Humans with function-disrupting variants in the myostatin gene (MSTN) have increased skeletal muscle mass and strength, and less adiposity

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Supplementary Data Captions (Supplementary Data 1 to 9 in Supplementary_Data.xlsx)

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Supplementary Table 1: Anthropometric data for three homozygote carriers of *MSTN* missense mutations found in UK Biobank. Data reported is untransformed, with % deviation from covariate-adjusted expected values shown alongside. Results for body fat percentage, body fat-free mass, and fat free mass index (FFMI) are derived from bioimpedance analysis (BIA). Expected values computed using a linear model with sex, age, age squared, height, height squared, and sex interaction terms as predictors.

Genotype	Hom Ile225Thr	Hom Ile225Thr	Hom Arg65His
Sex	F	F	F
Age	55-60	50-55	65-70
BMI (kg m^{-2})	36.8	22.3	25.7
Body fat %	43.3 (+17.3%)	30.0 (-16.4%)	25.7 (-31.8%)
Body fat-free mass (kg)	55.4 (+24.0%)	41.1 (-8.0%)	47.1 (+12.3%)
FFMI (kg m^{-2})	21.9 (+24.0%)	16.7 (-8.0%)	20.6 (+12.3%)
Creatinine (μmol dm^{-3})	75.3 (+16.8%)	46.7 (-26.0%)	77.1 (+17.8%)
Creatinine:cystatin C ratio	78.7 (-5.8%)	69.7 (-20.3%)	107.4 (+37.7%)

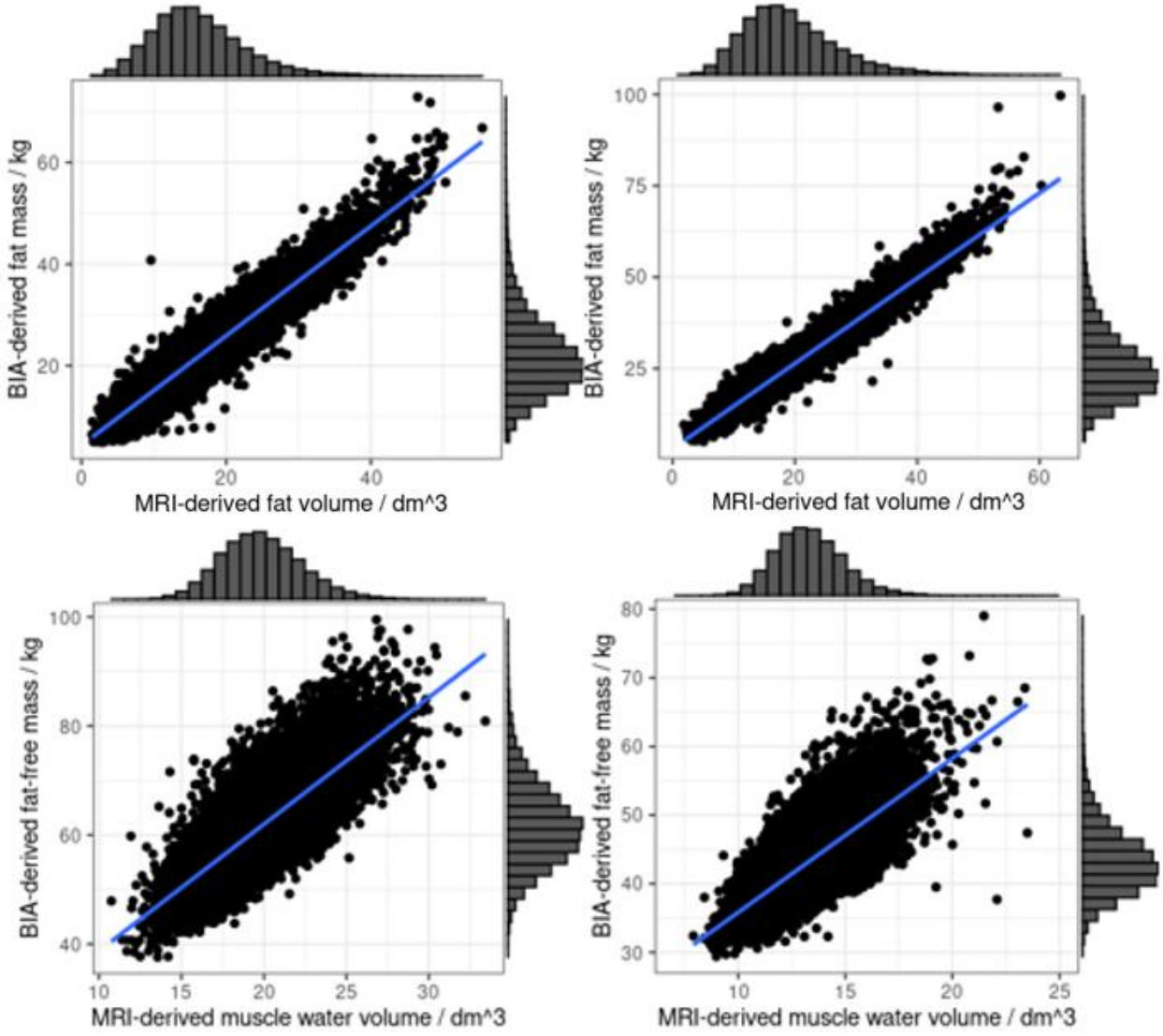
Supplementary Table 2: Five-fold cross-validation mean Dice scores (unitless) for the custom segmentation model of the four thigh muscle groups segmented for left and right legs, demonstrating strong concordance with manual annotations.

