


# Phenotypic differences between people varying in muscularity

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## Abstract

**Background** Body mass is the primary metabolic compartment related to a vast number of clinical indices and predictions. The extent to which skeletal muscle (SM), a major body mass component, varies between people of the same sex, weight, height, and age is largely unknown. The current study aimed to explore the magnitude of muscularity variation present in adults and to examine if variation in muscularity associates with other body composition and metabolic measures.

**Methods** Muscularity was defined as the difference (residual) between a person's actual and model-predicted SM mass after controlling for their weight, height, and age. SM prediction models were developed using data from a convenience sample of 492 healthy non-Hispanic (NH) White adults (ages 18–80 years) who had total body SM and SM surrogate, appendicular lean soft tissue (ALST), measured with magnetic resonance imaging and dual-energy X-ray absorptiometry, respectively; residual SM (SM<sub>R</sub>) and ALST were expressed in kilograms and kilograms per square meter. ALST mass was also evaluated in a population sample of 8623 NH-White adults in the 1999–2006 National Health and Nutrition Examination Survey. Associations between muscularity and variation in the residual mass of other major organs and tissues and resting energy expenditure were evaluated in the convenience sample.

**Results** The SM, on average, constituted the largest fraction of body weight in men and women up to respective BMIs of 35 and 25 kg/m<sup>2</sup>. SM in the convenience sample varied widely with a median of 31.2 kg and an SM<sub>R</sub> inter-quartile range/min/max of 3.35 kg/−10.1 kg/9.0 kg in men and 21.1 kg and 2.59 kg/−7.2 kg/7.5 kg in women; per cent of body weight as SM at 25th and 75th percentiles for men were 33.1% and 39.6%; corresponding values in women were 24.2% and 30.8%; results were similar for SM<sub>R</sub> indices and for ALST measures in the convenience and population samples. Greater muscularity in the convenience sample was accompanied by a smaller waist circumference (men/women:  $P < 0.001/0.085$ ) and visceral adipose tissue ( $P = 0.014/0.599$ ), larger liver ( $P = 0.065/<0.001$ ), kidneys ( $P = 0.051/<0.009$ ), and bone mineral ( $P < 0.001/<0.001$ ), and larger magnitude resting energy expenditure ( $P < 0.001/<0.001$ ) than predicted for the same sex, age, weight, and height.

**Conclusions** Muscle mass is the largest body compartment in most adults without obesity and is widely variable in mass across people of similar body size and age; and high muscularity is accompanied by distinct body composition and metabolic characteristics. This previously unrecognized heterogeneity in muscularity in the general population has important clinical and research implications.

**Keywords** Body composition; Skeletal muscle mass; Adiposity; Resting energy expenditure

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## Introduction

Body weight, including its portion related to stature, is the primary metabolic compartment related to a vast number of clinical indices and predictions. Body mass index (BMI) is the most widely used of these weight-related measures that associates with adiposity and an array of clinical conditions and outcome measures.<sup>1</sup> However, even after adjusting weight for height squared, BMI is only moderately associated with measures such as adiposity; correlations with per cent (%) fat in men and women leave 43% and 34% of the variance unaccounted for, respectively.<sup>2</sup>

Basal metabolic rate, or resting energy expenditure (REE), may be only second to BMI as a globally used measure predicted from body weight, height, and in some cases age in clinical settings.<sup>3</sup> Resting energy expenditure equations typically only account for about 47% and 62% of between individual differences in measured REE in men and women, respectively.<sup>4</sup> As with BMI–%fat associations, 53% and 38% of the variance in respective REE predictions based on weight, height, and age go unaccounted for.

A well-recognized limitation of body weight when applied as an adiposity or metabolic compartment surrogate is that people of similar weight, height, and age can vary greatly in their body composition proportions, notably in muscularity. Extreme enlargement of the skeletal muscle (SM) compartment is well recognized among athletes, primarily body builders, and is often cited as a basis for obesity misclassification.<sup>5–7</sup> That is, for the same BMI, body builders have a smaller percentage of body weight as fat mass than their sex-matched and age-matched inactive counterparts. Similarly, people of the same sex, age, and body mass but who differ in muscularity will also differ in REE; for the same mass, SM has a three-fold higher mass-specific metabolic rate than does adipose tissue.<sup>3</sup> Sparingly little is known about how muscularity and its accompanying physical and metabolic effects vary between people in the general population.

Most studies extending from body weight to body composition focus on between-individual differences in total body fat mass and related fat-free mass (FFM, body weight minus fat mass) as a source of variability in body weight indices or prediction equations.<sup>8</sup> However, an equally plausible hypothesis is that weight measures such as BMI and predictions such as REE fail to account for between individual differences in muscularity; that is, the relative anatomic and metabolic contributions of SM to body mass. While several studies have explored the associations of REE with SM,<sup>9–15</sup> data are limited as only a few centres currently quantify whole-body SM<sup>16</sup> along with other body composition and metabolic measures.

Understanding variation in adult muscularity might improve our grasp of the many body weight indexes and prediction models used in research and clinical settings by informing users on the magnitude of body composition heterogeneity in the general population. Moreover, this

information can open new research opportunities on how to identify and quantify individual differences in muscularity. Explorations such as these can go beyond simply aggregating SM mass into the large and heterogeneous FFM compartment. If muscularity is highly variable between people in the general population, what mechanisms might account for this phenotypic heterogeneity?

At present there are no firm definitions of the noun ‘muscularity’ other than ‘the degree of muscleness or amount of muscle in the human body’.<sup>17</sup> We fill this void by applying a working quantitative definition of muscularity as a physical trait describing how individuals differ in their SM mass beyond that accounted for by their sex, weight, height, and age. A person with a relatively large muscle mass according to this approach is characterized by the adjective ‘muscular’. A person with a relatively low muscle mass according to this definition might be considered hypomuscular or even sarcopenic, although at present no formal taxonomy is applied to this physical state. The aims of the current study were twofold: to explore the magnitude of variation in adult muscularity and to determine if the observed heterogeneity in muscularity is associated with other anthropometric (waist circumference), body composition (regional/whole-body adipose tissue and organs), and metabolic (REE) characteristics. The collective observations were compiled to create a distinct phenotype of people who are ‘muscular’ according to the applied working definition of muscularity.

## Methods

### Study design

The first study aim, to explore between-individual variation in muscularity, was examined in two groups, one a convenience sample of healthy non-Hispanic (NH) White adults and the other a large population sample of NH White adults. The convenience sample was composed of 492 adults 18 years of age and older who had total body SM mass measured by whole-body magnetic resonance imaging (MRI) as part of deep phenotyping studies at the Institute of Human Nutrition, Kiel University, Germany.<sup>18–21</sup> Regression analysis was used to develop sex-specific SM prediction models for the whole sample that included weight, height, and age as covariates. An individual’s muscularity status was then quantified as the difference (residual, in kg) between their measured total body SM mass and that predicted for their weight, height, and age. A relatively muscular person according to this approach has a larger SM mass than expected for their sex, weight, height, and age and has a positive value for residual SM ( $SM_R$ ). Residual SM mass was also expressed as an index analogous to BMI,  $SM_R$  mass/height<sup>2</sup> ( $SMI_R$ ); as with body weight, SM scales to height in adults with a power of

$\sim 2$ , and thus,  $SM/height^2$  is a height-independent measure of SM mass.<sup>22</sup>

Participants in the Kiel sample also had the SM surrogate, appendicular lean soft tissue (ALST) mass, measured with dual-energy X-ray absorptiometry (DXA).<sup>23,24</sup> ALST mass combines the DXA arm and leg lean mass estimates, and together, these extremity measurements are highly correlated with total body SM.<sup>23,24</sup> These surrogate SM estimates complemented those from the population sample, described later, that included DXA but not MRI evaluations. We confirmed the strong associations between ALST and total body SM in the Kiel sample, and details of these observations and analyses are presented in *Supporting information*. Residual ALST ( $ALST_R$ ) and  $ALST_R$  index ( $ALSTI_R$ ) were then derived for each participant as they were for SM. Variability in muscularity was explored by generating the distributions of  $SM_R$  and  $ALST_R$  and their related indices in the Kiel men and women.

