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Gluteus Maximus Shape Reveals Sex-Specific Associations Between Morphology and Metabolic Dysfunction

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ABSTRACT

Background: The gluteus maximus (GM) is a major hip extensor essential for mobility and metabolic health. Previous studies rely on global measures, such as muscle volume or fat fraction, which can overlook spatially localised differences in shape across the GM. Here, we integrate conventional volumetric and fat fraction metrics with 3D mesh-based shape phenotypes to provide a spatially resolved characterisation of GM morphology in relation to anthropometric, lifestyle and cardiometabolic factors, with a focus on type 2 diabetes (T2D) and sex-specific effects.

Methods: We analysed T1 Dixon MRI from UK Biobank participants to quantify GM muscle volume, fat fraction and regional surface morphology using 3D meshes. Statistical parametric mapping was used to assess regional associations with anthropometric, lifestyle and clinical variables. Statistical shape analysis was used to derive principal components (PCs) summarising major modes of GM shape variation, which were evaluated for associations with disease outcomes. Bidirectional causal mediation analyses were performed using GM volumetric and PCs of shape variation. Longitudinal changes in GM composition were assessed in participants with repeat imaging.

Results: GM muscle volume and fat fraction were strongly associated with age, adiposity and physical activity. Shape analysis identified spatially localised remodelling patterns that were not captured by global measures, revealing region-specific surface shrinkage linked to age, BMI, alcohol intake, grip strength, physical activity, frailty, osteoporosis and cardiometabolic disease. T2D exhibited distinct sex-specific patterns: Men showed predominantly inward deformation across the anterior and central GM, whereas women demonstrated outward deformation in corresponding anterior regions and throughout the posterior muscle, with several posterior regions significant only in women. Mediation analyses suggested that T2D-related changes in GM morphology partly mediated increases in fat fraction, indicating that diabetes influences regional muscle shape beyond overall muscle size. PCs representing variation in the central-superior posterior and anterior GM differentiated T2D cases from controls and were associated with incident T2D risk (men: left GM PC6 HR per SD 0.81 [0.70–0.95], false discovery rate [FDR]-adjusted $p = 0.038$; right GM PC6 HR 0.76 [0.65–0.88], $p = 0.002$; women: right GM PC5 HR 1.32 [1.08–1.61], $p = 0.032$).

Conclusions: Integrating 3D GM morphology with conventional muscle composition measures identifies regional shape biomarkers that extend beyond muscle volume and fat fraction. These biomarkers capture spatially specific remodelling associated with anthropometric, lifestyle and cardiometabolic factors, providing improved insight into muscle–fat phenotypes and enhancing risk stratification in population-based imaging studies.

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1 | Introduction

Skeletal muscle composition is a key determinant of mobility and metabolic health, with age- and disease-related fat infiltration (myosteatosis) increasingly recognised as an imaging marker of impaired muscle quality [1]. In the hip extensors, the gluteus maximus (GM) is the body's largest muscle and is central to bipedalism, pelvic stability, posture and high-intensity tasks such as climbing, sprinting and lifting [2, 3]. Its broad origin from the posterior ilium, sacrum, coccyx and sacrotuberous ligament narrows as its fibres converge to insert onto the iliotibial band and the gluteal tuberosity of the femur. This wide superior origin and focused distal insertion give the muscle a broad, fan-like appearance and expansive across the buttock, tapering downward toward the thigh. This anatomy means that the GM is not a uniform structure: Different regions contribute differently to hip extension, pelvic control and force transmission. Consequently, age- or disease-related remodelling may occur in spatially localised patterns that are not fully captured by global measures such as total muscle volume or mean fat fraction.

A growing literature using CT and MRI has linked muscle fatty degeneration to poorer function and clinical outcomes, highlighting that compositional change can be more informative than muscle size alone [4]. In the GM specifically, higher fat content has been associated with reduced mobility, greater fall risk and poorer performance [5], while population studies have shown that low physical activity is related to GM intramuscular fat [6]. Unlike many other skeletal muscles assessed in population imaging studies, the GM also has a well-defined anatomical boundary, making it suitable for reproducible 3D surface modelling. Its composition is responsive to physical inactivity and metabolic dysfunction, with prior studies linking GM fat infiltration to mobility limitation, frailty and insulin resistance [5, 7]. These features make the GM a biologically plausible and methodologically robust target for investigating muscle and metabolic interactions at scale.

These findings align with broader evidence that accumulation of ectopic fat is closely connected to metabolic dysfunction [8]. Individuals with type 2 diabetes (T2D) show distinct adipose tissue distribution patterns [9], and sex-related differences in body composition and insulin resistance may contribute to heterogeneity in metabolic risk [10]. However, existing work on GM measurements has typically been conducted in relatively small or disease-specific cohorts and has largely focused on global summaries (e.g., mean fat fraction or total volume), leaving important gaps. First, relationships between GM muscle volume, fat fraction, lifestyle and anthropometric factors and prevalent and future disease risk have not been characterised at scale within a harmonised imaging framework. Second, global measures cannot pinpoint where clinically relevant remodelling occurs within the GM, which limits biological interpretability and potentially obscures spatially specific signatures of metabolic dysfunction.

While conventional MRI-derived measures, such as muscle volume and fat infiltration, provide summary measures of overall muscle size and composition, three-dimensional (3D) mesh-derived phenotypes enable the assessment of regional

muscle morphology that is not captured by global measures such as volume or fat fraction. Instead of summarising the entire muscle as a single scalar value, statistical shape analysis (SSA) and statistical parametric mapping (SPM) quantify localised surface variation across the muscle geometry. SSA further reduces these high-dimensional spatial patterns into a small number of principal components (PCs), which represent dominant modes of shape variation independent of overall size. While these methods have been widely applied in bones [11], abdominal organs [12, 13], the brain [14], the heart [15] and the aorta [16], their application to skeletal muscle, especially the GM, remains limited.

In this study, we analyse T1 Dixon MRIs from the UK Biobank to quantify GM muscle volume, intermuscular adipose tissue (IMAT), muscle fat fraction and regional surface morphology. Our aims are first to establish and characterise the 3D mesh-derived shape phenotype itself in order to (i) characterise associations between GM muscle-fat phenotypes and anthropometric and lifestyle factors and (ii) quantify longitudinal changes using repeat imaging. Our aims were hypothesis-driven, testing the relevance of the GM phenotype to T2D risk and its interplay with established muscle measures to (i) assess associations between GM phenotypes and prevalent and incident disease, focusing on T2D and sex-specific effects; (ii) investigate interrelationships between GM morphology, T2D and fat fraction; and (iii) determine whether 3D mesh-derived phenotypes improve T2D diagnosis and prediction of future disease risk. This hierarchical approach distinguishes exploratory morphometric characterisation from hypothesis-driven analyses focused on T2D and clinical outcomes.

2 | Methods

2.1 | Data

Full details regarding the UK Biobank abdominal MRI acquisition protocol have previously been reported [17]. Briefly, the data included here focused on neck-to-knee Dixon MRI acquisitions, comprising six overlapping series. Data were obtained under UK Biobank applications 44 584 and 23 889. The UK Biobank has approval from the North West Multi-Centre Research Ethics Committee (REC reference: 11/NW/0382). All methods were performed in accordance with relevant guidelines, with informed consent obtained from all participants. Further information is available at www.ukbiobank.ac.uk.

2.2 | Image and Mesh-Derived Analysis of GM

2.2.1 | Image Analysis

All Dixon MRI data were preprocessed using previously described methods [18]. We utilised a three-dimensional (3D) U-net model architecture in the MONAI (Medical Open Network for AI) framework for segmentation [19]. Manual annotation of the GM muscles was performed on 158 datasets. Data augmentation was performed, and a total of 384 epochs were run; the final model was selected using the Dice score on

10% out-of-sample datasets. Left/right separation of the GM was performed in post-processing. The pipeline was applied to over 58 000 neck-to-knee T1-weighted Dixon MRI scans, with segmentation quality validated by experienced analysts at multiple stages.

IMAT was identified from Dixon fat images thresholded at a 50% fat fraction cut-off, with remaining tissue voxels classified as muscle (Figure S1). The fat/muscle ratio was calculated as follows: GM IMAT volume/(GM IMAT volume + GM muscle volume). Image-derived phenotypes (IDPs) included GM muscle volume, IMAT volume and IMAT/muscle ratio.

2.2.2 | Image Registration and Mesh Construction

Population-based templates [20, 21] were constructed separately for left/right GM in 600 participants (300 men, 300 women). Template characteristics and exclusions to identify healthy individuals are provided in Table S1 and in Data S1. 3D surface meshes were constructed from template and participant segmentations using the marching cubes algorithm. Rigid registration [20, 21] was used to remove positional and orientation differences between all participant-specific surfaces and the template surfaces, followed by affine and non-rigid registration of the template to each participant's segmentation. The template mesh was propagated to each participant using the resulting deformation fields, yielding meshes parameterised with approximately 16 000 vertices (men) and 13 000 vertices (women), ensuring anatomical consistency across all participants while preserving size and shape information.

Surface-to-surface (S2S) distances, the 3D mesh-derived phenotype, were measured as the signed distance between each template vertex and the corresponding participant vertex. Positive distances represent outward expansion while negative distances indicate inward shrinkage relative to the template [21] (Figure S2).

2.3 | Quality Control

The study included MRI data from 55 864 participants at initial imaging visit and 2912 participants with a follow-up scan approximately 2.5 years later [22]. We excluded 7826 participants with missing anthropometric, biological or lifestyle variables and four with zero GM volume. Outliers in the 3D mesh-derived phenotype were inspected visually; no further exclusions were required. The final baseline sample comprised 48 034 participants. For the longitudinal sample, 198 participants were excluded due to missing data, yielding 2720 participants (Figure S3).