	Fold 1	*Fold 2*	*Fold 3*	*Fold 4*	*Fold 5*
Right quadriceps femoris	0.96	0.93	0.91	0.98	0.96
Left quadriceps femoris	0.97	0.95	0.93	0.95	0.96
Right medial	0.93	0.94	0.91	0.97	0.96
Left medial	0.93	0.94	0.96	0.96	0.92
Right posterior	0.93	0.94	0.92	0.96	0.95
Left posterior	0.93	0.92	0.94	0.94	0.93
Right sartorius	0.92	0.89	0.88	0.93	0.90
Left sartorius	0.94	0.89	0.92	0.85	0.87

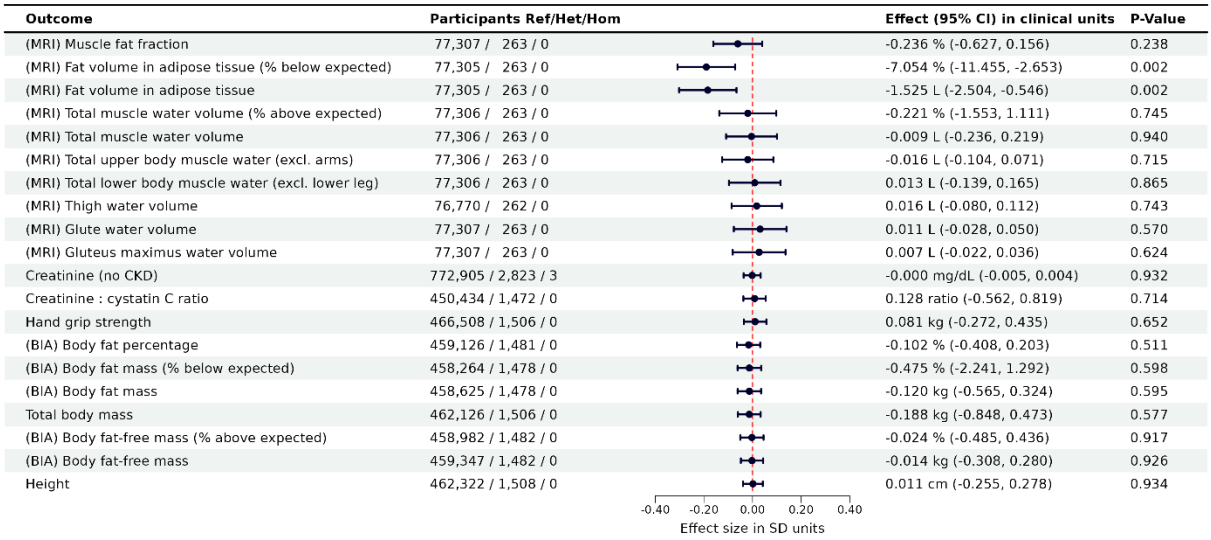
Supplementary Table 3: Five-fold cross-validation mean Dice scores (unitless) for the custom segmentation model of the five adipose tissue depots, demonstrating strong concordance with manual annotations.

	Fold 1	*Fold 2*	*Fold 3*	*Fold 4*	*Fold 5*
Upper body subcutaneous fat	0.89	0.93	0.96	0.84	0.96
Abdominal subcutaneous fat	0.92	0.90	0.93	0.86	0.93
Gluteofemoral subcutaneous fat	0.91	0.90	0.95	0.91	0.94
Visceral fat	0.92	0.91	0.93	0.89	0.85
Mediastinal fat	0.83	0.90	0.87	0.63	0.56