The findings on variation in muscularity in the Kiel sample were extended to a population sample that included 8623 NH White adults evaluated as part of the 1999–2006 National Health and Nutrition Survey (NHANES).<sup>25</sup> Details on the NHANES sampling strategy can be found at the Center for Disease Control and Prevention web site.<sup>25</sup>

Our aim was to examine variation in muscularity in the NHANES population sample without boundaries set by excluding adults with medical conditions or those participating in exercise programmes. The choice of NHANES race/ethnic group, NH White, was based on maintaining consistency across the two study samples; variation in muscularity across other race and ethnic groups was not explored. Race and ethnicity are self-identified in NHANES as previously reported.<sup>26</sup> ALST mass was also measured with DXA in the 1999–2006 NHANES. Sex-specific prediction models were developed for ALST in the NHANES sample with weight, height, and age as potential covariates. The difference between measured and predicted ALST by the model (residual ALST and  $ALST_R$ ) and  $ALSTI_R$  were then derived for each participant as they were in the Kiel sample. The distributions of  $ALST_R$  and  $ALSTI_R$  were examined in the NHANES population sample as they were in the convenience Kiel sample.

The second study aim, to explore muscularity-body composition and metabolic associations, was examined in the Kiel sample. Residual component mass and residual REE were calculated as the differences between a person's actual component mass or REE and that predicted for their sex, weight, height, and age. Correlations between  $SM_R$  and the residual mass of each organ/tissue and REE were derived as it was for SM.

### Data sources/study population

The Kiel participants were ambulatory and engaged in domestic, occupational, and/or recreational physical activities;

none reported specific exercise training programmes or were competitive athletes. Kiel participants all had complete SM, weight, height, and age measurements. Subgroups of these participants had measurements of organ/tissue mass by MRI (brain, liver, kidney, heart, spleen, and adipose tissue), ALST and bone mineral content (BMC) measured by DXA, and REE evaluated by indirect calorimetry; respective sample sizes are given in the Results section. These studies were approved by the Kiel University Institutional Review Board, and all participants signed an informed consent prior to evaluation.

Participants included in the NHANES sample were age 18 years and older with complete weight, height, age, and DXA data; those excluded had a history of amputations, were pregnant, or not in the NHANES race/ethnic category of NH White. Participants were excluded from the DXA examination if their weight exceeded 136 kg, height was above 1.96 m, or if they had a contrast-based radiological nuclear examination in the previous 72 hours. The disposition of NHANES participants in the current study is summarized in *Supporting information*. The NHANES protocols were approved by the institutional review board of the National Center for Health Statistics, Centers for Disease Control and Prevention, and all participants provided written informed consent.

### Measurements

Details of the Kiel measurement protocol are reported in previous publications.<sup>18–21</sup> Participant body weight and height were measured to the nearest 0.01 kg and 0.5 cm, using a digital scale (Tanita, Tokyo, Japan) and mechanical stadiometer (Seca, Hamburg, Germany), respectively. Waist circumference was measured under the midline of the participant's armpit, at the midpoint between the lower part of their last rib and the top of their hip. Adipose tissue, SM, heart, liver, kidney, spleen, and brain total volumes were measured using a 1.5 T Magnetom Vision or Avanto Siemens scanner (Siemens Medical Systems, Erlangen, Germany).<sup>20</sup> Subcutaneous adipose tissue and SM were measured in both arms and legs and in the trunk; the total visceral adipose tissue compartment was also quantified. The cross-sectional scan images were manually segmented by a trained analyst using SliceOmatic software (version 4.3, Tomovision, Montreal, Canada). Organ and tissue volumes were converted to mass using previously reported component densities.<sup>20</sup> Appendicular lean soft tissue mass and BMC were measured using a QDR 4500A DXA system (Hologic, Marlborough, Massachusetts) with software version V8.26a:3.<sup>19</sup>

Resting energy expenditure was quantified in the early morning after an overnight fast with an open circuit Vmax Spectra 29n indirect calorimetry system (SensorMedics, Viasys Healthcare; software V-max version 12-1A).<sup>27</sup> The measurement room was kept at a constant temperature

and humidity on a metabolic ward; minimum measurement duration was 45 min with the first 10 min excluded. The coefficient of variation for repeated REE measurements in our laboratory is 5%. Data collection and calibration procedures are reported by Bosy-Westphal *et al.*<sup>28</sup>

Details of the NHANES measurement protocols are reported in previous publications.<sup>29–31</sup> ALST mass was measured in NHANES using a Hologic QDR 4500A fan beam X-ray bone densitometer (Hologic Inc., and Hologic Discovery software, version 12.1).

## Statistical analysis

The data analyses progressed in three stages. Muscularity varies across men and women; for the same weight, height, and age, men have more SM than women.<sup>32–34</sup> This difference in muscularity can largely be accounted for by sex differences in adiposity; women have more adipose tissue than men of the same weight, height, and age. Not much beyond these empirical observations is reported on the sexual dimorphism in muscularity. Accordingly, in the first series of analyses, we examined how SM and adipose tissue vary as a function of body size and shape in the Kiel men and women.

The second series of analyses examined the variability in  $SM_R$ ,  $ALST_R$ , and their respective indices present in Kiel and NHANES men and women. The  $SM_R$  and  $ALST_R$  prediction models were fit using regression analysis with sex-specific models including weight, height, and age and their potential powers and interactions as independent variables. The variation in  $SM_R$  and  $ALST_R$  and their respective indices are reported in the text and figures as the 25th, 50th (median), and 75th percentiles, mean, and inter-quartile range (IQR). The X in these figures denotes the sample mean. Whisker end points are the maximum and minimum values below or above the median at 1.5 times the IQRs. Values exceeding 1.5

times the IQRs were considered outliers. The organ/tissue and REE regression models and residuals were derived as they were for SM and ALST.

A complex multistage sampling strategy is applied in NHANES, and probability sampling weights are applied to account for survey non-response, over-sampling, post-stratification, and sampling errors.<sup>25</sup> The ALST prediction model with weight, height, age, and sex as potential covariates was developed using the survey weights. The prediction model was then used to derive  $ALST_R$  in the NHANES participants as in the Kiel sample. Any observations missing data were also excluded.

The NHANES DXA body composition data require fitting separate models for each of five imputed data sets.<sup>29–31</sup> The analyses were carried out using procedures for sample survey data in R with *survey* and *mitools* packages to produce nationally representative estimates while accommodating for the complex, multistage NHANES design. The standard errors (SEs) were calculated using Taylor series linearization with statistical significance defined as  $P < 0.05$  (two tailed).

The third and final series of analyses, conducted in the Kiel sample, explored associations between  $SM_R$  and corresponding residual organ/tissue and REE estimates. Descriptive statistics of the two study cohorts are reported as the mean  $\pm$  standard deviation (SD) in the text and tables and as the mean  $\pm$  SE in the figures.