2.4 | Statistical Analysis

Across all analyses, we distinguish three modelling objectives using covariate selection to identify adjustment variables, association analyses of relationships between GM phenotypes and exposures and outcome modelling using diagnostic and survival analyses to evaluate the predictive value.

2.4.1 | Covariate Selection

This procedure was used to define a consistent set of covariates for subsequent regression models. The resulting variables were included as confounder adjustments in all downstream association analyses. We fitted least absolute shrinkage and selection operator (LASSO) regression models, implemented in the R package *glmnet*, via a stability selection procedure using the R package *stabs* [23] selecting models across 85 demographic, biomarker and disease data sets (Data S2). Stability selection was performed using the 'stabsel' function with the fitting function set to 'glmnet.lasso'. Stability selection used a probability cut-off of 0.95 and per-family error rate of one, with a unimodal assumption. The stability parameters were estimated using the 'stabsel_parameters' function, ensuring a robust selection of predictors [23]. Model-based boosting was implemented using the package *mboost* [24].

2.4.2 | Linear Regression Analysis

The purpose of the linear regression models is to test associations between GM IDPs and the covariates retained from stability selection. We further adjusted for time since the initial assessment visit to account for the time gap between the initial assessment visit, where the biomarkers were taken, and the imaging visit (9.9 ± 2.4 years later). Longitudinal analyses in 2720 participants used linear mixed-effects models fitted with the *lme4* package [25], included participant IDs as a random effect, T2D as a fixed effect, including data from both time points [26]. Models further included stability-selected covariates, assessment centre, imaging visit, T2D and their interaction. *p*-values were computed using the *lmerTest* package [27] with FDR correction (threshold < 0.05). Effect sizes are reported as standardised beta coefficients (β). All continuous variables were standardised prior to being included in the models.

2.4.3 | Mass Univariate Regression Analysis

Associations between S2S distances and anthropometric variables were estimated using a mass univariate regression (MUR) framework. To enhance the detection of spatially contiguous signals and discriminate them from noise, we applied threshold-free cluster enhancement (TFCE) [28] and permutation testing, with 1000 permutations and FDR correction, as previously described [20] (see Material S1 and Figure S4).

Sex-stratified linear regression was fitted at each vertex, adjusting for stability-selected covariates to correct for confounding associations. Interaction terms between age and T2D were included to assess accelerated change. All continuous variables, including S2S distances, were standardised prior to analysis to allow comparison.

Longitudinal S2S analyses in 2720 participants applied the same MUR mixed-effects framework with TFCE with 1000 permutation testing and FDR correction, and a threshold of < 0.05 determined significance. All continuous variables used as fixed effects were standardised before being included in the analysis. Wilcoxon rank-sum tests were used for paired

comparisons between visits as the variables were nonparametrically distributed.

2.4.4 | Dimensionality Reduction of GM Shape

To reduce the dimensionality of the 3D mesh-derived phenotypes, we computed robust sparse principal component analysis (SPCA) using the R package *sparsepca* [29] and extracted principal component (PC) scores to characterise variations in GM S2S distances for each gender and each GM. Modes of variation (-3 SD, mean, $+3$ SD) were mapped onto representative templates for visualisation of each phenotype's shape.

2.4.5 | Causal Mediation Analysis

Bidirectional causal mediation analyses were performed separately by sex and GM side to better understand the T2D-related effects on GM fat fraction, decomposing the relationship into direct effects (not operating through the mediator) and indirect effects (operating through intermediate mediators). Analyses considered GM muscle volume and the first 10 principal component (PC) scores derived from PCA of the S2S distances (capturing the major modes of GM shape variation). Specifically, we evaluated: (i) T2D as exposure, GM muscle volume as mediator, GM fat fraction as outcome; (ii) T2D as exposure, each PC score as mediator, GM fat fraction as outcome; (iii) GM muscle volume as exposure, T2D as mediator, GM fat fraction as outcome; and (iv) each PC score as exposure, T2D as mediator, GM fat fraction as outcome. All models were adjusted for stability-selected covariates, with continuous variables standardised prior to analysis. The average causal mediation effect (ACME), average direct effect (ADE) and total effect were estimated using nonparametric bootstrap resampling (5000 simulations), and p -values < 0.05 were considered statistically significant. Mediation analyses used the R package *mediation* [30].

2.4.6 | Diagnostic Modelling

To evaluate whether GM PCs improved T2D diagnosis beyond conventional IDPs, we identified prevalent T2D cases and matched controls (1:1) by age (± 2 years) and BMI (± 1.5 kg/m²) using *ccoptimalmatch* [31] stratified by sex. Sex-specific logistic regression models included bilateral GM volume, fat fraction and PC scores, alongside non-disease stability-selected covariates. The dataset was split by assessment centre into training (Cheadle, Bristol, Newcastle) and test (Reading) subsets. Models were trained using repeated 10-fold cross-validation (five repeats) with the R package *caret* [32].

Two nested models were compared: a baseline model with GM volume and fat fraction and an extended model additionally incorporating PC2–PC10 of S2S distances, excluding PC1, which explains the size of GM to avoid redundancy with muscle volume. Performance was assessed using AUC, accuracy, sensitivity and specificity. Odds ratios (ORs) with 95% confidence intervals were derived from the final fitted models, and multiple testing was controlled using FDR correction.

2.4.7 | Survival Analysis

Cox proportional hazards models evaluated incident T2D risk from the imaging visit, fitted separately by GM side and sex, adjusted for stability-selected covariates measured at the imaging visit. To minimise overfitting given limited events, penalised LASSO-Cox regression was applied. The dataset was split by assessment centre into a training set (Cheadle, Bristol, Newcastle) and an independent test set (Reading). LASSO selection was conducted in the training data using 10-fold cross-validation to identify the optimal penalty parameter. Variables retained by LASSO were entered into standard Cox models to estimate hazard ratios (HRs). Model discrimination was assessed using concordance indices (c-index) in the held-out test set.

Disease outcomes were defined using linked hospital records, primary care data, self-reports and death registries (see Material S1). Follow-up was calculated from the imaging visit and censored at first event, death or 30 November 2022 (median 4 years). Participants with prior T2D were excluded. Hazard ratios (HRs) with 95% confidence intervals were reported, with FDR-adjusted $p < 0.05$ indicating statistical significance. Survival analyses used the R package *survival* [33], and all continuous variables were standardised prior to analysis.

3 | Results

3.1 | Segmentation Performance

The deep learning model achieved a mean Dice similarity coefficient of 0.94 on a held-out 10% test set (15 participants). Visual inspection confirmed successful segmentation.

3.2 | Study Population Characteristics

The cohort included 23 364 men and 24 670 women. Among men, 96.6% were White ethnicity, ages ranged from 44 to 85 years and mean BMI was 27.0 ± 3.9 kg/m². In women, 96.8% were White, ages ranged from 45 to 84 years and mean BMI was 26.1 ± 4.8 kg/m² (Table S2). We identified 2628 participants with T2D (1699 men; 896 women), 1140 with frailty (472 men; 668 women), 3917 with osteoporosis (1034 men; 2883 women) and 17 615 with CVD, of whom 58% were men.

To align with the primary study objective, results are structured into three levels: global GM composition, regional morphology and clinical relevance, separating descriptive morphometric findings from hypothesis-driven analyses of disease association and risk prediction.

3.3 | Cross-Sectional Associations With Anthropometric Traits and Disease

We examined associations between GM muscle volume, IMAT volume and fat fraction with covariates selected by the stability selection model, including age, ethnicity, BMI, waist-to-hip ratio (WHR), alcohol intake, dominant handgrip strength (HGS), vigorous metabolic equivalent task (MET), serum creatinine, cystatin

TABLE 1 | Significance areas for covariates in the MUR model for the anthropometric variables ($N = 23\,364$ men; $N = 24\,670$ women) of the model for the left GM.

	Men		Women	
	$\hat{\beta} < 0$	$\hat{\beta} > 0$	$\hat{\beta} < 0$	$\hat{\beta} > 0$
Left GM	Median standardised beta coefficients (IQR, significance area [%])			
Age	−0.07 (0.07, 71.12%)	0.053 (0.05, 21.59%)	−0.07 (0.08, 71.54%)	0.05 (0.04, 21.39%)
BMI	−0.03 (0.01, 0.45%)	0.377 (0.21, 98.69%)	−0.03 (0.02, 1.48%)	0.30 (0.20, 97.7%)
WHR	−0.08 (0.07, 94.72%)	0.025 (0.02, 1.46%)	−0.05 (0.05, 38.22%)	0.07 (0.07, 53.95%)
Creatinine	−0.02 (0.01, 0.49%)	0.039 (0.03, 94.17%)	−0.02 (0.01, 0.76%)	0.05 (0.03, 98.12%)
Cystatin C	−0.03 (0.02, 69.84%)	0.021 (0.01, 6.93%)	−0.03 (0.03, 73.46%)	0.02 (0.01, 9.75%)
IGF-1	−0.02 (0.00, 1.07%)	0.027 (0.02, 81.39%)	−0.02 (0.01, 3.69%)	0.02 (0.02, 78.16%)
Creatinine in urine	—	0.02 (0.01, 77.87%)	−0.02 (0.01, 3.73%)	0.02 (0.01, 64.56%)
WBC count	−0.03 (0.02, 96.59%)	—	−0.04 (0.03, 84.34%)	0.02 (0.01, 1.28%)
Vigorous MET	−0.02 (0.01, 0.96%)	0.05 (0.03, 96.67%)	−0.02 (0.00, 1.5%)	0.04 (0.03, 95.26%)
Dominant HGS	—	0.091 (0.06, 99.06%)	−0.02 (0.00, 0.31%)	0.09 (0.07, 98.11%)
Alcohol intake frequency	−0.06 (0.03, 5.86%)	0.045 (0.03, 83.7%)	−0.06 (0.03, 4.83%)	0.06 (0.03, 81.51%)
T2D	−0.08 (0.05, 60.39%)	0.056 (0.02, 5.33%)	−0.10 (0.06, 8.41%)	0.10 (0.08, 64.07%)
Frailty	−0.10 (0.05, 79.61%)	0.009 (0.01, 0.01%)	−0.09 (0.06, 52.77%)	0.09 (0.04, 8.32%)
Osteoporosis	−0.14 (0.07, 93.53%)	—	−0.09 (0.06, 87.23%)	0.06 (0.03, 4.54%)
CVD	−0.05 (0.03, 93.62%)	—	−0.03 (0.02, 56.78%)	0.03 (0.01, 1.69%)
Age*T2D	−0.05 (0.02, 14.18%)	0.009 (0.00, 0.01%)	−0.07 (0.03, 39%)	—

Note: The total area has been split into positive- and negative-association areas. The standardised regression coefficients ($\hat{\beta}$) are presented as medians (interquartile ranges [IQR]), and the significance areas are expressed as percentages (%) of the vertices with statistically significant associations.