Supplementary Figure 1. Concordance between MRI-and BIA-derived measures of fat and fat-free mass for subjects in the UK Biobank imaging cohort, shown for men (left) and women (right).
Linear model fits were:
Men: $FM_{BIA} = 3.57 + 1.13 * FV_{MRI}$ ($R^2 = 0.90$) and $FFM_{BIA} = 15.46 + 2.33 * WV_{MRI}$ ($R^2 = 0.62$)
Women: $FM_{BIA} = 3.04 + 1.17 * FV_{MRI}$ ($R^2 = 0.95$) and $FFM_{BIA} = 13.39 + 2.24 * WV_{MRI}$ ($R^2 = 0.56$)
where FM = fat mass, FV = fat volume, FFM = fat-free mass, and WV = muscle water volume. MRI fat volumes are computed using the total across all fat depots, and total muscle water volume was computed using the sum over muscle groups segmented by TVS. The expected slope for fat mass versus fat volume given a fat density of 0.9 kg/dm^3 would be 0.9, and the slope of fat-free mass versus muscle water volume would be 2 in the case that muscle constitutes approximately 50% of BIA-derived fat-free mass. The higher estimated slope values versus these expectations are likely due to exclusion of arms and lower legs from the MRI-derived measurements, since these are partially or fully outside the field of view in most subjects. As an approximate estimate, the volume of muscle contained within lower legs may constitute around 1.3 dm^3 (Fuchs *et al.*, 2023) and the volume in shoulders and arms may constitute approximately 2 dm^3 (Holzbaur *et al.*, 2007); excluding these volumes will lead to an average underestimate of around 18% of the total muscle volume in UKB.

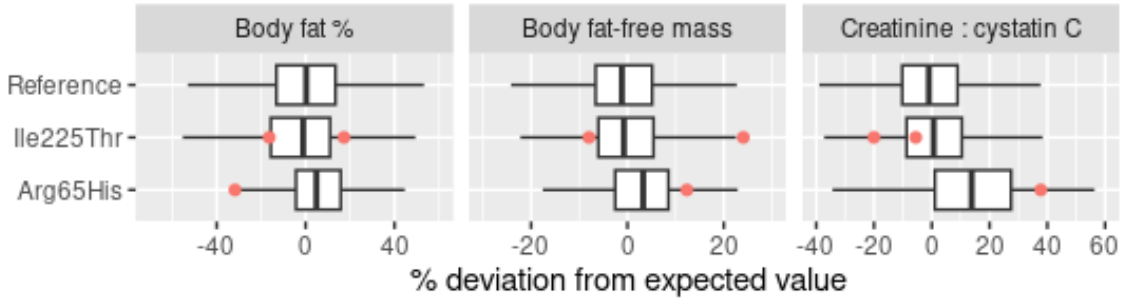


Supplementary Figure 2. *MSTN* Arg88Gln single variant associations with body composition, quantitative biomarkers, and MRI-derived fat and muscle metrics. This variant was not included in the set of predicted function-disrupting variants as defined by the 5-algorithm consensus described in the Methods. Effect size estimates are plotted in standard deviation units with numerical values shown alongside in clinical units; p-values are computed from gene burden test statistics using a chi-squared test (see Methods for additional details). Error bars indicate 95% confidence intervals (±1.96 SE); arrows indicate the error bar extends beyond axis limits. Summary statistics are included in Supplementary Data 6.



Outcome	Participants Ref/Het/Hom	Effect (95% CI) in clinical units	P-Value
(MRI) Muscle fat fraction	77,307 / 263 / 0	-0.236 % (-0.627, 0.156)	0.238
(MRI) Fat volume in adipose tissue (% below expected)	77,305 / 263 / 0	-7.054 % (-11.455, -2.653)	0.002
(MRI) Fat volume in adipose tissue	77,305 / 263 / 0	-1.525 L (-2.504, -0.546)	0.002
(MRI) Total muscle water volume (% above expected)	77,306 / 263 / 0	-0.221 % (-1.553, 1.111)	0.745
(MRI) Total muscle water volume	77,306 / 263 / 0	-0.009 L (-0.236, 0.219)	0.940
(MRI) Total upper body muscle water (excl. arms)	77,306 / 263 / 0	-0.016 L (-0.104, 0.071)	0.715
(MRI) Total lower body muscle water (excl. lower leg)	77,306 / 263 / 0	0.013 L (-0.139, 0.165)	0.865
(MRI) Thigh water volume	76,770 / 262 / 0	0.016 L (-0.080, 0.112)	0.743
(MRI) Glute water volume	77,307 / 263 / 0	0.011 L (-0.028, 0.050)	0.570
(MRI) Gluteus maximus water volume	77,307 / 263 / 0	0.007 L (-0.022, 0.036)	0.624
Creatinine (no CKD)	772,905 / 2,823 / 3	-0.000 mg/dL (-0.005, 0.004)	0.932
Creatinine : cystatin C ratio	450,434 / 1,472 / 0	0.128 ratio (-0.562, 0.819)	0.714
Hand grip strength	466,508 / 1,506 / 0	0.081 kg (-0.272, 0.435)	0.652
(BIA) Body fat percentage	459,126 / 1,481 / 0	-0.102 % (-0.408, 0.203)	0.511
(BIA) Body fat mass (% below expected)	458,264 / 1,478 / 0	-0.475 % (-2.241, 1.292)	0.598
(BIA) Body fat mass	458,625 / 1,478 / 0	-0.120 kg (-0.565, 0.324)	0.595
Total body mass	462,126 / 1,506 / 0	-0.188 kg (-0.848, 0.473)	0.577
(BIA) Body fat-free mass (% above expected)	458,982 / 1,482 / 0	-0.024 % (-0.485, 0.436)	0.917
(BIA) Body fat-free mass	459,347 / 1,482 / 0	-0.014 kg (-0.308, 0.280)	0.926
Height	462,322 / 1,508 / 0	0.011 cm (-0.255, 0.278)	0.934