## Results

### Sample characteristics

The baseline characteristics of the evaluated Kiel and NHANES participants are summarized in Table 1. The Kiel sample included 241 men and 251 women who had complete

**Table 1** Kiel and NHANES sample demographic and body composition characteristics

	Kiel			NHANES		
	Men	Women	Total	Men	Women	Total
N	241	251	492	4399	4224	8623
Age (years)	41.8 $\pm$ 16.1	40.6 $\pm$ 15.5	41.2 $\pm$ 15.7	47.1 $\pm$ 16.5	45.0 $\pm$ 17.3	46.1 $\pm$ 17.0
Weight (kg)	87.6 $\pm$ 17.2	81.1 $\pm$ 23.1 <sup>a</sup>	84.3 $\pm$ 20.7	88.6 $\pm$ 19.2	74.0 $\pm$ 19.2 <sup>a</sup>	81.2 $\pm$ 20.5
Height (cm)	179.1 $\pm$ 6.2	167.0 $\pm$ 7.0 <sup>a</sup>	173.2 $\pm$ 8.7	177.5 $\pm$ 7.2	163.2 $\pm$ 6.5 <sup>a</sup>	170.3 $\pm$ 9.9
BMI (kg/m <sup>2</sup> )	27.3 $\pm$ 5.0	28.8 $\pm$ 7.4 <sup>a</sup>	28.1 $\pm$ 6.4	28.1 $\pm$ 5.7	27.8 $\pm$ 6.9 <sup>a</sup>	27.9 $\pm$ 6.4
SM (kg)	31.4 $\pm$ 5.3	21.6 $\pm$ 4.3 <sup>a</sup>	28.1 $\pm$ 6.4	—	—	—
SMI (kg/m <sup>2</sup> )	9.8 $\pm$ 1.5	7.7 $\pm$ 1.2 <sup>a</sup>	8.7 $\pm$ 1.7	—	—	—
SM (%)	36.3 $\pm$ 4.4	27.5 $\pm$ 4.4 <sup>a</sup>	31.8 $\pm$ 6.3	—	—	—
ALST <sup>b</sup> (kg)	29.6 $\pm$ 4.4	21.0 $\pm$ 4.4 <sup>a</sup>	24.9 $\pm$ 6.2	26.9 $\pm$ 4.8	17.6 $\pm$ 3.7 <sup>a</sup>	26.8 $\pm$ 6.3
ALSTI (kg/m <sup>2</sup> )	9.3 $\pm$ 1.2	7.4 $\pm$ 1.3 <sup>a</sup>	8.2 $\pm$ 1.5	8.5 $\pm$ 1.3	6.6 $\pm$ 1.2 <sup>a</sup>	7.5 $\pm$ 1.6
ALST (%)	33.6 $\pm$ 3.5	27.0 $\pm$ 3.5 <sup>a</sup>	30.0 $\pm$ 4.8	30.7 $\pm$ 3.3	24.2 $\pm$ 3.3 <sup>a</sup>	27.4 $\pm$ 4.6

ALST, appendicular lean soft tissue; ALSTI, appendicular lean soft tissue index; BMI, body mass index; NHANES, National Health and Nutrition Survey; SM, skeletal muscle mass; SMI, skeletal muscle mass index.

Results are shown as mean  $\pm$  SD.

<sup>a</sup>Between-sex group differences (*t* test)  $P < 0.001$ .

<sup>b</sup>Kiel sample size: 178 men and 208 women.



SM, weight, height, and age measurements. Of that sample, 380 adults, 178 men and 208 women, had complete data for the ALST analysis. The men and women were, on average, in their early 40s (range, 18 to 80 years) and had a BMI of about  $28 \text{ kg/m}^2$  (range, 17 to  $48 \text{ kg/m}^2$ ). The NHANES sample included 4399 men and 4224 women who had complete weight, height, age, and DXA measurements. The NHANES men and women were, on average, in their mid-40s (range, 18 to 85 years) and had a BMI of about  $27.9 \text{ kg/m}^2$  (range, 18.15 to  $48.3 \text{ kg/m}^2$ ).

### Skeletal muscle

Kiel men had  $31.4 \pm 5.3 \text{ kg}$  of SM and a SM index (SMI) of  $9.8 \pm 1.5 \text{ kg/m}^2$ . Kiel women had  $21.6 \pm 4.3 \text{ kg}$  of SM and a SMI of  $7.7 \pm 1.2 \text{ kg/m}^2$ . The percentage of body weight as SM in the Kiel sample was larger in men than in women ( $36.3 \pm 4.4$  vs.  $27.5 \pm 4.4\%$ ;  $P < 0.001$ ) (Table 1).

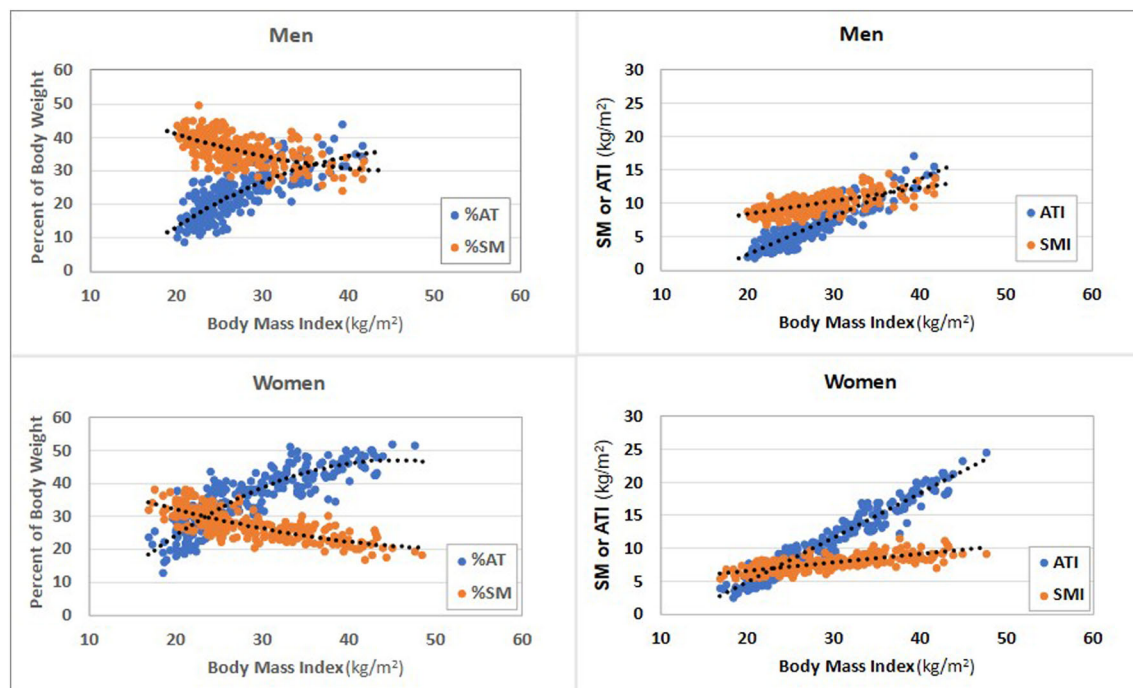
There was a reciprocal relationship between per cent of body weight as SM and adipose tissue as a function of BMI in the Kiel men and women (Figure 1). With increasing BMI, there was a curvilinear decrease in SM as a per cent of body weight accompanied by a curvilinear rise in the per cent of body weight as adipose tissue. SM was a larger percentage

body weight than adipose tissue in the men up to a BMI of about  $35 \text{ kg/m}^2$ , a level much higher than that present in the women of about  $25 \text{ kg/m}^2$ . Adipose tissue prevails beyond the BMI levels of 35 and  $25 \text{ kg/m}^2$  in men and women, respectively. The figure shows the wide variation in percentage of body weight as SM at any level of BMI.

