were measured using standard clinical procedures with participants wearing a light hospital gown and no shoes. BMI was calculated as weight (kilograms) divided by height (meters squared) and categorized according to the World Health Organization (WHO) standards as follows: participants with normal weight = 18.5 to 24.9 kg/m²; participants with overweight = 25.0 to 29.9 kg/m², and participants with obesity ≥ 30 kg/m². Fat mass was calculated using dual-energy x-ray absorptiometry (model DPX-L; Lunar Radiation, Madison, Wisconsin) and expressed as a percentage of overall weight.

Central adiposity: waist and hip circumferences, waist to height ratio, and visceral fat area. Waist and hip circumferences were measured to the nearest 0.1 cm. Three measurements were taken for each circumference, and the average of the three measurements was used for analysis. Waist circumference was measured at the midpoint between the lowest rib and the iliac crest. Hip circumference was measured at the widest point over the buttock area. Waist to height ratio was calculated by dividing the waist circumference (centimeters) by height (centimeters) and multiplied by 10 to facilitate interpretation.

Abdominal visceral and subcutaneous fat concentrations were measured by CT scan; cross-sectional images were obtained at the lumbar spine level, between the fourth and fifth vertebrae. Geanie software version 2.1 (BonAlyse Oy, Jyvaskyla, Finland) was used to quantify the cross-sectional area, expressed as centimeters squared. Food residue was removed from the images before quantification of fat areas (24). A visceral to subcutaneous ratio was calculated by dividing visceral fat by subcutaneous fat.

Measure of perceived fatigability

Perceived fatigability was assessed immediately after a slow-paced 5-minute treadmill walk (1.5 mph; 0.67 m/s; 0% grade) by asking participants to rate their perceived exertion using the Borg Rating of Perceived Exertion (RPE) (range 6-20; 6 = no exertion at all, 11 = light, 13 = somewhat hard, and 20 = maximal exertion). Instructions about the treadmill test and a detailed explanation about the fatigability scale (how to rate their exertion) were given before the test to allow participants to become acquainted with the scale. The speed of 0.67 m/s was selected because it is a sufficiently low demand to minimize participant exclusion (15). In the current analyses, perceived fatigability was treated as a continuous variable (6-20) as well as a binary outcome, with higher perceived fatigability defined as an RPE of 10 or greater (15). Fatigability was assessed during one of the two following testing time blocks: morning (at least 90 minutes after breakfast) or afternoon (at least 90 minutes after lunch). The temperature of the clinical unit is maintained at 72°F, and participants were well hydrated before performing the test.

Covariates

Age in years, sex, race (Caucasian, African American, or other), smoking history, and history of chronic conditions were self-reported in a questionnaire administered by trained interviewers. Participants were asked whether a doctor or other health professional had ever told them they had any of the following conditions: myocardial infarction, angina, congestive heart failure, peripheral arterial disease, vascular procedures, hypertension, diabetes, stroke, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, cancer, or osteoarthritis. A chronic conditions index was created by adding the number of positive responses.

Statistical analysis

Participants were classified into the WHO BMI groups at the time of their most recent visit in which perceived fatigability was measured. Demographic and anthropometric characteristics of participants were
summarized and compared by BMI category. For continuous variables, means ± SD were calculated, and ANOVA tests were used to test differences. For categorical variables, frequencies and percentages were calculated, and χ² tests were used to test differences.

Linear regression models were used to estimate the continuous association between each adiposity measure and perceived fatigability. All models were adjusted for age, sex, race, history of smoking, and number of comorbidities. The percent body fat model was also adjusted for body weight to provide an index of body size. The visceral and subcutaneous abdominal fat models were adjusted for height squared to account for differences in body size that may partially explain abdominal fat area. Logistic regression models were used to estimate the odds of reporting higher perceived fatigability (RPE ≥ 10) by adiposity measures adjusting for the same set of covariates as the linear models.

Based on exploratory data analyses, we tested for nonlinearity between BMI and perceived fatigability by introducing a spline term with a knot at 25 kg/m² and by stratifying by categories of BMI. Participants with overweight and obesity were further classified by central adiposity, defined as high waist circumference using the WHO thresholds (102 cm for men and 88 cm for women). Linear and logistic regression models, adjusted for the same set of covariates as the previous models, were used to compare the associations between central adiposity and fatigability in these groups. For these comparisons, participants with normal weight served as the reference group, and we further tested if having high waist circumference was associated with greater fatigability within each BMI group. Finally, sensitivity analyses were performed to account for additional covariates that could potentially confound the association between adiposity and fatigability. First, women who had not gone through menopause were excluded to assess the potential effect of hormonal changes on perceived fatigability. Second, serum total cholesterol and fasting glucose levels were included as covariates to account for differences in health status that were not captured by other variables.