Supplementary Figure 3: Distributions of deviations from expected values for fat-free mass and creatinine:cystatin c ratio for homozygote and heterozygote carriers of Arg65His and Ile225Thr. Homozygote missense carriers (red dots) are shown relative to heterozygote carriers (box plots) for Ile225Thr (second row, N=1,786 for body fat percentage and fat-free mass, N=1,793 for creatinine:cystatin c ratio) and Arg65His (third row, N=113 for body fat percentage and fat-free mass, N=114 for creatinine:cystatin c ratio). The distribution of homozygous reference individuals is shown on the top row for comparison (N= 458,758 for body fat percentage and fat-free mass, N=461,190 for creatinine:cystatin c ratio). Expected values computed using a linear model with sex, age, age squared, height, height squared and sex interaction terms as predictors. Boxes show medians and interquartile ranges (IQR); whiskers extend in each direction to the most extreme data point that is no further than 1.5 multiples of the IQR from the upper and lower quartile. Mean (SD) percent deviations for Arg65His heterozygotes were +5.3% (17.7) for body fat percentage, +3.8% (9.75) for body fat-free mass, and +13.9% (20.2) for creatinine : cystatin C ratio. Mean (SD) percent deviations for Ile225Thr heterozygotes were -2.3% (20.6) for body fat percentage, +0.3% (9.23) for body fat-free mass, and +1.8% (16.0) for creatinine : cystatin C ratio. While homogygous effect sizes cannot be accurately estimated due to the low sample sizes, Z-scores for the homozygotes relative to the heterozygote distribution were calculated, and converted to one-sided p-values, to provide a measure of deviation of the homozygote(s) from the heterozygote distributions. For the single Arg65His homozygote, the Z-scores and corresponding p-values obtained by this procedure were 2.08 (p=0.018) for body fat percentage, 0.87 (p=0.19) for body fat-free mass, and 1.18 (p=0.12) for creatinine : cystatin C ratio.



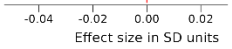
Supplementary Figure 4. Gene burden association analysis of *MSTN* with cardiometabolic disease outcomes (A) and quantitative biomarkers (B). Predicted loss-of-function and deleterious missense variants in *MSTN* with allele frequency below 0.5% were included in the gene burden tests. For the Malmo cohort the Ile225Thr variant has a frequency of 0.66%, but was included in the gene burden test for this cohort since the allele frequency is below 0.5% in all other cohorts. Effect sizes are reported in odds ratios (OR) for disease outcomes (**A**), and standard deviation (SD) and clinical units for quantitative traits (**B**). Error bars indicate 95% confidence intervals, calculated as ±1.96 SE from the effect estimate; for binary traits, the interval was calculated on the logistic scale and converted to OR units. p-values are computed from gene burden test statistics using a chi-squared test (see Methods for additional details). Arrows indicate the error bar extends beyond axis limits. Summary statistics are included in Supplementary Data 8.

A.

Outcome	Cases Ref/Het/Hom	Controls Ref/Het/Hom	OR (95% CI)	P-Value
Cardiomyopathy (Hypertrophic)	3,403 / 18 / 0	588,838 / 3,945 / 3	0.799 (0.525, 1.218)	0.298
Coronary Artery Disease (Loose)	152,007 / 1,012 / 1	667,381 / 4,210 / 3	0.972 (0.899, 1.051)	0.477
Liver Disease (Non Alcoholic)	51,863 / 331 / 1	741,063 / 4,942 / 3	0.973 (0.867, 1.092)	0.637
Liver Cirrhosis (Any)	14,601 / 96 / 0	741,063 / 4,942 / 3	1.001 (0.810, 1.236)	0.994
Type 2 diabetes	159,939 / 1,010 / 1	632,830 / 3,955 / 3	1.011 (0.933, 1.095)	0.793
Heart failure	82,813 / 610 / 1	592,427 / 3,956 / 3	1.028 (0.934, 1.131)	0.570
Cardiomyopathy (unspecified)	24,131 / 184 / 0	588,838 / 3,945 / 3	1.096 (0.930, 1.292)	0.272

B.