Unlike the curvilinear functions relating per cent SM and adipose tissue as a function of BMI, the functions adipose tissue mass/height<sup>2</sup> and SM/height<sup>2</sup>, indices comparable to BMI, vs. BMI were linear (Figure 1). SM and adipose tissue indices in men accounted for 49% and 86% of the variance in BMI, respectively. When combined in a multiple regression model, SM and adipose tissue indices together in the men accounted for 97% of the variance in BMI. SM and adipose tissue indices in women accounted for 56% and 94% of the variance in BMI, respectively; the indices together accounted for 98% of the variance in BMI.

### Appendicular lean soft tissue

Kiel men had  $29.6 \pm 4.4 \text{ kg}$  of ALST and an ALST index (ALSTI) of  $9.3 \pm 1.2 \text{ kg/m}^2$ ; corresponding values in the NHANES men were  $26.9 \pm 4.8 \text{ kg}$  and  $8.5 \pm 1.3 \text{ kg/m}^2$ . Kiel women had  $21.0 \pm 4.4 \text{ kg}$  of ALST and an ALSTI of  $7.4 \pm 1.3 \text{ kg/m}^2$ ;



**Figure 1** Per cent of body weight as skeletal muscle (%SM) and adipose tissue (%AT) vs. body mass index (BMI) in Kiel men (upper left panel) and women (lower left panel); and SM mass index (SMI) and adipose tissue mass index (ATI) vs. BMI in Kiel men (upper right panel) and women (lower right panel). Index ratios calculated as component mass/height<sup>2</sup>. The data in all panels of the figure were fit with polynomial and linear regression lines. In men, skeletal muscle was a larger percentage body weight than adipose tissue up to a BMI of  $\sim 35 \text{ kg/m}^2$ , a higher level than present in the women of  $\sim 25 \text{ kg/m}^2$ . Wide variation in %SM is present at any specific level of BMI in both the men and women. Sample *N* for men, 240; women, 245.

NHANES women had  $17.6 \pm 3.7$  kg of ALST with an ALSTI of  $6.6 \pm 1.2$  kg/m<sup>2</sup>. The percentage of body weight as ALST in the Kiel and NHANES samples were larger in men than in women ( $33.6 \pm 3.5\%$  vs.  $27.0 \pm 3.5\%$  and  $30.7 \pm 3.3\%$  vs.  $24.2 \pm 3.3\%$ ; both  $P < 0.001$ ). SM index was highly correlated with ASLTI in both the men and women ( $R^2$ , 0.79 and 0.76; both  $P < 0.001$ ; Table 1).

### Variation in muscularity

The sex-specific SM mass prediction equations with weight, height, and age as covariates developed in the Kiel sample had high  $R^2$ s and low standard of the estimates (SEE) for both the men ( $R^2$ , 0.84; SEE, 2.9 kg) and women ( $R^2$ , 0.88; SEE, 2.1 kg) (Table 2). These two equations were used to derive  $SM_R$  and  $SMI_R$  for each Kiel participant. The variation in  $SM_R$  is shown for men and women in Figure 2A as box and whisker plots. The men's  $SM_R$  and  $SMI_R$  varied beyond that predicted for age, weight, and height, from  $-10.1$  to  $9.0$  kg (IQR, 3.35 kg; median, 31.2 kg) and  $-3.1$  to  $2.6$  kg/m<sup>2</sup> (IQR, 1.05 kg/m<sup>2</sup>; median, 9.6 kg/m<sup>2</sup>), respectively. The variation for  $SM_R$  and  $SMI_R$  was also large in women, from  $-7.2$  to  $7.5$  kg (IQR, 2.59 kg; median, 21.1 kg) and  $-2.56$  to  $2.4$  kg/m<sup>2</sup> (IQR, 0.94 kg/m<sup>2</sup>; median, 7.3 kg/m<sup>2</sup>), but smaller in magnitude than in the men. The per cent of body weight as SM at the 25th and 75th percentiles for men were 33.1% and 39.6%; corresponding values in women were 24.2% and 30.8%.

The ALST prediction equations with weight, height, and age as covariates had high  $R^2$ s and low SEEs for both the men (Kiel:  $R^2$ , 0.75; SEE, 2.2 kg; NHANES:  $R^2$ , 0.93; SEE, 1.9 kg) and women (Kiel:  $R^2$ , 0.82; SEE, 1.9 kg; NHANES:  $R^2$ , 0.93; SEE, 1.4 kg) (Table 2). Residual ALST was well correlated ( $P < 0.001$ ) with residual SM in both the Kiel men ( $r$ , 0.71) and women ( $r$ , 0.66) (Figure 3). ALST as measured by DXA thus similarly characterizes variation in muscularity as does MRI, the reference method for measuring SM.

As with SM,  $ALST_R$  and  $ALSTI_R$  varied widely in the Kiel men beyond that predicted for age, weight, and height, from  $-7.85$  to  $5.59$  kg (IQR, 2.85 kg; median, 29.2 kg) and  $-2.40$  to  $1.68$  kg/m<sup>2</sup> (IQR, 0.90 kg/m<sup>2</sup>; median, 9.1 kg/m<sup>2</sup>), respectively; and in NHANES from  $-11.2$  to  $9.8$  kg (IQR, 2.45 kg; median, 25.9 kg) and  $-3.3$  to  $3.2$  kg/m<sup>2</sup> (IQR, 0.78 kg/m<sup>2</sup>; median, 8.2 kg/m<sup>2</sup>) (Figure 2B), respectively.  $ALST_R$  and  $ALSTI_R$  also varied widely in the Kiel women, from  $-6.19$  to  $5.00$  kg (IQR, 2.00 kg; median, 20.0 kg) and  $-2.07$  to  $1.75$  kg/m<sup>2</sup> (IQR, 0.73 kg/m<sup>2</sup>; median, 7.2 kg/m<sup>2</sup>), respectively; and in NHANES, from  $-5.34$  to  $6.29$  kg (IQR, 1.72 kg; median, 16.7 kg) and  $-2.05$  to  $2.72$  kg/m<sup>2</sup> (0.66 kg/m<sup>2</sup>; median, 6.2 kg/m<sup>2</sup>), respectively. The per cent of body weight comprised of ALST at the 25th and 75th percentiles for Kiel men were 31.4% and 35.9% and in NHANES men 27.9% and 32.6%, 4.7%; corresponding values in Kiel women were 24.7% and 29.4% (IQR, 4.7%) and in NHANES women, 21.8% and 26.0%.

The magnitude of variation in muscularity in the Kiel sample was next evaluated by separating men and women according to  $SM_R$  tertiles; 'muscular' people in the high tertile, those with a larger SM mass than predicted for their age, weight, and height, were then compared with their lower-muscle counterparts in the low-tertile. SM mass was  $41.1 \pm 2.0\%$  of body weight in the high-tertile group of men and  $31.4 \pm 2.3\%$  in the low-tertile group ( $P < 0.001$ ), a difference of 9.7% (Figure 4). By contrast, adipose tissue in men was  $17.3 \pm 4.7\%$  of body weight in the high-tertile group and  $28.3 \pm 6.1\%$  in the low-tertile group ( $P < 0.001$ ), a difference of 11.0%. The same pattern of body composition effects was present in the women: per cent of body weight as SM in the high-tertile group ( $29.8 \pm 3.8\%$ ) exceeded that of the low-tertile group ( $24.5 \pm 4.0\%$ ;  $P < 0.001$ ;  $\Delta$ , 5.3%); and the per cent adipose tissue in the high-tertile group of  $33.6 \pm 8.4\%$  was lower than that of the low-tertile group ( $38.1 \pm 8.3\%$ ;  $P < 0.001$ ) by 4.6%. Variation in muscularity is thus reciprocally related to corresponding between-individual differences in adiposity.