Abbreviations: BMI: body mass index; CVD: cardiovascular disease; GM: gluteus maximus; HGS: hand grip strength; IGF-1: insulin-like growth factor 1; MET: metabolic equivalent task; MUR: mass univariate regression; T2D: type-2 diabetes; WBC: white blood cell count; WHR: waist-to-hip ratio.

C, urinary creatinine, IGF-1, white blood cell count (WBC) and clinical conditions including T2D, frailty, osteoporosis and CVD (Figure S5). Effect sizes are reported as standardised beta coefficients (β) with FDR-adjusted p -values (Figure S6 and Table S3).

GM muscle volume was negatively associated with age, cystatin C, WBC, frailty, CVD and osteoporosis in both sexes. In men, T2D was additionally associated with lower muscle volume (left: $\beta = -0.14$, $p = 1.9 \times 10^{-13}$; right: $\beta = -0.11$, $p = 5.3 \times 10^{-9}$). By contrast, dominant HGS and vigorous physical activity were positively associated with GM muscle volume. IMAT volume and fat fraction were positively associated with BMI, alcohol intake, IGF-1, T2D, frailty and osteoporosis, while HGS and physical activity were inversely associated with fat fraction. Age $\times$ T2D interactions showed sex-specific patterns: In women, older age was associated with lower GM muscle and IMAT volume (left muscle: $\beta = -0.10$, $p = 0.028$; right muscle: $\beta = -0.10$, $p = 0.015$; left IMAT: $\beta = -0.09$, $p = 1.8 \times 10^{-4}$; right IMAT: $\beta = -0.12$, $p = 5.5 \times 10^{-7}$), whereas in men, age was positively associated with GM fat fraction (left: $\beta = 0.15$, $p = 0.045$; right: $\beta = 0.14$, $p = 0.040$).

MUR analysis of S2S distances generated SPMs adjusted for all relevant covariates (Tables 1 and 2 and Figure S7). Age was predominantly negatively associated with S2S distances in both sexes (men: 71%–75% of GM surface; women: 71% bilaterally), indicating

inward shape variation. BMI showed positive associations across nearly the entire GM surface (men: 98.7% left, 99.6% right; women: 97.7% left, 98.6% right). WHR patterns differed by sex: men showed mainly negative associations, while women exhibited a mixed pattern, with positive associations covering 54% (left) and 58% (right), extending from the lateral border towards the inferior corners of GM and negative associations confined to the smaller superior border and iliosacral areas. Serum creatinine, IGF-1, urinary creatinine, vigorous activity and HGS were positively associated with S2S distances across > 75% of GM. Cystatin C and WBC were negatively associated, particularly in men. Alcohol intake showed predominantly positive associations.

To facilitate interpretation in the associations with diseases, unstandardised regression coefficients translating shape variation into mm are provided in Table S4. Based on the median SD of S2S distances in men (4.74 mm bilaterally), T2D corresponded to inward shape variation in the superior and inferior posterior GM and the anterior aspect of the inferior corners (corresponding to the femoral insertions), with median displacements of −0.38 mm (left) and −0.33 mm (right) in men. Conversely, women exhibited outward shape variation in the anterior and posterior aspects of the inferior corners, with median displacements of 0.42 mm (left) and 0.40 mm (right), together with significant outward remodelling throughout the posterior GM in regions that were not significantly

TABLE 2 | Significance areas for covariates of the MUR models for the anthropometric variables ($N = 23\,364$ men; $N = 24\,670$ women) of the model for the right GM.

	Men		Women	
	$\hat{\beta} < 0$	$\hat{\beta} > 0$	$\hat{\beta} < 0$	$\hat{\beta} > 0$
Right GM	Median standardised beta coefficients (IQR, significance area [%])			
Age	−0.08 (0.08, 75.23%)	0.05 (0.04, 19.18%)	−0.07 (0.08, 71.14%)	0.05 (0.04, 20.98%)
BMI	—	0.38 (0.20, 99.63%)	−0.03 (0.02, 0.84%)	0.31 (0.18, 98.55%)
WHR	−0.08 (0.07, 94.44%)	0.022 (0.01, 1.09%)	−0.05 (0.05, 33.44%)	0.07 (0.07, 57.92%)
Creatinine	−0.02 (0.01, 0.62%)	0.041 (0.03, 94.97%)	−0.02 (0.01, 0.56%)	0.05 (0.03, 97.68%)
Cystatin C	−0.03 (0.02, 65.8%)	0.022 (0.01, 7.92%)	−0.03 (0.03, 81.42%)	0.02 (0.01, 4.35%)
IGF-1	−0.02 (0.00, 0.82%)	0.027 (0.02, 86.2%)	−0.02 (0.00, 4.45%)	0.02 (0.02, 74.99%)
Creatinine in urine	—	0.019 (0.01, 82.5%)	−0.02 (0.01, 4.11%)	0.02 (0.01, 62.37%)
WBC count	−0.03 (0.02, 94.64%)	—	−0.03 (0.03, 86.41%)	0.02 (0.01, 0.63%)
Vigorous MET	−0.02 (0.01, 1.04%)	0.046 (0.03, 97.21%)	−0.01 (0.00, 0.3%)	0.04 (0.03, 96.01%)
Dominant HGS	−0.02 (0.00, 0.09%)	0.087 (0.06, 99.13%)	—	0.09 (0.06, 98.57%)
Alcohol intake frequency	−0.04 (0.02, 3.44%)	0.053 (0.03, 89.95%)	−0.05 (0.02, 2.47%)	0.06 (0.04, 87.73%)
T2D	−0.07 (0.05, 56.56%)	0.056 (0.02, 6.75%)	−0.10 (0.04, 5.2%)	0.09 (0.06, 64.52%)
Frailty	−0.15 (0.07, 87.87%)	0.01 (0.00, 0.01%)	−0.08 (0.05, 52.81%)	0.09 (0.03, 7.24%)
Osteoporosis	−0.14 (0.08, 93.73%)	0.072 (0.01, 0.12%)	−0.10 (0.06, 87.84%)	0.06 (0.04, 3.71%)
CVD	−0.05 (0.02, 89.61%)	—	−0.03 (0.02, 56.38%)	0.04 (0.02, 4.46%)
Age*T2D	−0.06 (0.03, 14.91%)	—	−0.07 (0.03, 55.18%)	—

Note: The total area has been split into positive- and negative-association areas. The standardised regression coefficients ($\hat{\beta}$) are presented as medians (interquartile ranges, IQR), and the significance areas are presented as percentages (%) of the vertices with statistically significant associations.

Abbreviations: BMI: body mass index; CVD: cardiovascular disease; GM: gluteus maximus; HGS: hand grip strength; IGF-1: insulin-like growth factor 1; MET: metabolic equivalent task; MUR: mass univariate regression; T2D: type-2 diabetes; WBC: white blood cell; WHR: waist-to-hip ratio.

associated with T2D in men. Frailty showed widespread inward deformation in men (−0.47 mm left, −0.71 mm right) and more heterogeneous effects in women, with inward deformations across roughly half the GM (−0.37 mm left, −0.36 mm right) and localised outward deformations. Osteoporosis was consistently associated with inward deformation in both sexes (men: −0.66 mm bilaterally; women: −0.37 mm left, −0.45 mm right). CVD was associated with predominantly inward remodelling across large areas of both GM surfaces, with larger effects in men (−0.24 mm bilaterally) than women (−0.12 mm left, −0.13 mm right) (Videos S1).

Age $\times$ T2D interaction analysis showed that age-related inward deformation was more pronounced in participants with T2D in both sexes. In men, age was associated with stronger inward GM deformation particularly in the anterior right GM, with an additional median S2S distances of −0.14 versus −0.08 (right) for T2D versus non-T2D participants while in women, median S2S distances were −0.14 versus −0.07 in both GM, affecting mainly around the inferior-anterior region adjacent to the femoral insertion (Table 2 and Figures 1 and 2). Interactions between T2D and GM fat fraction revealed stronger outward shape variation in those with higher fat fraction in men (left: 0.10 vs. 0.05; right: 0.11 vs. 0.06), affecting 33% of the left and 55% of the right GM, with the largest expansion in the central-posterior right GM. Similar patterns were observed in women (left: 0.09 vs. 0.05;

right: 0.12 vs. 0.05), affecting 54% of the left and 21% of the right GM, with regional predominance in the central left and central-anterior right GM along the border with the gluteus medius and minimus (Figure S8).