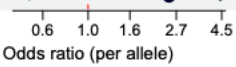
Outcome	Participants Ref/Het/Hom	Effect (95% CI) in clinical units	P-Value
Waist Hip Ratio adjusted for BMI	617,278 / 3,589 / 4	-0.002 ratio (-0.004, 0)	0.049
HbA1c (all)	807,828 / 4,929 / 4	-0.021 % (-0.043, 0.001)	0.056
Alanine Aminotransferase	895,752 / 5,664 / 5	-0.277 U/L (-0.643, 0.088)	0.137
Random glucose (all)	963,619 / 6,080 / 5	-0.232 mg/dL (-0.864, 0.4)	0.474
Triglycerides	863,359 / 5,560 / 5	-0.863 mg/dL (-3.274, 1.548)	0.486
Body Mass Index	985,795 / 6,044 / 6	-0.035 kg/m2 (-0.168, 0.097)	0.600
Aspartate Aminotransferase	913,721 / 5,827 / 5	-0.007 U/L (-0.268, 0.253)	0.956
Systolic Blood Pressure	1,105,210 / 6,921 / 6	0.011 mmHg (-0.359, 0.381)	0.954
LDL cholesterol (Friedewald)	809,201 / 5,244 / 5	0.139 mg/dL (-0.975, 1.253)	0.805
HDL cholesterol	821,563 / 5,313 / 5	0.126 mg/dL (-0.258, 0.51)	0.519



Supplementary Figure 5. Gene burden association analysis of *MSTN* with fertility-related quantitative traits (A) and fertility and polycystic ovary syndrome (PCOS; B). Burden test associations are reported for predicted loss-of-function and deleterious missense variants in *MSTN* with allele frequency below 0.5% and fertility-related traits. Effect sizes are reported in odds ratios (OR) for disease outcomes (**A**), and standard deviation (SD) and clinical units for quantitative traits (**B**). Error bars indicate 95% confidence intervals, calculated as ±1.96 SE from the effect estimate; for binary traits, the interval was calculated on the logistic scale and converted to OR units. p-values are computed from gene burden test statistics using a chi-squared test (see Methods for additional details). Arrows indicate the error bar extends beyond axis limits. PCOS indicates polycystic ovary syndrome. FSHB indicates follicle stimulating hormone subunit beta levels. Summary statistics are included in Supplementary Data 9.

A.

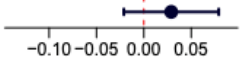
Outcome	Cases Ref/Het/Hom	Controls Ref/Het/Hom	OR (95% CI)	P−Value
PCOS (diagnosis)	965 / 3 / 0	189,029 / 1,152 / 3	0.607 (0.264, 1.397)	0.24
PCOS (diagnosis or Rotterdam)	1,128 / 8 / 0	189,029 / 1,152 / 3	1.205 (0.559, 2.597)	0.63
Infertility (female, any)	2,917 / 22 / 0	232,234 / 1,392 / 3	1.333 (0.823, 2.160)	0.24
Infertility (sex−combined)	3,189 / 25 / 0	431,548 / 2,537 / 3	1.393 (0.879, 2.210)	0.16
Infertility (male, any)	272 / 3 / 0	199,314 / 1,145 / 0	2.486 (0.516, 11.983)	0.26



Odds ratio (per allele)

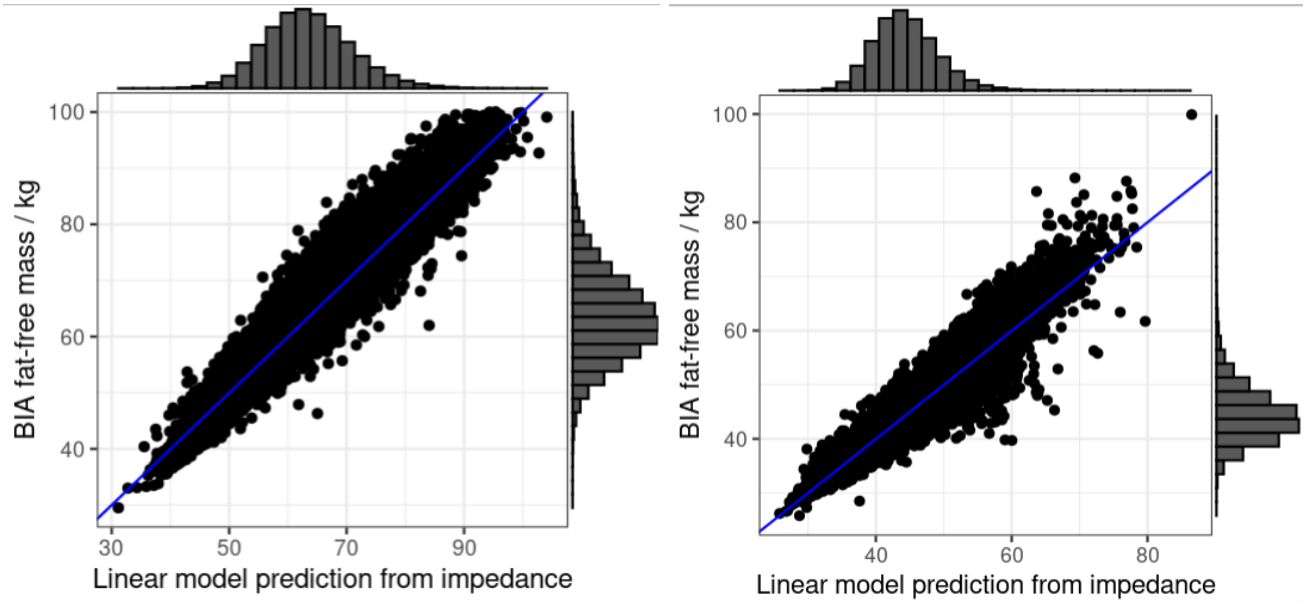
B.