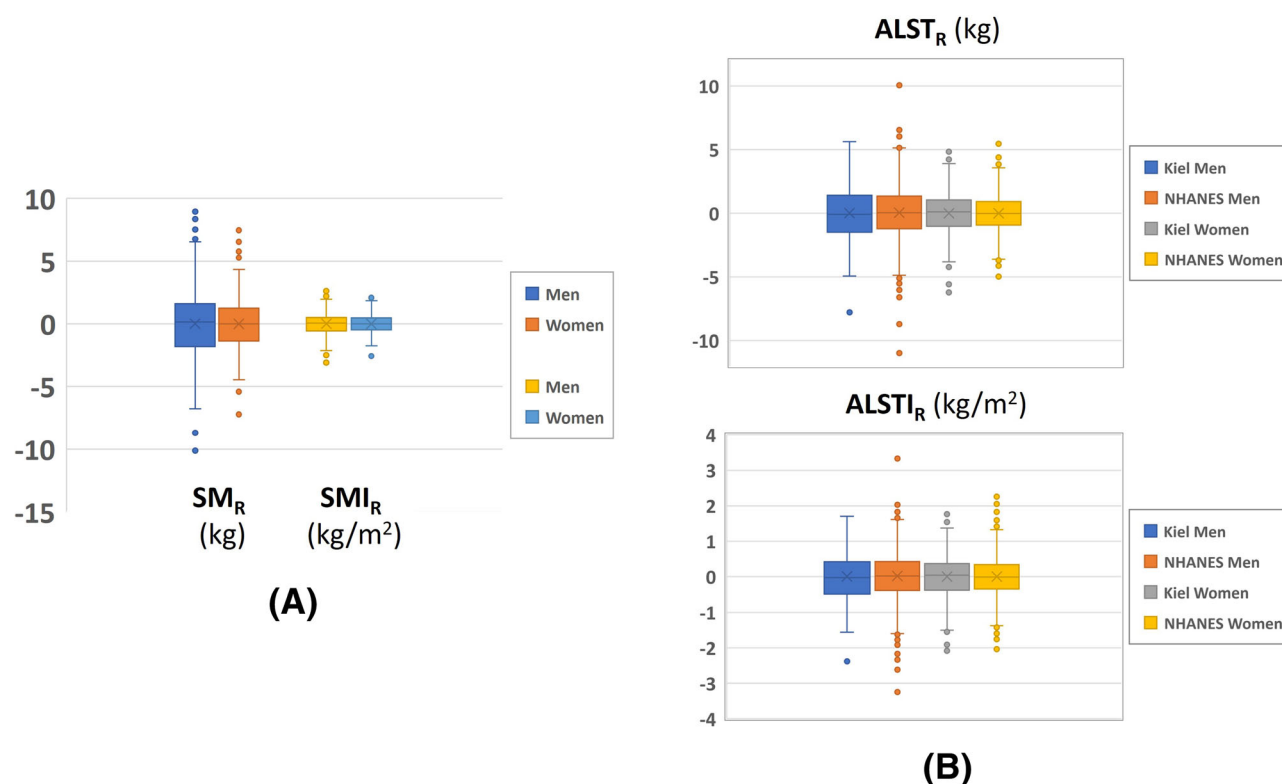
**Table 2** Skeletal muscle and appendicular lean soft tissue (ALST) mass prediction models with weight, height, and age as covariates developed on the Kiel and NHANES samples in men and women

Group	Model <sup>a</sup>	$R^2$	SEE <sup>b</sup>
Skeletal muscle (kg)			
Kiel			
Men ( $n = 178$ )	$0.204 \times W + 0.129 \times H + 0.164 \times A - 0.003 \times A^2 - 10.9$	0.84	2.9
Women ( $n = 208$ )	$0.113 \times W + 0.190 \times H - 0.052 \times A - 17.3$	0.88	2.1
ALST (kg)			
Kiel			
Men ( $n = 172$ )	$0.186 \times W + 0.148 \times H - 0.033 \times A - 12.2$	0.75	2.2
Women ( $n = 208$ )	$0.161 \times W + 0.153 \times H - 0.022 \times A - 16.7$	0.82	1.9
NHANES			
Men ( $n = 4399$ )	$0.202 \times W + 0.127 \times H - 0.063 \times A - 10.6$	0.93	1.9
Women ( $n = 4224$ )	$0.162 \times W + 0.093 \times H - 0.035 \times A - 7.9$	0.93	1.4

A, age (years); ALST, appendicular lean soft tissue (kg); H, height (cm); NHANES, National Health and Nutrition Survey; SM, skeletal muscle; W, weight (kg).  $R^2$  from NHANES model calculated from first imputation only.

<sup>a</sup>All  $P$  values are  $< 0.001$ .

<sup>b</sup>SEE calculated as the standard error of the residuals.



**Figure 2** (A) Variation in residual SM mass ( $SM_R$ ) and index ( $SMI_R$ ) present in the Kiel men ( $N$ , 241) and women ( $N$ , 251) presented as box-whisker plots. For men, %SM at the 25th and 75th percentiles were 33.1% and 39.6%, and for women 24.2% and 30.8%. (B) Variation in residual ALST mass ( $ALST_R$ ) and index ( $ALSTI_R$ ) present in the Kiel and NHANES men ( $N$ , 172/4,399) and women ( $N$ , 208/4,224). In Kiel men, %ALST at the 25th and 75th percentiles were 31.4% and 35.9%; in NHANES men, 27.9% and 32.6%; in Kiel women, 24.7% and 29.4%; and in NHANES women, 21.8% and 26.0%.

### Body composition–metabolic associations

The associations between  $SM_R$  and residual organ/tissue mass, visceral adipose tissue, waist circumference, and REE are summarized for the Kiel participants in Table 3. Consistent with the adiposity findings presented earlier,  $SM_R$  was inversely correlated with residual total (men, women;  $P < 0.001$ ) and visceral (men,  $P = 0.014$ ; women,  $P = 0.599$ ) adipose tissue mass. Residual SM mass was also negatively correlated with residual waist circumference in men ( $P < 0.001$ ) but not in women ( $P = 0.085$ ). Greater muscularity was thus accompanied by less visceral adipose tissue and a smaller waist circumference, although these associations were weaker or non-significant in the women.