Two-tailed P < 0.05 was considered statistically significant. All statistical analyses were performed using Stata software (version 15.1; Stata Corp., College Station, Texas).

Results

The mean BMI was 27.2 ± 4.5; 375 (35.6%) participants were classified as having normal weight, 421 (39.9%) had overweight, and 258 (24.5%) had obesity. Participants with obesity tended to be younger, had greater fat mass, fat percentage, waist to height ratio, and visceral and subcutaneous fat area, and were more likely to have two or more chronic conditions (Table 1). In unadjusted comparisons, there were no differences in perceived fatigability (RPE score, P = 0.119 for ANOVA) or proportion of participants who presented higher fatigability across BMI categories (RPE ≥ 10, P = 0.722 for χ²).

In fully adjusted models (Table 2, Model 1), a 1% greater body fat was associated with 0.03 higher RPE (P = 0.045). Furthermore, weight as a covariate in the same model was not significant (P = 0.67), suggesting the association between percent body fat and fatigability is independent of body weight. Other measures of adiposity were also associated with greater perceived fatigability, including BMI (Model 2, β = 0.07 RPE), waist circumference (Model 3, β = 0.02 RPE), hip circumference (Model 4, β = 0.03 RPE), waist to height ratio (Model 5, β = 0.33 RPE), and visceral fat area (Model 6, β = 0.005 RPE). Participants with a high waist circumference had, on average, a 0.55 greater RPE score (Model 3).

When compared with participants with normal weight, those with obesity had higher fatigability (Table 2, Model 9, β = 0.72 RPE, P < 0.001), but participants with overweight did not (Model 9, β = 0.15 RPE, P = 0.30). Furthermore, other tests for nonlinearity between BMI and RPE indicated no association between BMI and fatigability among those with normal weight. When the spline term was introduced with a knot at 25 kg/m², we found a strong positive association between BMI and RPE only for participants who had overweight and obesity (for BMI between 18.5 and 25: β = −0.09 RPE, P = 0.07; for BMI ≥ 25: β = 0.11 RPE, P < 0.001). In age- and BMI-stratified analyses, the association between obesity and perceived fatigability remained significant only among participants with obesity who were also ≥65 years (β = 1.13 RPE, P < 0.001; Table 3).

In fully adjusted categorical models (Table 2, Model 1), a one-unit higher BMI was associated with 7% higher odds of reporting higher fatigability (Model 2, OR = 1.07, 95% CI: 1.03-1.11, for RPE ≥ 10), and a one-unit greater (1 cm²) subcutaneous fat area was associated with 0.2% greater odds of higher fatigability (Model 3, OR = 1.002, 95% CI: 1.00-1.005). No other measures of general adiposity were associated with higher fatigability, but measures of central adiposity were, including waist circumference (Model 3, OR = 1.12, 95% CI: 1.01-1.04), hip circumference (Model 4, OR = 1.04, 95% CI: 1.02-1.05), and waist to height ratio (Model 5, OR = 1.42, 95% CI: 1.12-1.79).

In categorical analyses of BMI categories (Table 2, Model 9), having overweight was not associated with greater odds of higher fatigability, but having obesity increased the odds of higher fatigability by 94% (Model 3, OR = 1.94, 95% CI: 1.28-2.91 for RPE ≥ 10) compared with those with normal BMI. Tests for nonlinearity between BMI and high RPE indicated no association between BMI and higher fatigability among those who had a normal weight (for BMI between 18.5 and 25: OR = 0.94, 95% CI: 0.83-1.06 for RPE ≥ 10), but a positive association was observed among the participants living with overweight and obesity (for BMI ≥ 25: OR = 1.11, 95% CI: 1.06-1.16 for RPE ≥ 10) (data not shown).

To further understand the association between central obesity and perceived fatigability, we compared participants with high versus normal waist circumference within each BMI group (Figure 1). Presenting with overweight or obesity was not associated with greater odds of higher fatigability, but having obesity increased the odds of higher fatigability by 94% (Model 3, OR = 1.94, 95% CI: 1.28-2.91 for RPE ≥ 10) compared with those with normal BMI. Tests for nonlinearity between BMI and high RPE indicated no association between BMI and higher fatigability among those who had a normal weight (for BMI between 18.5 and 25: OR = 0.94, 95% CI: 0.83-1.06 for RPE ≥ 10), but a positive association was observed among the participants living with overweight and obesity (for BMI ≥ 25: OR = 1.11, 95% CI: 1.06-1.16 for RPE ≥ 10) (data not shown).