3.4 | Longitudinal Associations in GM

Among 2720 participants with repeat imaging after 2.25 ± 0.12 years (1362 men; 1358 women), sex-stratified linear mixed-effects models adjusted for age, assessment centre, ethnicity, BMI, WHR, alcohol intake, HGS, vigorous MET and T2D $\times$ visit interaction revealed consistent longitudinal changes across sexes (Figures S9 and S10). Independent of T2D status, the second imaging visit was associated with declines in GM muscle volume and increases in IMAT volume and fat fraction. Women showed decreases in muscle volume and increases in IMAT and fat fraction while men exhibited greater muscle loss and larger increases in IMAT and fat fraction (Table S5).

Longitudinal changes using mass univariate linear mixed-effect models in GM S2S distances showed no significant impact of T2D on overall shape trajectories. However, both sexes exhibited notable regional shape changes at follow-up (Figure 3). In

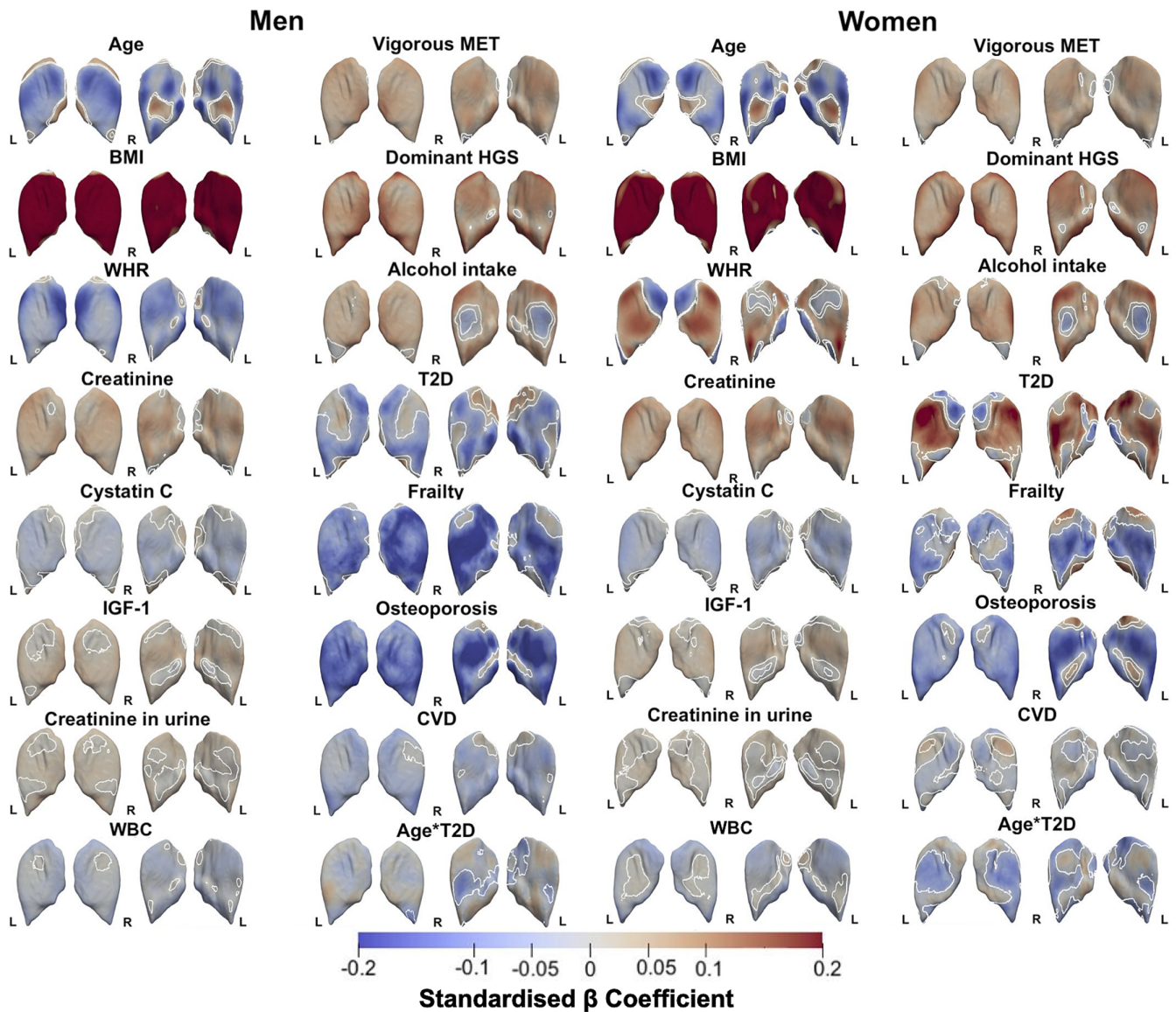


FIGURE 1 | Three-dimensional sex-specific SPMs of GM morphology; projections are for both left (L) and right (R) GM in both posterior (left plots) and anterior (right plots) views. The SPMs show the local strength of association for each covariate in the model with S2S distances in men ($N=23\,364$) and women ($N=24\,670$). White contour lines indicate the boundary between statistically significant regions ($p < 0.05$) after correction for multiple testing, with bright red showing an outward deformation (fatty hypertrophy) and bright blue showing inward deformation (atrophy). The standardised regression coefficients ($\hat{\beta}$) are shown with units in standard deviations for each covariate. Abbreviations: BMI: body mass index; CVD: cardiovascular disease; GM: gluteus maximus; HGS: hand grip strength; IGF-1: insulin-like growth factor 1; MET: metabolic equivalent task; S2S: surface-to-surface; SPM: statistical parametric map; T2D: type-2 diabetes; WBC: white blood cell count; WHR: waist-to-hip ratio.

men, median S2S distances decreased by 0.49 mm (left, 41.5% significance area) and 0.51 mm (right, 32.6%) in inferior posterior/anterior areas and in the sciatic notch, with increases of 0.30 mm (left, 42.7%) and 0.37 mm (right, 28.4%) in central posterior and inferior/lateral anterior regions (Tables S6 and S7). Similar median longitudinal differences were observed in women (Figure S11).

3.5 | Mediation Effects in the Association of GM Morphology, T2D and GM Fat Fraction

SPCA captured over 70% of S2S variation across the first 10 PCs in both sexes (Figure S12 and Video S2).

In men, GM muscle volume showed significant indirect effects on fat fraction when mediated by T2D (left: $ACME = -0.003$, $p < 1 \times 10^{-16}$; right: $ACME = -0.003$, $p = 0.001$), with strong direct effects remaining (left: $ADE = -0.150$, $p < 1 \times 10^{-16}$; right: $ADE = -0.100$, $p < 1 \times 10^{-16}$). Conversely, when T2D was the exposure and GM muscle volume the mediator, significant indirect effects were also observed (left: $ACME = 0.022$, $p < 1 \times 10^{-16}$; right: $ACME = 0.012$, $p < 1 \times 10^{-16}$). In women, no significant indirect effects on muscle volume were observed (Figures S13 and S14).

PC-based mediation revealed sex-specific effects. In men, T2D was negatively associated with PC1 (reflecting smaller GM size), while PC1 was positively associated with GM fat



FIGURE 2 | Three-dimensional sex-specific SPMs of GM morphology; projections are for both left (L) and right (R) GM in both posterior (left plots) and anterior (right plots) views. The SPMs show the local rate of change as a function of age for S2S distances in participants (a) without T2D and (b) with T2D, referred to the sums of the regression coefficients for Age and Age $\times$ T2D, in men ($N = 23\,364$) and women ($N = 24\,670$). Positive associations are in red, and negative associations are in blue. Regression coefficients ($\hat{\beta}$) are shown with units in standard deviations for each covariate. Abbreviations: GM: gluteus maximus; S2S: surface-to-surface; SPM: statistical parametric map; T2D: type-2 diabetes.

fraction, producing a significant negative indirect effect that slightly attenuated the total T2D–fat fraction association, with the direct effect remaining dominant (Figure S15). PC3, representing the remodelling in the superior-lateral border and the central posterior and inferior femoral insertion regions, significantly mediated the T2D–fat fraction association in the right GM (ACME = 0.003, $p = 0.005$) but not the left GM. In the left GM, PC4 capturing central, superior and inferior expansion and shrinkage in the sciatic notch, and PC7 reflecting femoral region shrinkage and central/superior expansion, showed significant mediation effects (PC4: $p = 0.016$; PC7: $p = 0.006$; Figures S16–S18).

In women, PC1 showed no significant indirect effects through T2D in either direction ($p > 0.05$, Figure 4a,b). However, when T2D was the exposure and PC1 the mediator, small but significant indirect effects were observed bilaterally (left: ACME = 0.003, $p = 0.02$; right: ACME = 0.004, $p = 0.006$), indicating that part of the T2D-related increase in fat fraction operates through GM size variation (Figure 4c–e). PC2, explaining superior and inferior and ilioscral expansion and central and femoral region shrinkage, significantly mediated the T2D–left GM fat fraction association in both directions (as exposure: ACME = -0.001 , $p < 0.05$; as mediator: ACME = 0.005, $p = 8 \times 10^{-4}$), with no significant effects observed in the right GM (Figure S19).

3.6 | Diagnostic and Survival Analysis

Two models were compared in T2D case–control cohorts (men $N = 2058$; women $N = 1318$) using 81%/78% training and 19%/21% test splits: a volume model including GM volume, fat fraction and non-disease stability-selected covariates and an extended

volume + PCs model additionally incorporating PC2–PC10 of GM S2S distances (Figures S20 and S21).