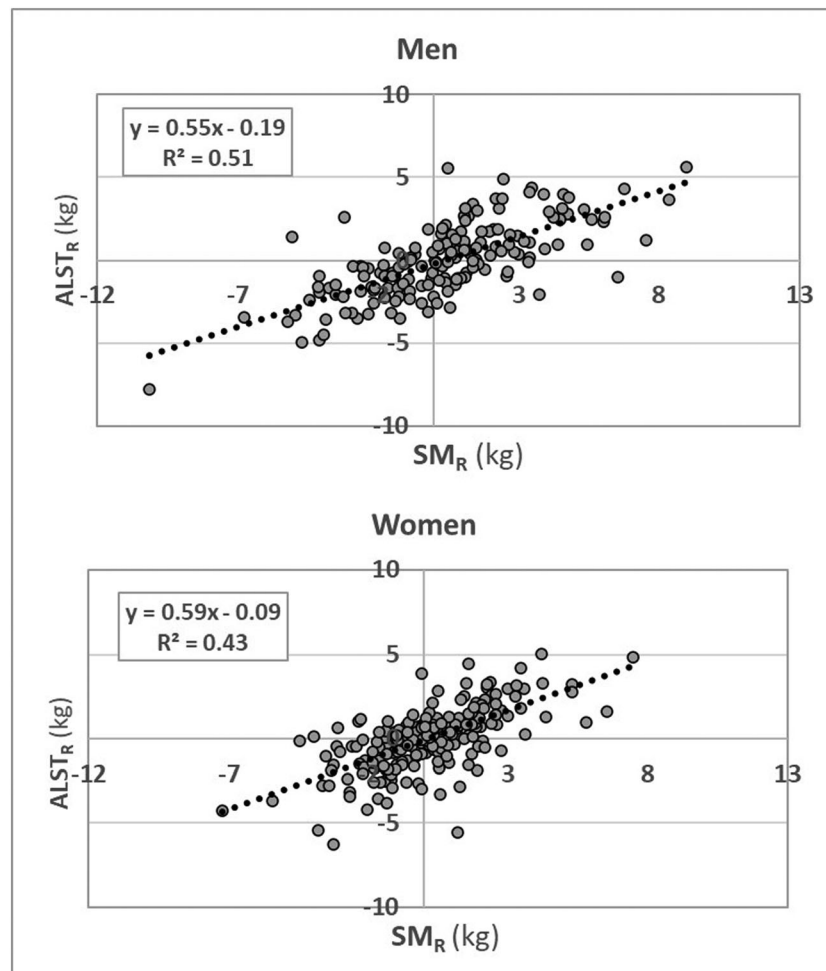
Positive associations were present between  $SM_R$  and residual liver, kidney, heart, and spleen mass. The associations between  $SM_R$  and residual liver mass were significant in women ( $P < 0.001$ ) and borderline significant in men ( $P = 0.065$ ). The associations between  $SM_R$  and residual kidney mass were significant in both the men and women ( $P < 0.051$  and  $P = 0.009$ , respectively); the other  $SM_R$ –organ associations for heart and spleen were non-significant. The prediction models used to develop residual brain mass estimates were much weaker than those for the other organs (e.g.  $R^2$ s  $\sim 0.1$  vs.  $\sim 0.7$ ), and

the correlations between residual brain mass and  $SM_R$  were non-significant in both the men and women.

Residual SM mass was also significantly correlated with residual DXA-measured ALST ( $P < 0.001$ ) and BMC ( $P < 0.001$ ) in men and women. Residual SM mass was significantly correlated with residual REE in both men ( $P < 0.001$ ) and women ( $P < 0.001$ ). The composite findings are shown in Figure 5 that characterizes the phenotypic differences between people varying in muscularity.

### Discussion

The current study is the first, to our knowledge, that comprehensively examines the variation present in muscularity among men and women in the general population and how this variability translates to between-individual differences in organ-tissue level body composition and related REE. Our study was prompted by the unexplained variance observed in commonly used measures of adiposity and REE that failed to account for the anatomic and metabolic effects of what we now have established as the largest body compartment, SM, in most people who are not obese.



**Figure 3** Residual ALST ( $ALST_R$ ) vs. residual SM ( $SM_R$ ) in the Kiel men ( $N$ , 172) and women ( $N$ , 208) (both,  $P < 0.001$ ). The results of linear regression analyses are presented in both panels of the figure. Variation in muscularity is thus similarly characterized by DXA estimates of ALST compared with SM as measured by the reference method, whole-body MRI.

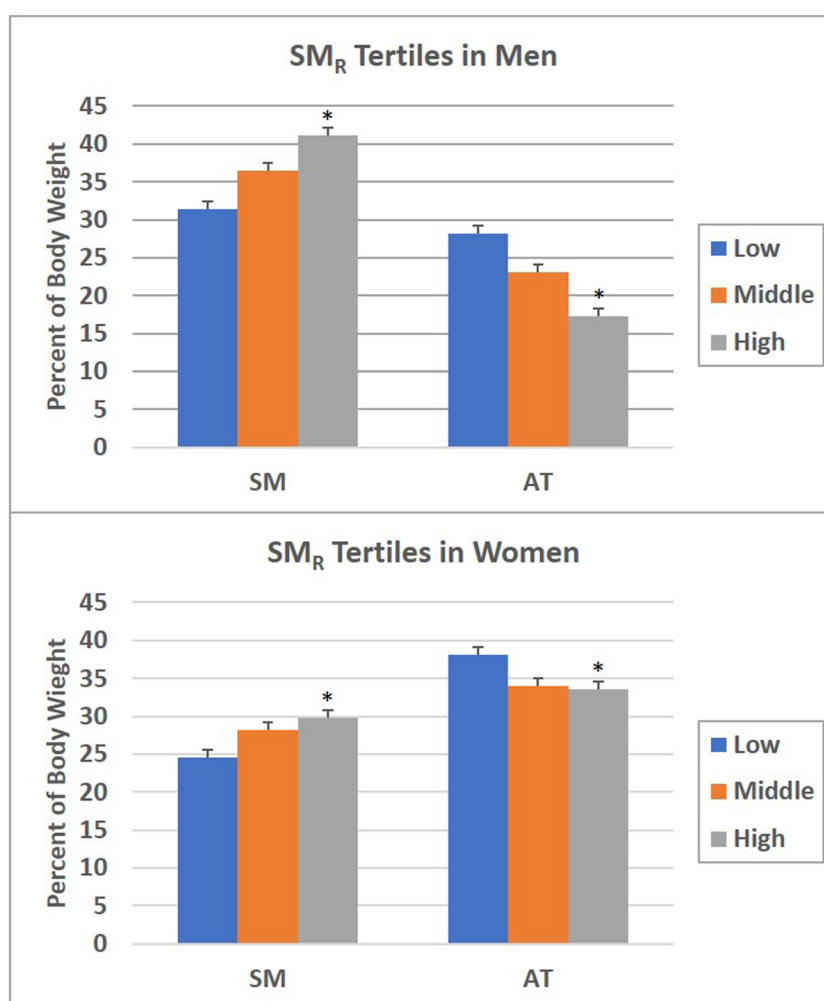
A void in the scientific literature on quantitative definitions of muscularity led us to apply a working construct with which we classified people based on the difference between their actual and predicted SM mass, or related ALST mass, according to that expected for their sex, weight, height, and age. As defined, muscularity varied widely and similarly in the men and women evaluated in two different samples. Our approach, applied across multiple measurements, uncovered distinct body composition and metabolic differences between people varying in muscularity.

### *Skeletal muscle-adipose tissue relations*

The most pervasive finding of our study was that people with greater muscularity had less adipose tissue mass than their lower muscled counterparts. Visceral adipose tissue mass, as part of the total adipose tissue compartment, was also associated with variation in muscularity. Men with a large SM

mass had less visceral adipose tissue than their low-muscle counterparts ( $P < 0.01$ ; Table 3), although the correlation between  $SM_R$  and residual visceral adipose tissue mass was non-significant in women. Persons with high muscularity also had smaller waist circumferences, but again, the effect size was borderline significant in women ( $R^2$ , 0.012;  $P = 0.08$ ) in whom the range of  $SM_R$  was smaller than in men; women also had less visceral adipose tissue than the men ( $1.8 \pm 1.1$  kg vs.  $3.4 \pm 2.2$  kg). Muscular people, notably men, thus have a distinctly different shape than their less-muscled peers with more of their body mass distributed in the extremities and upper trunk. These observations may explain why waist circumference adds to weight, height, and age in SM mass prediction models,<sup>35</sup> a finding confirmed in exploratory studies in the current study. As might be predicted from our current study results, a larger waist circumference associates with a smaller SM mass as the slope of the waist circumference covariate in SM prediction equations (men,  $P < 0.01$ ; women,  $P = 0.08$ ) was negative in models