Standardized beta coefficients suggest that continuous BMI, hip circumference, and visceral fat area have the strongest associations with
perceived fatigability (Table 2, standardized $\beta=0.13$ for all). However, given that the sample sizes for BMI ($n=1,054$) and hip circumference ($n=1,043$) were more than double that of the CT sample ($n=383$), separate analyses were performed that restricted the sample to the 383 participants who received CT scans. In this restricted sample, only the association between visceral fat and fatigability remained significant ($\beta=0.005$ RPE, $P<0.001$).

Sensitivity analyses excluding the 53 women who had not gone through menopause did not materially alter the results. Furthermore, including serum total cholesterol and fasting glucose as covariates yielded no significant differences.

## Discussion

Findings indicate that high perceived fatigability is common among well-functioning, community-dwelling volunteers aged 40 and older, and that the presence of obesity substantially increases the likelihood of having higher fatigability by 94% compared with participants with normal weight. Furthermore, nearly all measures of adiposity except for subcutaneous adipose fat were associated with greater fatigability, independent of chronic health conditions. Together, these results suggest that obesity is a strong risk factor for higher fatigability with aging, which may exacerbate the well-established risks between muscle-mass loss, low physical activity, and functional decline with aging (4,5,10).

Among participants with normal weight, there was no association between BMI and fatigability. However, among participants with overweight and obesity, each one-unit increase in BMI was associated with 0.11 higher RPE. These findings indicate that the relationship between BMI and fatigability is nonlinear and suggest that small increments of weight gain may be more detrimental among those who already have overweight or obesity. This may be an indication of biomechanical or metabolic inefficiencies that contribute to higher energy costs for mobility (25) and/or lower physical activity (26,27) for those with greater adiposity, inducing a cycle of higher fatigability, low activity, and further weight gain (28).

Central adiposity showed a particularly strong association with fatigability. For participants with overweight or obesity, only those with...
### TABLE 2 Fully adjusted linear and logistic regression models for perceived fatigability (RPE), high fatigability (RPE ≥ 10), and measures of adiposity

#### Continuous analyses

| Model | Predictor                  | n     | β for RPE | Standardized β | 95% CI         | P     |
|-------|----------------------------|-------|-----------|----------------|----------------|-------|
| 1     | Fat, %b                    | 1,023 | 0.03      | 0.10           | 0.001 to 0.052 | 0.045 |
| 2     | BMI, kg/m²                 | 1,054 | 0.07      | 0.13           | 0.038 to 0.095 | <0.001|
| 3     | WC, cm                     | 1,043 | 0.02      | 0.11           | 0.007 to 0.030 | 0.001 |
| 4     | High WC                    | 1,043 | 0.55      | —              | 0.284 to 0.821 | <0.001|
| 5     | Hip circumference, cm      | 1,043 | 0.03      | 0.13           | 0.017 to 0.044 | <0.001|
| 6     | Waist to height ratio      | 1,043 | 0.33      | 0.1            | 0.143 to 0.520 | 0.001 |
| 7     | Visceral fat area, cm²b    | 383   | 0.005     | 0.13           | 0.001 to 0.009 | 0.010 |
| 8     | Subcutaneous fat area, cm²b| 383   | 0.001     | 0.07           | −0.000 to 0.003 | 0.148 |
| 9     | Visceral/subcutaneous fat area² | 383 | 0.954     | 0.95           | −0.074 to 1.982 | 0.069 |

#### Categorical analyses

| Model | Predictor                  | n     | OR for high RPE | 95% CI     | P     |
|-------|----------------------------|-------|-----------------|------------|-------|
| 1     | Fat, %b                    | 1,023 | 1.01            | —          | 0.98 to 1.04 | 0.446 |
| 2     | BMI, kg/m²                 | 1,054 | 1.07            | —          | 1.03 to 1.11 | <0.001|
| 3     | WC, cm                     | 1,043 | 1.02            | —          | 1.01 to 1.04 | 0.003 |
| 4     | High WC                    | 1,043 | 1.59            | —          | 1.16 to 2.17 | 0.004 |
| 5     | Hip circumference, cm      | 1,043 | 1.04            | —          | 1.02 to 1.05 | <0.001|
| 6     | Waist to height ratio      | 1,043 | 1.42            | —          | 1.12 to 1.79 | 0.004 |
| 7     | Visceral fat area, cm²b    | 383   | 1.00            | —          | 0.99 to 1.00 | 0.062 |
| 8     | Subcutaneous fat area, cm²b| 383   | 1.00            | —          | 1.00 to 1.005 | 0.043|
| 9     | Visceral/subcutaneous fat area² | 383   | 1.69            | —          | 0.53 to 5.73 | 0.363 |

Each row represents fully adjusted model.