Outcome	Participants Ref/Het/Hom	Effect (95% CI)	P−Value
FSHB	50,129 / 316 / 0	−3.00 % change (−9.31, 3.74))	0.37
FSHB (females)	27,033 / 170 / 0	−5.79 % change (−13.13, 2.10)	0.15
FSHB (males)	23,096 / 146 / 0	−2.67 % change (−12.82, 8.67)	0.63
Age of menarche	245,507 / 1,486 / 2	−0.027 years (−0.103, 0.050)	0.5
Age of menopause	155,650 / 968 / 2	0.299 years (−0.010, 0.608)	0.058
Number of live births	466,619 / 2,754 / 3	0.013 count (−0.030, 0.055)	0.56
Number of live births (female)	252,235 / 1,521 / 3	−0.005 count (−0.059, 0.048)	0.84
Number of live births (male)	211,704 / 1,219 / 0	0.039 count (−0.029, 0.107)	0.26

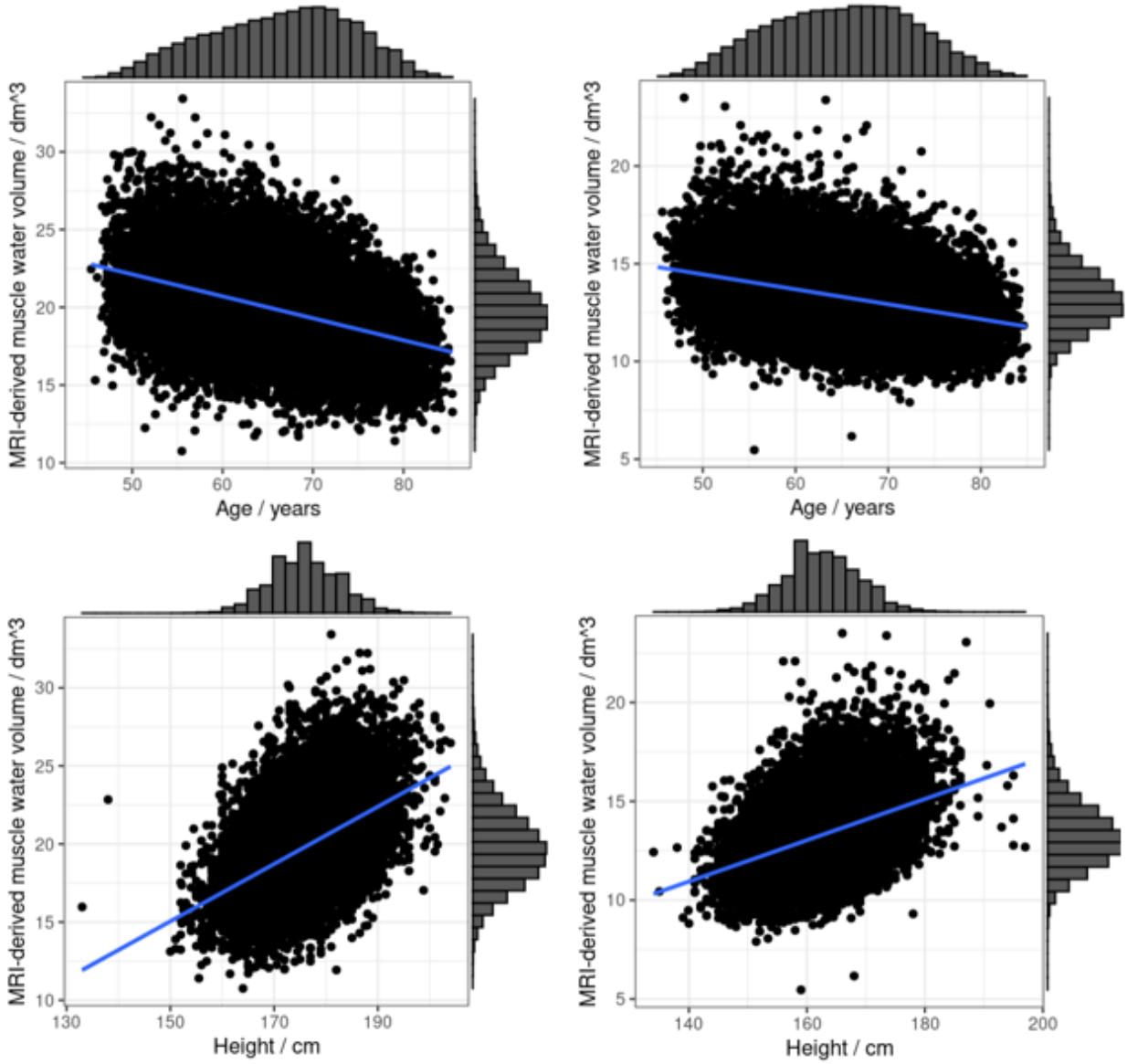


Per allele beta (95% CI) in SD units

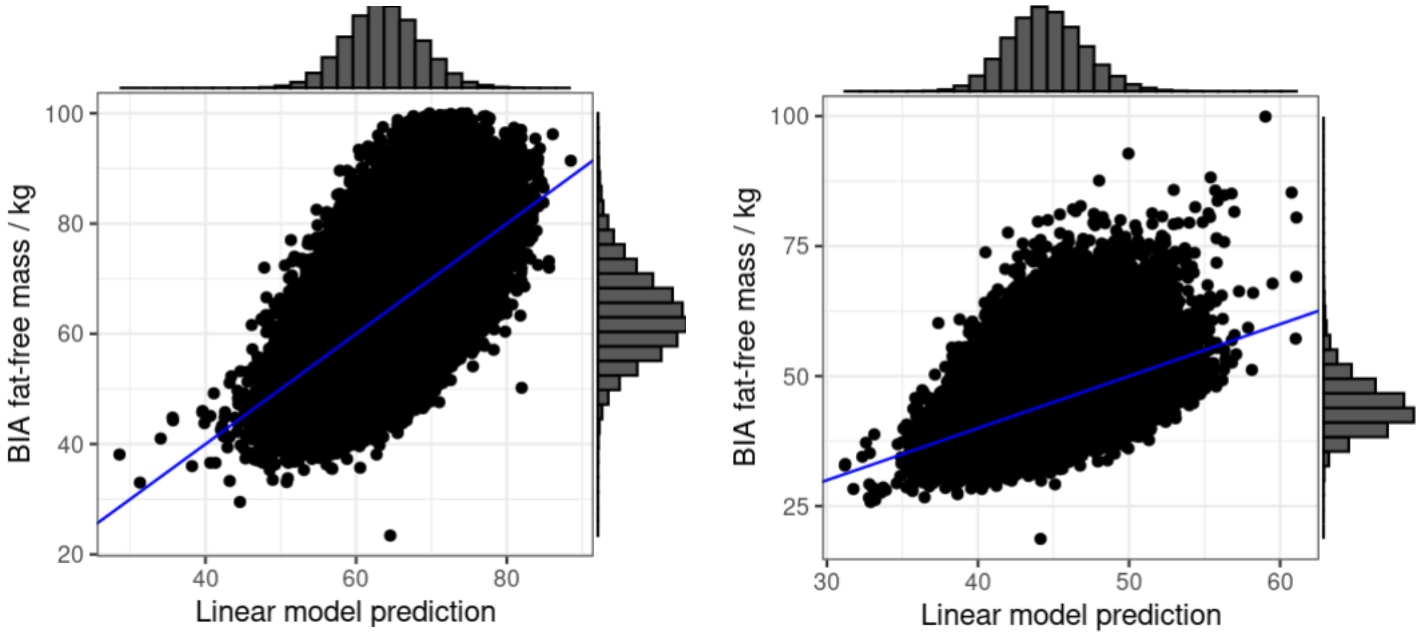
Supplementary Figure 6. Comparison between downloaded values of fat-free mass from UKB (field 23101) and values obtained from a linear fit of inverse whole-body impedance (UKB field 23106) of the form FFM ~ $1/R + h^2/R + age + age^2$, where R is impedance in Ohms and h is height, fitted separately for men (left) and women (right). Instance 0 values were used to fit the model, after filtering outliers with impedance < 360 Ohms. Identity lines are shown in blue. All terms in the model were estimated as significantly different from zero, and the R^2 for men and women were 0.93 and 0.91 respectively, indicating that the proprietary model used to derive these fat-free mass values from the impedance measurements is well approximated by an equation of this form, as noted in previous studies (Janssen *et al.*, 2000). A corollary of this is that estimated fat-free mass will have a positive genetic correlation with height.