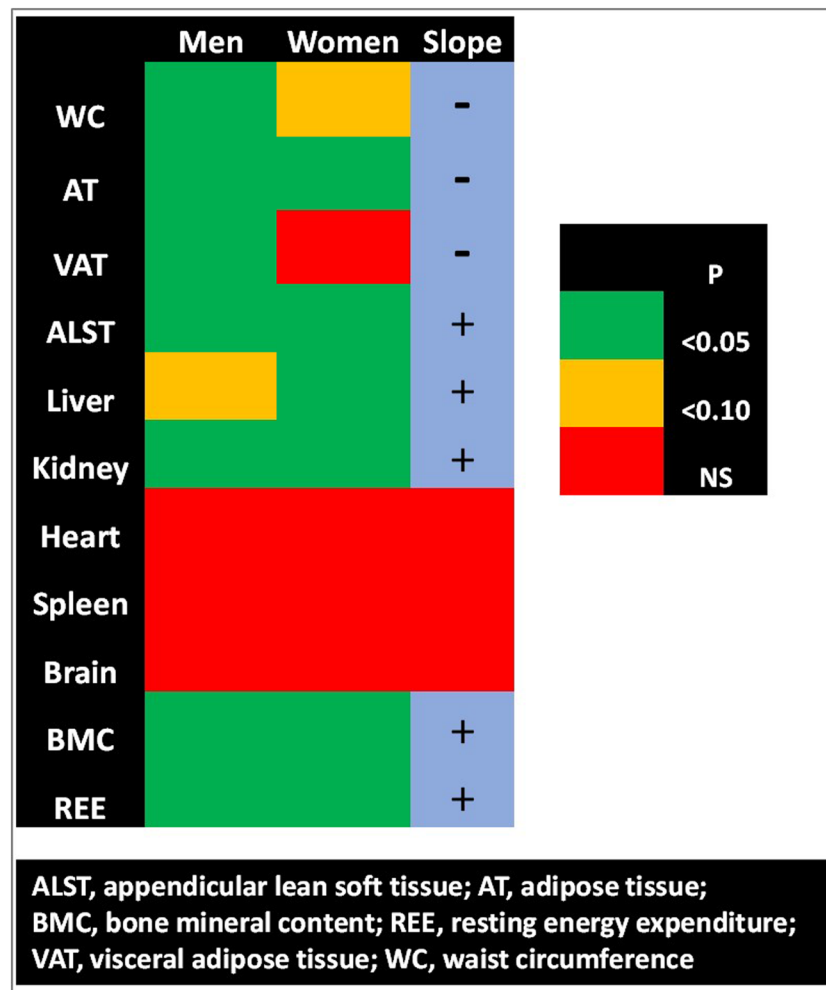
**Figure 4** Skeletal muscle (SM) and adipose tissue (AT) as a percentage of body weight in Kiel men (upper panel) and women (lower panel) as mean  $\pm$  SE within high, medium, and low SM<sub>R</sub> tertiles. Skeletal muscle in the high-tertile group of men was 9.7% larger and adipose tissue 11.0% lower compared with men in the low-tertile group. Corresponding results in women were 5.3% and 4.6%. \*  $P < 0.001$  for low vs. high-tertile group. Sample  $N$  for men, 240; women, 245.

**Table 3** Associations of residual skeletal muscle mass (SM<sub>R</sub>) with corresponding residual anthropometric, body composition, and metabolic measures

Component	Men		Women	
	Model (n)	R <sup>2</sup> (P)	Model (n)	R <sup>2</sup> (P)
WC (cm)	$-0.590 \times \text{SM}_R + 0.074$ (241)	0.165 (<0.001)	$-0.328 \times \text{SM}_R - 0.81$ (251)	0.012 (0.085)
AT (kg)	$-0.733 \times \text{SM}_R - 0.085$ (240)	0.315 (<0.001)	$-0.913 \times \text{SM}_R + 0.035$ (245)	0.330 (<0.001)
VAT (kg)	$-0.084 \times \text{SM}_R - 0.008$ (234)	0.026 (0.014)	$-0.009 \times \text{SM}_R - 0.001$ (241)	0.0012 (0.599)
Liver (kg)	$0.010 \times \text{SM}_R \times 0.004$ (172)	0.020 (0.065)	$0.030 \times \text{SM}_R + 0.001$ (184)	0.0094 (<0.001)
Kidneys (kg)	$0.003 \times \text{SM}_R - 0.012$ (191)	0.021 (0.051)	$0.005 \times \text{SM}_R + 0.000$ (207)	0.033 (0.009)
Heart (kg)	$0.002 \times \text{SM}_R + 0.001$ (188)	0.002 (NS)	$0.001 \times \text{SM}_R - 0.000$ (196)	0.001 (NS)
Spleen (kg)	$0.003 - \text{SM}_R + 0.019$ (139)	0.004 (0.461)	$0.001 \times \text{SM}_R - 0.000$ (177)	0.001 (0.682)
Brain (kg)	$0.001 \times \text{SM}_R - 0.000$ (199)	0.0002 (NS)	$0.003 \times \text{SM}_R + 0.202$ (206)	0.002 (NS)
BMC (kg)	$0.044 \times \text{SM}_R - 0.003$ (174)	0.171 (<0.001)	$0.035 \times \text{SM}_R - 0.153$ (200)	0.090 (<0.001)
ALST (kg)	$0.547 \times \text{SM}_R - 0.189$ (172)	0.515 (<0.001)	$0.590 \times \text{SM}_R - 0.088$ (208)	0.434 (<0.001)
REE (kcal)	$14.79 \times \text{SM}_R + 2.21$ (241)	0.077 (<0.001)	$17.91 \times \text{SM}_R - 0.706$ (247)	0.090 (<0.001)

ALST, appendicular lean soft tissue; AT, total adipose tissue; BMC, bone mineral content; REE, resting energy expenditure; VAT, visceral adipose tissue; WC, waist circumference.

Residual SM and other measures were derived as the difference between actual and predicted values; the predicted values were calculated using multiple regression models with weight, height, and age as potential covariates. SM<sub>R</sub> is in kg. Regression model dependent variables are listed in the component column.



**Figure 5** Combined body composition and metabolic observations that characterize the phenotypic differences between people varying in muscularity. A plus or minus slope describes a positive or negative respective association between  $SM_R$  and the residual estimate of the designated measure.

also controlling for weight, height, and age, again defining the distinct shape differences between muscular and non-muscular people.

The importance of exploring variation in muscularity separately in men and women is highlighted by our finding of a distinct sex difference in how adipose tissue and SM, as a percentage of body weight, vary as a function of body shape as defined by BMI. These observations extend earlier findings on a small relatively young (33–45 years) Cardia population sample.<sup>32,34</sup> Our study and these earlier reports show that SM mass decreases and total adipose tissue mass increases as a percentage of body weight with greater BMI in both men and women, although there is a distinct sex difference in these two curvilinear functions (Figure 1). SM, on average, constitutes the largest proportion of body mass up to a BMI of about  $35 \text{ kg/m}^2$  in men and is only exceeded by adipose tissue after that level. By contrast, SM is the largest proportion of body mass in women only up to a BMI of  $25 \text{ kg/m}^2$ , after which adipose tissue becomes the dominant body com-

partment. These observations bring into focus the critical and variable interplay between adipose tissue and SM across the BMI spectrum and the sexual dimorphism present in these relations that have clinically relevant functional, metabolic, and pathophysiological implications that are worthy of future study.