In men, the volume model achieved AUC = 0.77 for both GM, with a modest improvement on adding PCs (AUC = 0.78). T2D was associated with higher GM fat fraction (left OR = 1.56 [1.36–1.81], $p = 1.4 \times 10^{-8}$; right OR = 1.61 [1.40–1.86], $p = 1 \times 10^{-9}$) and PC6 reflecting lateral and inferior GM variations (left OR = 0.85 [0.77–0.95], $p = 0.015$; right OR = 1.21 [1.08–1.35], $p = 0.002$). In women, the volume model achieved AUC = 0.75, increasing to 0.76 with the addition of PCs for both GM. T2D was associated with lower PC5 and PC6 in the left GM, capturing central shrinkage with sciatic notch expansion.

Cox proportional hazards models were used to assess the risk of incident T2D after the imaging visit, adjusting selected covariates measured at the imaging visit, GM volume, fat fraction and PC2–PC10 (Figure S22). Data were split into 84%/83.5% training and 16%/16.5% testing for men and women, respectively. Models demonstrated good discrimination (C-index: men 0.82 bilaterally; women 0.74 left, 0.76 right). In men, higher PC6, reflecting reduced variations in the central and superior GM, was consistently associated with lower T2D risk (left HR = 0.81 [0.70–0.95], FDR-adjusted $p = 0.038$; right HR = 0.76, 95% CI 0.65–0.88, p -value = 0.002). In women, PC5 of the right GM, encompassing the central posterior and superior anterior GM, was significantly associated with increased T2D risk (HR = 1.32 [1.08–1.61], $p = 0.032$) (Figure 5).

4 | Discussion

This study provides a multi-scale characterisation of gluteus maximus morphology in a large population-based cohort,

2nd Imaging Visit

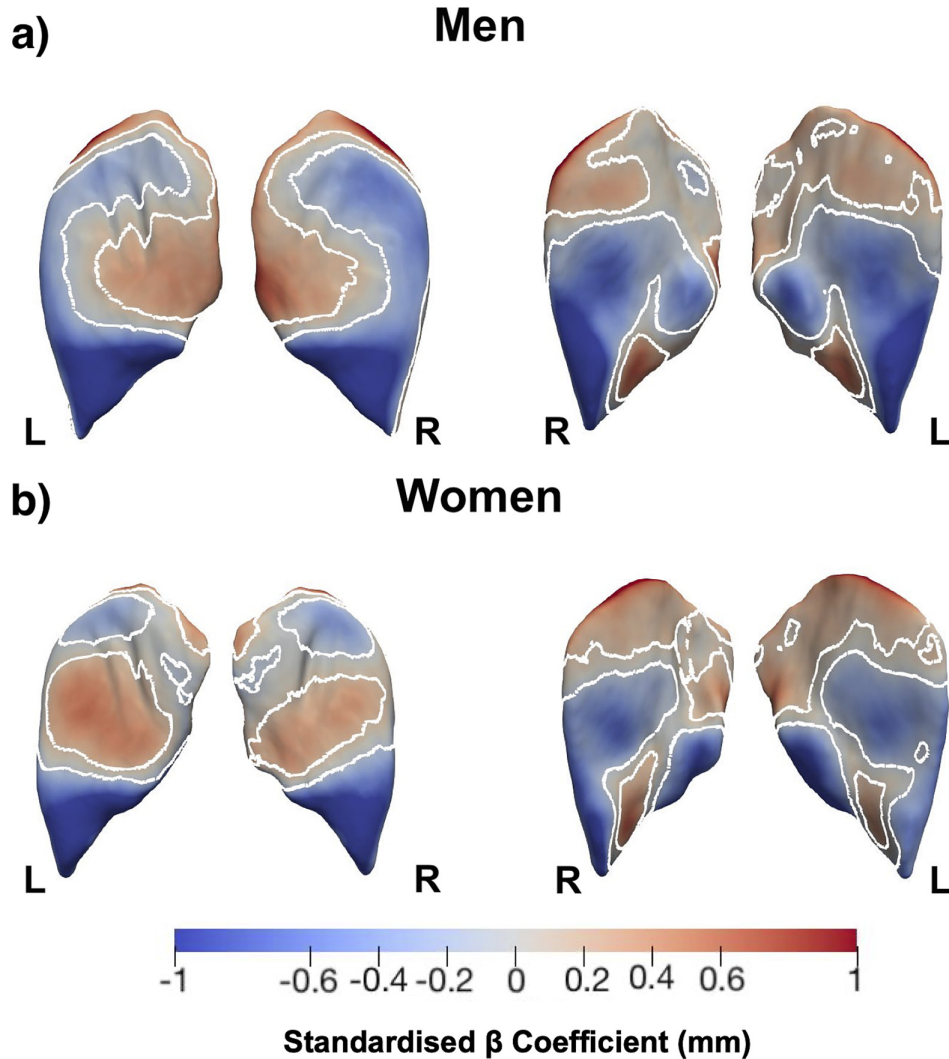


FIGURE 3 | Three-dimensional sex-specific SPMs of GM morphology; projections are for both left (L) and right (R) GM in both posterior (left plots) and anterior (right plots) views. The SPMs show the local strength of association of S2S distances and the imaging visit for (a) men ($N = 1362$) and (b) women ($N = 1358$). White contour lines indicate the boundary between statistically significant regions ($p < 0.05$) after correction for multiple testing, with positive associations in bright red and negative associations in bright blue. The standardised regression coefficients ($\hat{\beta}$) are shown with units in standard deviations for each covariate. Abbreviations: GM: gluteus maximus; S2S: surface-to-surface; SPM: statistical parametric map.

integrating global measures of muscle composition with spatially resolved shape analysis. The key finding is that regional GM remodelling provides information about metabolic health and T2D beyond conventional MRI-derived metrics such as muscle volume and fat fraction. Importantly, these associations show clear sex-specific patterns and are consistent across cross-sectional, longitudinal and survival analyses.

IMAT and fat fraction are clinically meaningful indicators of muscle quality beyond muscle size alone. The GM contributes substantially to pelvic stability and high-demand locomotor tasks, and altered gluteal muscle composition has been shown to differentiate fallers from non-fallers in older adults [5]. Consistent with this, we observed broad associations between GM fat-related phenotypes and frailty-related traits, and prior work confirms that GM IMAT varies with physical activity [6].

Interpretation of fat fraction requires caution, as myosteatosis encompasses multiple lipid depots, each with distinct physiological implications [34]. Dixon-derived fat fraction provides a scalable measure [1] consistent with links between ectopic fat and insulin resistance. CT-based studies demonstrate that myosteatosis relates to hyperinsulinaemia and insulin resistance independent of overall adiposity, and longitudinal evidence links myosteatosis to incident diabetes [35]. Ectopic lipid accumulation frequently coexists with loss of contractile tissue, suggesting that the fat fraction may serve as a surrogate for progressive muscle loss in metabolically compromised individuals, while also capturing local alterations that contribute to reduced strength and performance in T2D [36].

S2S distances provided spatially resolved insight into regional remodelling beyond what volume and fat fraction capture. Statistical