Supplementary Figure 7: Correlations of total body muscle water volume with age and height, stratified by sex. Scatter plots show total muscle water volume versus age (top) for men (left) and women (right); and versus height (bottom) for men (left) and women (right). As expected, muscle water volume decreases with age (top rows), and increases in an approximately linear fashion with height (fit of linear model with single predictor shown in blue).



Supplementary Figure 8: Comparisons between BIA-derived fat-free mass values obtained from UK Biobank, and predicted values using a linear model with age, sex and height, plus squared and interaction terms, for men (left) and women (right). The overall R^2 for this model was 0.80, and 0.41 and 0.25 for men and women respectively. Percentage deviations from these predicted values were used to assess the effects on fat-free mass in excess of variation expected due to differences in height. Identity lines are shown in blue for reference. The fit for fat mass, defined as weight minus fat-free mass, was poor with this model (overall R^2=0.08), suggesting that estimated fat mass may be less sensitive to variations in body size.



Supplementary Data Captions (data provided in Supplementary_Data.xlsx)

For summary statistic tables, effect values are in standard deviation (SD) units for quantitative traits or odds ratios (ORs) for binary traits. Effect estimates and p-values for single-variant and gene burden tests were obtained via REGENIE v4.1, using default settings.

The lci_effect and uci_effect columns indicate lower and upper bounds for the 95% confidence intervals. For quantitative traits these are calculated as ±1.96 standard errors from the effect estimate; for binary traits, the confidence interval is computed on the logistic scale and converted into OR units.

The num_cases and num_controls columns indicate the total number of cases and controls included in the analysis. The case_ref, case_het, and case_alt columns indicate the case counts who respectively do not carry a variant in the burden test, are heterozygous for a variant included in the burden test, or homozygous for a variant included in the burden test.

The control_ref, control_het, and control_alt columns indicate the control counts who respectively do not carry a variant in the burden test, are heterozygous for a variant included in the burden test, or homozygous for a variant included in the burden test.

In all cases, our analyses were based on the GRCh38 genome assembly.

Supplementary Data 1. List of cohorts included for each phenotype where cross-cohort meta-analyses were available.
Supplementary Data 2. List of all variants predicted to induce loss of function of MSTN as detected in whole exome sequencing data from 11 cohorts (see Supplementary Data 1 for cohort list). Positions are based on the GRCh38 genome assembly.
Supplementary Data 3. Summary statistics for gene burden associations between MSTN and quantitative traits related to lean mass and fat mass, including (1) MSTN pLoF + missense (5/5), AAF<0.5%, (2) MSTN pLoF, AAF<0.5%, and (3) MSTN non-function-disrupting missense, AAF<0.5% (the latter includes all missense variants not present in the other two categories). AAF indicates alternative allele frequency. pLoF indicates putative loss-of-function. Also included are summary statistics for sex-stratified analyses.
Supplementary Data 4. Summary statistics for associations between MSTN gene burden variants and DXA-derived measures of lean and fat mass. AAF indicates alternative allele frequency. pLoF indicates putative loss-of-function.
Supplementary Data 5. Summary statistics for associations between individual MSTN missense variants and measures of lean and fat mass. Positions are based on the GRCh38 genome assembly.
Supplementary Data 6. Summary statistics for custom gene burden associations between MSTN missense masks and MRI-derived fat volume traits, including (1) MSTN pLoF + missense (5/5), AAF<0.5%, (2) MSTN any other missense, AAF<0.5%, and (3) MSTN any other missense, AAF<0.5% removing the Arg88Gln variant. AAF indicates alternative allele frequency. pLoF indicates putative loss-of-function. Also included are summary statistics for associations with the single Arg88Gln variant.

Supplementary Data 7. Summary statistics for associations between MSTN missense variants and cardiac wall thickness. Positions are based on the GRCh38 genome assembly.
Supplementary Data 8. Summary statistics for gene burden test associations across cardiometabolic traits. AAF indicates alternative allele frequency. pLoF indicates putative loss-of-function.
Supplementary Data 9. Summary statistics for gene burden test associations across infertility-related traits. Within the outcome column, FSHB indiciates follicle stimulating hormone subunit beta levels and PCOS indicates polycystic ovary syndrome. AAF indicates alternative allele frequency. pLoF indicates putative loss-of-function.

Supplementary References

1. Fuchs, C.J.*, et al.* Thigh muscles are more susceptible to age-related muscle loss when compared to lower leg and pelvic muscles. *Exp Gerontol* 175, 112159 (2023).
2. Holzbaur, K.R., Murray, W.M., Gold, G.E. & Delp, S.L. Upper limb muscle volumes in adult subjects. *J Biomech* 40, 742-749 (2007)
3. Janssen, I., Heymsfield, S.B., Baumgartner, R.N. & Ross, R. Estimation of skeletal muscle mass by bioelectrical impedance analysis. *J Appl Physiol (1985)* 89, 465-471 (2000).