### Variation in muscularity

Muscularity within sex groups ranged widely, even at any specific level of BMI (Figure 1), and variation was largely independent of the measure used. The maximum and minimum  $SMI_R$  and  $ALSTI_R$  ranged from approximately 4 to  $6 \text{ kg/m}^2$  with an IQR of  $1 \text{ kg/m}^2$  in both the Kiel and NHANES samples. For a frame of reference, the average SMI was about  $8 \text{ kg/m}^2$  in people with a BMI of  $\sim 28 \text{ kg/m}^2$ . Translated into more tangible effects, per cent SM in the high  $SM_R$  tertile Kiel ‘muscular’ men was 41.1% vs. 31.4% in their low-tertile

counterparts. Comparable respective observations in women were 29.8% vs. 24.5%. SM, expressed as SMI, accounted for 49% and 56% of between-individual differences in BMI in men and women, respectively. These observations reveal the remarkably large range in muscularity present across people after controlling for their weight, height, and age. SM prediction models based on these easily acquired covariates will not reveal this heterogeneity in population muscularity.

### Body composition–metabolic associations

An enlarged SM compartment and reciprocally lowered adipose tissue compartment were not isolated findings in people with a relatively large  $SM_R$ . Significant or borderline significant correlations were also present between  $SM_R$  and the residual mass of liver, kidney, and BMC. Residual SM was also significantly correlated with residual REE. The associations between  $SM_R$  and residual BMC are expected as both components are part of the relatively large musculoskeletal system that responds collectively to mechanical and hormonal stimuli.<sup>36</sup> Similar mechanical and metabolic demands may drive the mass and function of other related organs and tissues<sup>37,38</sup> and REE. For example, people who are relatively muscular may be more active,<sup>32</sup> eat more, require higher hepatic nutrient processing, and generate more metabolic end products such as urea, all of which can impact whole body metabolic and functional demands, notably those of the liver and kidney.

The significant correlations between residual REE and  $SM_R$  have an anatomic basis that can be accounted for by findings in the current study. When residual REE was regressed on  $SM_R$ , the resulting slopes (Table 3) were 14.8 and 17.9 kcal/kg SM/day in men and women, respectively. This observation implies that for each 1 kg increase in SM, there is a REE increase of 14.8 and 17.9 kcal/day in REE in men and women, respectively. SM has a mass-specific energy expenditure of 13 kcal/kg/day<sup>3</sup> so that most of this increment in heat production can be accounted for by muscle tissue. We next added the heat-production effects of adipose tissue, liver, and kidney to that of SM; these components all had significant or borderline significant correlations with  $SM_R$ . Our calculated values (13.0 and 17.1 kcal/kg SM/day) shown in *supporting information* agreed well with those measured. Because the across-tertile differences in SM mass ranged from about 4 to 6 kg, muscular people would be expected to have roughly a larger REE of 50 to 100 kcal/day or an increase in their mass specific REE of about 0.5 to 1 kcal/kg body weight/day.

The associations of organs such as liver and kidney with variation in muscularity provide an explanation for why measures such as body weight and FFM are less than optimum predictors of REE. Body weight combines organs and tissues

into a single mass value independent of their mass-specific metabolic rates, thus not accounting for body composition heterogeneity. The same applies to FFM alone or combined with fat mass in REE prediction models. In the present study, we observed that high muscularity was accompanied mainly by a larger liver and kidney mass but not by a larger brain mass, an organ with a high mass-specific metabolic rate (240 kcal/kg/day).<sup>3</sup> Resting energy expenditure prediction equations with weight, height and age as covariates have lower  $R^2$ s and SEEs than those that include individual organs and tissues, as do REE prediction equations formulated on fat mass, FFM, and age as covariates.<sup>8</sup> These previously reported observations are confirmed in current study examples: for Kiel participants, weight-based, FFM-based, and organ-based REE prediction models had respective  $R^2$ s of (men/women) 0.72/0.78; 0.76/0.79; 0.79/0.81 (*supporting information*). Notably, brain mass entered the organ based REE regression models as a significant covariate after controlling for SM, again affirming the metabolic heterogeneity of FFM. Our findings suggest that REE estimation errors will arise when prediction models based on weight or FFM are applied in samples that vary widely in muscularity as well as other major organs and tissues.

### Limitations

Although large by current whole body MRI standards, the Kiel convenience sample is still comparatively small and selective for establishing population variability in muscularity. To compensate for this limitation, we used ALST as a SM surrogate to evaluate the NHANES population sample. We avoided converting ALST to SM using published empirical prediction equations.<sup>23,24</sup> Additionally, we found strong correlations between  $ALST_R$  and  $SM_R$ , implying our two measures of muscularity track together. However, ALST includes lean components of adipose tissue in addition to SM and we found in the current study that a larger appendicular SM was accompanied by a smaller appendicular adipose tissue mass. The proportion of ALST as appendicular SM will thus be larger in people who are muscular. In exploratory studies (*supporting information*), we found that adding per cent fat to SM prediction models based on ALST led to a small increase in model  $R^2$ s, supporting our hypothesis. A gap thus needs to be filled with development of accurate and practical methods of quantifying whole-body SM that can be applied in evaluating large race/ethnically diverse population samples. Our approach of deriving SM residuals is clearly population specific, and new SM prediction equations would need to be developed on new samples in future studies.

Our two samples also included NH White adults, and thus, a gap exists in muscularity variation in other race and ethnic groups. Another important gap is muscularity variation among non-adults as adult body size and shape is formed

during childhood and adolescence, a time when differentiating mechanisms may become apparent.

Our main study goal was to explore the magnitude of variation in adult muscularity and how this variability related to other body composition and energy expenditure measures. We did not quantify activity levels, diet, blood biomarkers, or other measures that might further refine the muscular phenotype. These are important topics for future investigation, particularly in large studies with sufficient power to detect what are likely small moderating effects.<sup>37,39</sup>

Lastly, we chose to frame our study as an exploration of variation in muscularity. This strategy led us to establish a distinct phenotype of people who have a high muscularity relative to their similar weight, height, and age low-muscle peers. We show that in many people, particularly men, the SM compartment constitutes a larger fraction of body weight than adipose tissue. Nevertheless, an alternative view is that our study was an exploration of variation in adiposity. To examine this contention, we developed an alternative model that defined muscularity as individual differences in SM after controlling for adipose tissue mass, height, and age. We found that SM<sub>R</sub> using this approach was highly correlated with SM<sub>R</sub> as derived in the current study ( $R^2$ , men 0.84 and women, 0.95; both  $P < 0.001$ ) and that the identified body composition and metabolic features of muscular people were identical. The one difference between the approaches is that 'muscular' people according to the adipocentric model weighed more than their low-muscle counterparts. Thus, whether body weight or adipose tissue mass are controlled for, large between individual differences in SM mass are present in both men and women.

## Conclusions

Clinical science is now moving towards identifying individual phenotypes as part of advancing precision medicine initiatives.<sup>40</sup> Here we show that variation in muscularity, as defined in the current study, is likely among the most common factors that moderates adult human phenotypes. Our findings show that variation in muscularity provides a firm ex-

planation for the long-held clinical observation that per cent of body weight as fat is highly variable at any level of BMI.<sup>1,2</sup> Similarly, heterogeneity in muscularity explains in-part why people vary in their REE even after controlling for body size and composition measures such as weight, height, fat mass, and FFM.<sup>8</sup> The current study affirms that SM is the largest body compartment in most people who are not obese and is highly variable between individuals, a finding that poses the critical question of what mechanisms drive these differences. Variation in muscularity is thus not solely a topic worthy of intense study in athletes or people with cachexia or sarcopenia, but more broadly in the general population.

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The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle*.<sup>41</sup>

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## Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

## Conflicts of interest

S. B. H. is on the Tanita Medical Advisory Board. No conflicts of interest are reported by the other authors of this study.

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