Women

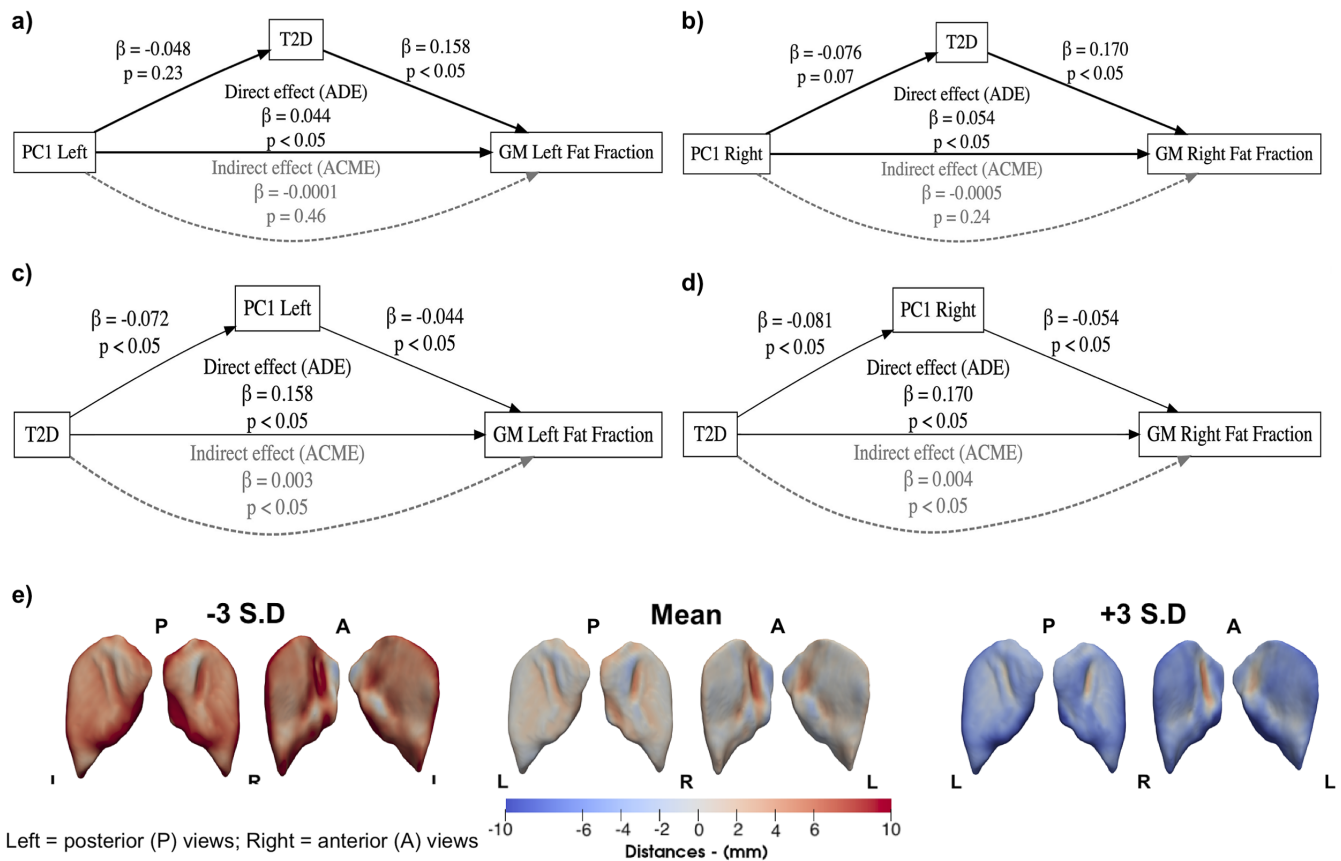


FIGURE 4 | Causal mediation analysis on the relationship between PC1 explaining GM size (from larger to smaller), T2D and GM fat fraction in women ($N = 24\,670$). Upper panels (a) and (b) show exposure PC1 of GM left and right with mediator T2D. Lower panels (c) and (d) show exposure T2D with mediator PC1 of GM left and right. (e) The mean shape and the shape at the ± 3 SD are displayed for PC1, showing the S2S distance variation in mm. The GM shape variations are shown in the anterior (A) and posterior (P) views of each left (L) and right (R) GM. Direct effects are indicated by solid black arrows, whereas mediation effects are indicated by dashed grey arrows. Labels indicate effect size and p -values. Abbreviations: GM: gluteus maximus; PC: principal component; S2S: surface-to-surface; T2D: type-2 diabetes.

parametric maps revealed distinct patterns of inward and outward deformation associated with anthropometry, lifestyle and disease, reflecting the GM's heterogeneous architecture and region-specific functional roles [2, 37]. Ageing was characterised by widespread inward deformation consistent with atrophy, whereas BMI was associated with outward deformation indicating region-specific expansion. Higher handgrip strength and vigorous physical activity were associated with outward deformation, consistent with more robust GM morphology in stronger, more active individuals.

Disease-related maps highlighted marked sex differences. In men, T2D was associated with predominantly inward deformation, whereas in women it was mainly associated with outward deformation. A plausible explanation is that T2D-related fat increases in women contribute to apparent GM surface expansion, while in men the dominant signal reflects muscle loss and inward remodelling [1, 34]. This interplay between sex, ageing and T2D-related muscle changes aligns with evidence that later life hormonal changes exert sex-specific effects on muscle mass and adiposity [38]. Frailty and osteoporosis showed widespread inward deformation, while CVD, especially in men, showed inward remodelling, suggesting a shared adverse musculoskeletal phenotype.

Bidirectional mediation analyses revealed sex-specific and mechanism-specific patterns. In men, GM muscle volume mediated the relationship between T2D and GM fat fraction, highlighting a bidirectional link between muscle structure and metabolic status. In women, muscle volume did not mediate, suggesting that overall muscle size contributes less to fat fraction variation. PCA-derived shape components further revealed sex-specific patterns, with specific regional PCs reflecting lateral and central-superior GM expansions that mediate parts of the T2D-fat fraction relationship in men, and GM size mediating effects in women. This suggests that in women, T2D-related variation in GM 2S distances may contribute to increased fat fraction, potentially reflecting sex-specific morphological adaptations. These findings align with evidence that body fat distribution and ectopic fat show marked sexual dimorphism in individuals with T2D [10] and with prior mediation analyses linking physical activity, skeletal muscle measures and glycaemic control in T2D [7].

Prediction and survival analyses demonstrated that integrating shape descriptors adds value beyond conventional image-derived phenotypes. In case-control models, GM fat fraction was the strongest single MRI-derived predictor, consistent

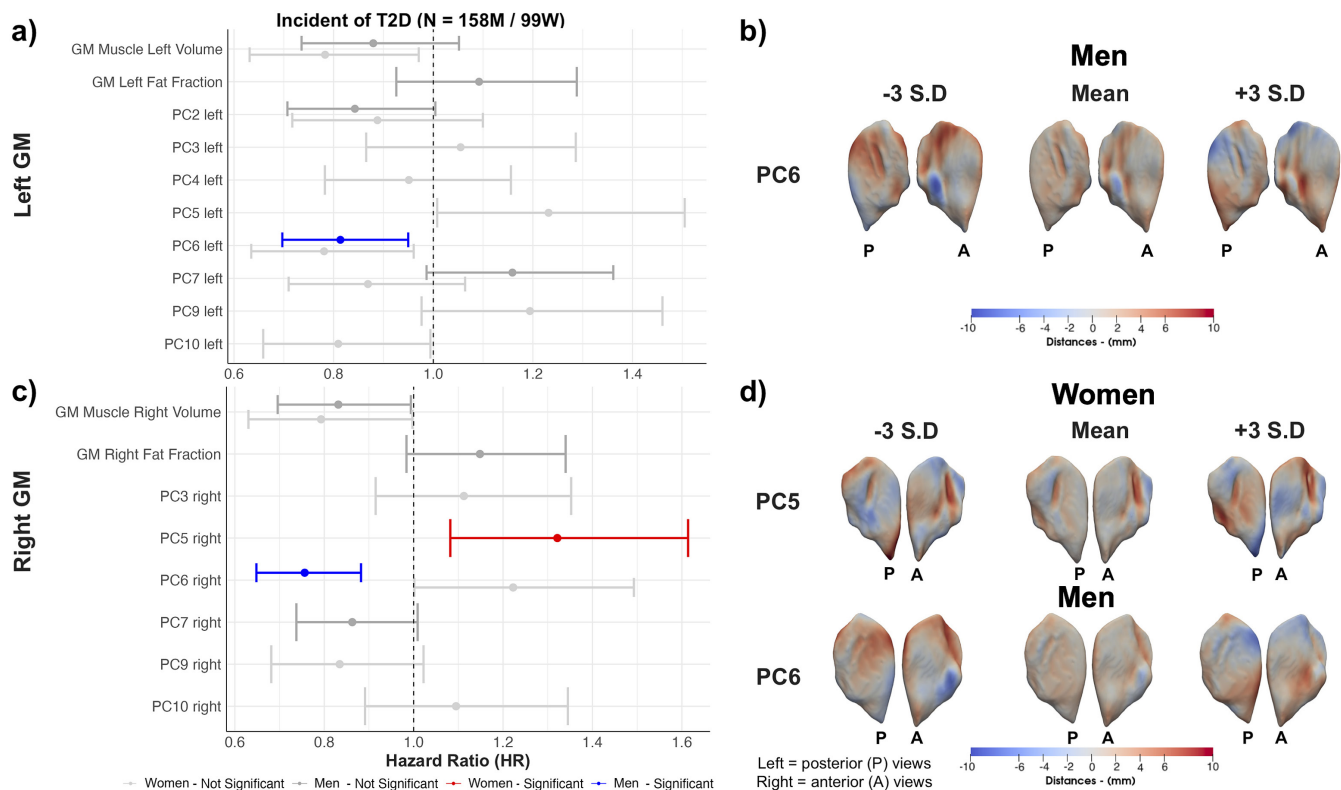


FIGURE 5 | Hazard ratios and 95% CIs for T2D outcome for (a) the men ($N = 158$) and (c) women ($N = 99$) participants in both left and right GM, adjusted for variables selected from the LASSO selection, including anthropometric, lifestyle factors and the first 10 PC scores for GM S2S distances. Statistically significant associations (FDR-adjusted $p < 0.05$) are shown in red. The PCs are visualised for (b) men and (d) women, representing the significant PCs of shape variation for the left and right GM. The mean GM shape and the shapes at ± 3 SD are displayed for each PC, showing the S2S distance variation in mm. The GM shape variations are shown in the anterior (A) and posterior (P) views of each GM. Abbreviations: FDR: false discovery rate; GM: gluteus maximus; LASSO: least absolute shrinkage and selection operator; PC: principal component; S2S: surface-to-surface; T2D: type-2 diabetes.

with the literature linking ectopic lipid accumulation to impaired insulin action and poorer metabolic health [39, 40]. Prevalent T2D was associated with substantially higher GM fat fraction, reinforcing its clinical relevance as a marker of adverse muscle health. Adding PC scores improved diagnostic performance by capturing regional remodelling not reflected in global size or fat fraction. Notably, the PC describing central-superior posterior and anterior GM variation was associated with lower future risk of T2D, suggesting a structurally protective phenotype.

Strengths include the large UK Biobank sample and harmonised imaging/phenotyping framework. Limitations include selection bias, limited generalisability beyond predominantly European ancestry [41], exclusion of participants with missing data, low incidence of future T2D ($\sim 0.5\%$) and relatively short follow-up (4 years). These factors may reduce the power of time-to-event analyses. In addition, blood biomarkers were obtained at the initial assessment visit, whereas MRI was acquired approximately 10 years later; these associations should be interpreted as relationships between baseline biomarker status and later imaging-derived muscle phenotypes rather than assuming that biomarker values remained unchanged at the time of imaging. Furthermore, as these findings derive from a single cohort without external validation, the morphology-derived markers identified here should be considered hypothesis-generating. Future

work should validate findings in independent cohorts, extend follow-up and evaluate predictive value beyond established risk factors. Incorporating genetic and hormonal data into future analyses may be key to uncovering the mechanisms underlying the GM remodelling patterns identified here.