*aAdjusted for age, sex, race, number of comorbidities, and smoking history.

*bAdjusted for covariates + body weight (kilograms).

*cAdjusted for covariates + height squared (centimeters squared).

WC, waist circumference (high ≥ 102 cm for men; ≥ 88 cm for women).

### TABLE 3 Adjusted differences in RPE and OR for high RPE by BMI category, stratified by age

#### Continuous analysis

| Age category | n     | β for RPE, overweight | P     | β for RPE, obesity | P     |
|--------------|-------|-----------------------|-------|--------------------|-------|
| <65 years    | 308   | 0.004                 | 0.987 | 0.399              | 0.149 |
| ≥65 years    | 746   | 0.335                 | 0.060 | 1.124              | <0.001|

#### Categorical analysis

| Age category | n     | OR for high RPE, overweight | P     | OR for high RPE, obesity | P     |
|--------------|-------|-----------------------------|-------|---------------------------|-------|
| <65 years    | 308   | 0.99                        | 0.989 | 1.84                      | 0.227 |
| ≥65 years    | 746   | 1.44                        | 0.060 | 2.22                      | 0.001 |

Adjusted for age, sex, race, number of comorbidities, and smoking history.

Participants with normal weight (BMI between 18.5 and 25) are reference in each age category.
a high waist circumference had higher fatigability than participants with normal weight. Furthermore, within the group of participants with overweight, those with central obesity had greater perceived fatigability than those without central obesity. These findings are consistent with the literature on central obesity, which show that individuals with overweight and central obesity have greater overall mortality and higher cardiovascular risk relative to those without central obesity (29). Standardized coefficients indicate that a simple measure of BMI or hip circumference may infer as much meaning about the risk of fatigability as more sophisticated measures of body composition derived from dual-energy x-ray absorptiometry and further emphasize the detrimental association of central obesity. Nevertheless, results from the analysis restricted to the sample with CT measures suggest that visceral adipose tissue may be the single most important factor in predicting fatigability risk. These findings are consistent with previous studies showing a strong association between visceral fat and metabolic health and inflammation (30,31), which may provide insights into mechanisms of fatigability. A plausible explanation of this association is that inflammatory markers, elevated in persons with excess body weight, may act at the level of the central nervous system to reduce levels of physical activity. Furthermore, previous research has linked higher inflammation with greater fatigability, but the role of visceral adipose tissue was not explored (17,32). Future longitudinal follow-up is warranted to further elucidate the magnitude and temporality of this association with aging.

Our findings are consistent with the previous literature, particularly the nonlinear association between BMI and fatigability, recently shown by Cooper et al. (17). The current findings expand on this knowledge by exploring type and location of adiposity as well as including a broader age range. Although there is currently no clinical threshold for RPE scores, to put our results in some context, we compared the differences in RPE that we found with the β coefficients for age from the same regression models. The difference in RPE score between participants with overweight who had central obesity versus those who did not (0.49 RPE score) was equivalent to a 5.4-year difference in age. Similarly, the difference between participants with normal weight and those with obesity who had high waist circumference (0.81 RPE score) was equivalent to a 10.13-year difference in age. Together, these results suggest that relatively small increments on the RPE scale translate to substantial differences in age. Importantly, the age-stratified analysis found that the association between BMI and fatigability was only present in participants 65 years and older, suggesting that the effect of excessive adipose tissue on fatigability may become more relevant in older age.

This study has limitations. The participants of the BLSA, even those with obesity, are healthier than the general population, making the findings less generalizable. In the general population, in which the prevalence of chronic conditions is higher, it is likely that the association between adiposity and fatigability would be even greater because of the coexistence of several factors that increase fatigability, such as cardiovascular diseases (33), chronic inflammation (17,32), and cancer (34), among others. Furthermore, because of the cross-sectional design, we were unable to assess temporality of the adiposity and fatigability association or how change in adiposity affects change in fatigability. Future longitudinal follow-up and replication in more generalizable cohorts is warranted to refine these results and help define clinically meaningful thresholds of fatigability.

Fatigability is associated with poorer physical function (15,16) and reduced physical activity in older adults (27). As fatigue and fatigability are common in mid- to late life, it is essential to identify potentially modifiable risk factors, amenable for intervention that may delay declines in physical function and physical activity, that lead to disability and poor quality of life (35). Measures of adiposity, particularly central adiposity, were strongly associated with fatigability, even among well-functioning middle-aged and older adults. These associations were strongest among those aged 65 or older, suggesting that weight management during midlife and may be an effective target for curbing fatigability and maintaining quality of life in older age.
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