5 | Conclusions

In this large population-based imaging study, integrating conventional MRI-derived GM composition with mesh-based morphometry revealed that muscle fat fraction and regional shape remodelling capture complementary aspects of muscle health. GM morphology contains clinically relevant information beyond standard MRI-derived measures. While fat fraction remains the strongest global marker of metabolic dysfunction, regional shape variation captures additional spatially specific information related to ageing, lifestyle and type 2 diabetes. Longitudinal and mediation analyses demonstrated that structural and metabolic pathways linking GM morphology and T2D differ by sex. Importantly, incorporating shape PCs improved diagnostic and prognostic performance beyond standard phenotypes, highlighting the value of spatially resolved muscle phenotyping. These findings suggest that regional structural shrinkage, fatty replacement and metabolic dysregulation interact to drive progressive muscle deterioration and that spatially resolved muscle

phenotyping may provide sensitive imaging biomarkers of early muscle loss.

Author Contributions

Marjola Thanaj: formal analysis, software, writing – review and editing, visualization, methodology, writing – original draft, investigation, conceptualization, data curation, validation. **Brandon Whitcher:** validation, methodology, writing – review and editing, writing – original draft, supervision, software, data curation, conceptualization. **Hamzah Raza:** writing – review and editing, investigation. **Camilo Bradford-Bell:** investigation, writing – review and editing. **Marili Niglas:** writing – review and editing, data curation. **Jimmy D. Bell:** supervision, project administration, funding acquisition, writing – review and editing, conceptualization, resources. **Dimitri Amiras:** writing – review and editing, supervision, conceptualization, investigation, project administration. **E. Louise Thomas:** supervision, project administration, writing – review and editing, funding acquisition, conceptualization.

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Ethics Statement

The data resources used in this study have approval from ethics committees. Full anonymised images and participants metadata from the UK Biobank cohort were obtained through UK Biobank Access Application number 44584. The UK Biobank has approval from the North West Multi-Centre Research Ethics Committee (REC reference: 11/NW/0382), and obtained written informed consent from all participants prior to the study. All methods were performed in accordance with the relevant guidelines and regulations as presented by the relevant authorities, including the Declaration of Helsinki (<https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/about-us/ethics>).

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the UK Biobank (<https://www.ukbiobank.ac.uk>), but restrictions apply to the availability of these data, which were used under licence for the current study, and so are not publicly available. Data are however returned by us to the UK Biobank where they will be fully available on request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Example of GM segmentation on T1 Dixon sequences showing the extraction of IMAT (thresholded at 0.5 fat fraction cut-off) mapped on the fat images and muscle mapped on the opposed phase images. Relevant GM predictors were identified via LASSO with stability selection. Participant segmentations were used to register images, create 3D GM reference meshes for men and women and compute 3D GM S2S. Associations between S2S and T2D were mapped onto the template meshes. Projections showing the anterior and posterior views for both left (L) and right (R) GM. White contour lines indicate the boundary between statistically significant regions ($p < 0.05$) after correction for multiple testing, with positive associations in bright red and negative associations in bright blue. Reproduced by kind permission of UK Biobank. Abbreviations: LASSO: least absolute shrinkage and selection operator; GM: Gluteus maximus; S2S: Surface-to-surface; T2D: type-2 diabetes; IMAT: intermuscular adipose tissue. **Figure S2:** Dixon MRI images from UK Biobank are used to segment the GM. GM participant's segmentation are used to register images to a common space and create a 3D reference GM template mesh for men and women. The templates were then propagated to each participant's mesh, ensuring anatomical consistency across all participants. 3D GM S2S is computed, mapped to meshes and analysed via mass univariate regression, with the results of the associations between S2S and T2D visualised on the template mesh for men and women. Projections showing the posterior views for both left (L) and right (R) GM. White contour lines in the MUR model indicate the boundary between statistically significant regions ($p < 0.05$) after correction for multiple testing, with positive associations in bright red and negative associations in bright blue. Reproduced by kind permission of UK Biobank. Abbreviations: GM: Gluteus maximus; S2S: Surface-to-surface; T2D: type-2 diabetes; MUR: Mass univariate regression. **Figure S3:** Flow diagram of the study population used in this study ($N = 48\,034$; 23 364 men and 24 670 women) of which 2628 with T2D, 1140 with frailty, 3917 with osteoporosis and 17 615 with CVD. Abbreviations: T2D: type-2 diabetes; CVD: cardiovascular disease. **Figure S4:** Flow diagram for the MUR analysis of the 3D GM S2S phenotypes mapped onto a template surface (posterior views). The 3D phenotypes are used to construct the linear regression model. MUR analysis produces parameter estimates ($\hat{\beta}$) and their null distribution via permutation. TFCE is applied to the t -statistics from the regression analysis to produce a significance threshold. The associated TFCE-derived p -values are corrected for multiple comparisons and mapped onto the GM template mesh for visualisation. This diagram was modified from Biffi et al.⁸ Abbreviations: MUR: Mass univariate regression; TFCE: threshold-free cluster enhancement. **Figure S5:** Plot showing the covariates selected after stability selection as predictors of GM muscle, IMAT volume and fat fraction. Red bars indicate variables selected after stability selection. Abbreviations: GM: gluteus maximus; IMAT: intermuscular adipose tissue. **Figure S6:** Summary of linear regression coefficients for GM muscle, IMAT volume and fat fraction, for left, right and overall GM, representing the associations with the most relevant baseline characteristics in women ($N = 24\,670$) and men ($N = 23\,364$), separately. Standardised beta coefficients are displayed with 95% confidence intervals. Significant associations for FDR-adjusted p -value < 0.05 are shown in red for women and blue for men and non-significant associations in grey. Abbreviations: BMI: body mass index; WHR: waist-to-hip ratio; IGF-1: insulin-like growth factor 1; WBC: white blood cell; MET: metabolic equivalent task; T2D: type-2 diabetes; CVD: cardiovascular disease; GM: gluteus maximus; IMAT: intermuscular adipose tissue; FDR: false discovery rate. **Figure S7:** Histograms of the

statistically significant regression coefficients across the vertices (approximately 16000 in men and 13000 in women) of the GM for each covariate in the model the separated by gender, for each left and right GM. Positive associations are in red and negative associations in blue, with men participants ($N = 23\,364$) in a darker colour and women participants ($N = 24\,670$) in a lighter colour. The regression (beta) coefficients are provided with units in standard deviations for each covariate. Abbreviations: BMI: body mass index; WHR: waist-to-hip ratio, IGF-1: insulin-like growth factor 1; WBC: white blood cell; MET: metabolic equivalent task; T2D: type-2 diabetes; CVD: cardiovascular disease; GM: gluteus maximus. **Figure S8:** Three-dimensional sex-specific SPMs of GM morphology, for both left (L) and right (R) GM in both posterior (left plots) and anterior (right plots) views. The SPMs show the local rate of change as a function of GM fat fraction for S2S distances in participants (a) without T2D and (b) interactions between GM FF and T2D, (c) participants with T2D, referred to the sums of the regression coefficients for GM fat fraction and GM fat fraction*T2D, in men ($N = 23\,364$) and women ($N = 24\,670$). Positive associations are in red and negative associations are in blue. Regression coefficients ($\hat{\beta}$) are shown with units in standard deviations for each covariate. Abbreviations: GM: gluteus maximus; T2D: type-2 diabetes; SPMs: statistical parametric maps; S2S: surface-to-surface. **Figure S9:** Annual changes in gluteus maximus (GM) muscle volume, IMAT volume and fat fraction between the first and second imaging visits, shown in relation to age at the first imaging visit across BMI categories ($10-20$, $20-25$, $25-30$, $30-35$, ≥ 35 kg/m²). Results are presented separately for men ($N = 1362$) and women ($N = 1358$). Abbreviations: BMI: body mass index; GM: gluteus maximus; IMAT: intermuscular adipose tissue. **Figure S10:** Summary of linear mixed effects regression coefficients for GM muscle, IMAT volume and fat fraction, for left, right and overall GM, representing the associations with the most relevant baseline characteristics for men ($N = 1362$) and women ($N = 1358$), separately. Standardised beta coefficients are displayed with 95% confidence intervals. Significant associations for FDR-adjusted p -value < 0.05 are shown in red for women and blue for men and non-significant associations in grey. Abbreviations: BMI: body mass index; WHR: waist-to-hip ratio, MET: metabolic equivalent task; T2D: type-2 diabetes; GM: gluteus maximus; FDR: false discovery rate; IMAT: intermuscular adipose tissue. **Figure S11:** Three-dimensional GM morphology, showing the median changes in the GM S2S between the first and second imaging visit for men ($N = 1362$) and women ($N = 1358$). Projections are posterior and anterior views for both left (L) and right (R) GM in both posterior (left plots) and anterior (right plots) views. White contour lines indicate the boundary between statistically significant regions (FDR-adjusted $p < 0.05$) after multiple-testing correction, with positive changes shown in bright red and negative changes in bright blue. Abbreviations: GM: gluteus maximus; S2S: surface-to-surface. **Figure S12:** The percentage of shape variation explained by the first 10 modes of PCA for the (a, b) left and right GM in men ($N = 23\,364$) and (c, d) women ($N = 24\,670$). Abbreviations: PCA: principal component analysis; GM: gluteus maximus. **Figure S13:** Causal mediation analysis on the relationship between GM muscle volume, T2D and GM fat fraction in men ($N = 23\,364$). Upper panels (a) and (b) show exposure GM left and right muscle volume with mediator T2D. Lower panels (c) and (d) show exposure T2D with mediator GM left and right muscle volume. Direct effects are indicated by solid black arrows, whereas mediation effects are indicated by dashed grey arrows. Labels indicate effect size and p -values. Abbreviations: T2D: type-2 diabetes; GM: gluteus maximus. **Figure S14:** Causal mediation analysis on the relationship between GM muscle volume, T2D and GM fat fraction in women ($N = 24\,670$). Upper panels (a) and (b) show exposure GM left and right muscle volume with mediator T2D. Lower panels (c) and (d) show exposure T2D with mediator GM left and right muscle volume. Direct effects are indicated by solid black arrows, whereas mediation effects are indicated by dashed grey arrows. Labels indicate effect size and p -values. Abbreviations: T2D: type-2 diabetes; GM: gluteus maximus. **Figure S15:** Causal mediation analysis on the relationship between PC1 explaining GM size (from smaller to larger), T2D and GM fat fraction in men ($N = 23\,364$). Upper panels (a) and (b) show exposure PC1 of GM left and right with mediator T2D. Lower panels (c) and (d) show exposure T2D with mediator PC1 of GM

left and right. (e) The mean shape and the shape at the ± 3 SD are displayed for PC1, showing the S2S distance variation in mm. The GM shape variations are shown in the anterior (A) and posterior (P) views of each GM. Direct effects are indicated by solid black arrows, whereas mediation effects are indicated by dashed grey arrows. Labels indicate effect size and p -values. Abbreviations: PC: principal component; GM: gluteus maximus; S2S: surface-to-surface; T2D: type-2 diabetes. **Figure S16:** Causal mediation analysis on the relationship between PC3, explaining the right GM lateral and iliosacral expansion and shrinkage in the supero-inferior and femoral head regions, T2D and GM fat fraction in men ($N = 23\,364$). Upper (a) and (b) show exposure T2D with mediator PC3 of GM left and right. T2D did not significantly mediate the effect of PC3 of GM (left and right) on GM fat fraction (left and right). (c) The mean shape and the shape at the ± 3 SD are displayed for PC3, showing the S2S distance variation in mm. The GM shape variations are shown in the anterior (A) and posterior (P) views of each GM. Direct effects are indicated by solid black arrows, whereas mediation effects are indicated by dashed grey arrows. Labels indicate effect size and p -values. Abbreviations: PC: principal component; GM: gluteus maximus; S2S: surface-to-surface; T2D: type-2 diabetes. **Figure S17:** Causal mediation analysis on the relationship between PC4, explaining the left GM central/superior/inferior expansion and shrinkage in the sciatic notch and femoral head region, T2D and GM fat fraction in women ($N = 23\,364$). Upper panels (a) and (b) show exposure PC4 of GM left and right with mediator T2D. Lower panels (c) and (d) show exposure T2D with mediator PC4 of GM left and right. (e) The mean shape and the shape at the ± 3 SD are displayed for PC4, showing the S2S distance variation in mm. The GM shape variations are shown in the anterior (A) and posterior (P) views of each GM. Direct effects are indicated by solid black arrows, whereas mediation effects are indicated by dashed grey arrows. Labels indicate effect size and p -values. Abbreviations: PC: principal component; GM: gluteus maximus; S2S: surface-to-surface; T2D: type-2 diabetes. **Figure S18:** Causal mediation analysis on the relationship between PC7, explaining the left GM central/superior and femoral region shrinkage and expansion in the inferior region, T2D and GM fat fraction in women ($N = 23\,364$). Upper panels (a) and (b) show exposure PC7 of GM left and right with mediator T2D. Lower panels (c) and (d) show exposure T2D with mediator PC7 of GM left and right. (e) The mean shape and the shape at the ± 3 SD are displayed for PC7, showing the S2S distance variation in mm. The GM shape variations are shown in the anterior (A) and posterior (P) views of each GM. Direct effects are indicated by solid black arrows, whereas mediation effects are indicated by dashed grey arrows. Labels indicate effect size and p -values. Abbreviations: PC: principal component; GM: gluteus maximus; S2S: surface-to-surface; T2D: type-2 diabetes. **Figure S19:** Causal mediation analysis on the relationship between PC2, explaining the left GM superior/inferior and iliosacral region expansion and central and femoral head region shrinkage, T2D and GM fat fraction in women ($N = 24\,670$). Upper panels (a) and (b) show exposure PC2 of GM left and right with mediator T2D. Lower panels (c) and (d) show exposure T2D with mediator PC2 of GM left and right. (e) The mean shape and the shape at the ± 3 SD are displayed for PC2, showing the S2S distance variation in mm. The GM shape variations are shown in the anterior (A) and posterior (P) views of each GM. Direct effects are indicated by solid black arrows, whereas mediation effects are indicated by dashed grey arrows. Labels indicate effect size and p -values. Abbreviations: PC: principal component; GM: gluteus maximus; S2S: surface-to-surface; T2D: type-2 diabetes. **Figure S20:** Diagnostic performance of the logistic regression model in the men case-control cohort with T2D ($N = 2058$) for the left GM. (a, e) The variable importance for T2D of the volume + PCs model of the left (a) and right (e) GM. (b, f) The odds ratios from the logistic regression for T2D for left (b) and right (f) GM adjusted for all variables in the volume + PCs model. Significant associations with FDR-adjusted p -values < 0.05 are shown in red, and non-significant associations are shown in grey. (c, g) ROC curve comparing the volume and the volume + PCs logistic model performance for the left (c) and right (g) GM. (d, h) The significant PCs of shape variation for the left (d) and right (h) GM. The mean GM shape and the shapes at ± 3 SD are displayed for each PC, showing the S2S distance variation in mm. The GM shape variations are shown in the anterior (A) and posterior (P) views of the left GM.

Abbreviations: BMI: body mass index; WHR: waist-to-hip ratio; IGF-1: insulin-like growth factor 1; WBC: white blood cell; HGS: hand grip strength; T2D: type-2 diabetes; GM: gluteus maximus; S2S: surface-to-surface; PC: principal component; FDR: false discovery rate; ROC: receiver operating characteristic curves. **Figure S21:** Diagnostic performance of the logistic regression model in women for the case-control cohort with T2D ($N=1,318$). (a, e) The variable importance for T2D of the volume + PCs model of the left (a) and right (e) GM. (b, f) The odds ratios from the logistic regression for T2D for left (b) and right (f) GM adjusted for all variables in the volume + PCs model. Significant associations with FDR-adjusted p -values <0.05 are shown in red, and non-significant associations are shown in grey. (c, g) ROC curve comparing the volume and the volume + PCs logistic model performance for the left (c) and right (g) GM. (d, h) The significant PCs of shape variation for the left (d) and right (h) GM. The mean GM shape and the shapes at ± 3 SD are displayed for each PC, showing the S2S distance variation in mm. The GM shape variations are shown in the anterior (A) and posterior (P) views of each GM. Abbreviations: BMI: body mass index; WHR: waist-to-hip ratio; IGF-1: insulin-like growth factor 1; WBC: white blood cell; HGS: hand grip strength; T2D: type-2 diabetes; GM: gluteus maximus; S2S: surface-to-surface; PC: principal component; FDR: false discovery rate; ROC: receiver operating characteristic curves. **Figure S22:** Plot showing the hazard ratios of each of the left, right GM and for all men and women participants, with all stability-selected covariates measured at the imaging visit, further using LASSO regression and 10-fold cross-validation for the T2D outcome. Red bars indicate variables selected after LASSO selection. Abbreviations: BMI: body mass index; WHR: waist-to-hip ratio; MET: metabolic equivalent task; T2D: type-2 diabetes; LASSO: least absolute shrinkage and selection operator; GM: gluteus maximus; PC: principal component. **Table S1:** Summary statistics (mean $\pm$ standard deviation) for continuous variables and counts (%) for discrete variables of the 300-participant sex-specific cohort for the template construction. Abbreviations: BMI: body mass index; WHR: waist-to-hip ratio; IGF-1: insulin-like growth factor 1; WBC: white blood cell; MET: metabolic equivalent task; GM: gluteus maximus; IMAT: intermuscular adipose tissue. **Table S2:** Summary statistics (mean $\pm$ standard deviation) for continuous variables and counts (%) for discrete variables in the full cohort (23364 men and 24670 women). Abbreviations: BMI: body mass index; WHR: waist-to-hip ratio; IGF-1: insulin-like growth factor 1; WBC: white blood cell; MET: metabolic equivalent task; HGS: hand grip strength; GM: gluteus maximus; IMAT: intermuscular adipose tissue. **Table S3:** Summary of regression coefficients for the linear regression models for GM muscle volume, IMAT volume and fat fraction, (left, right, both) representing the associations with relevant baseline characteristics on women and men separately. Values are shown in standardised beta coefficients and 95% confidence interval (CI) values in parentheses. An asterisk (*) indicate statistically significant for FDR-adjusted p -value <0.05 . Significant associations are shown in bold. Abbreviations: BMI: body mass index; WHR: waist-to-hip ratio; IGF-1: insulin-like growth factor 1; WBC: white blood cell; MET: metabolic equivalent task; HGS: hand grip strength; T2D: type-2 diabetes; CVD: cardiovascular disease; GM: gluteus maximus; IMAT: intermuscular adipose tissue. **Table S4:** Significance areas for covariates of the MUR models for the disease states of the model for the left GM and right GM ($N=38,868$). The total area has been split into areas of positive and negative associations. The unstandardised (raw) regression coefficients ($\hat{\beta}$) are presented as median (interquartile range [IQR], significance area [%]) across all vertices of the left and right GM surfaces for the vertices with statistically significant associations. The unstandardised (raw) regression coefficients are based on the standardised coefficients and the median standard deviation of the S2S distances across all vertices (SD for the S2S distances is 4.74 mm (left & right GM) in men and 4.15 mm (left GM), 4.48 mm (right GM) in women. Abbreviations: T2D: type-2 diabetes; CVD: cardiovascular disease; GM: gluteus maximus; S2S: Surface-to-surface. **Table S5:** Summary of regression coefficients for the linear mixed-effect models for GM muscle volume, IMAT volume and fat fraction, (left, right, both) representing the associations with relevant baseline characteristics on women and men separately. Values are shown in standardised beta coefficients and 95% confidence

interval (CI) values in parentheses. An asterisk (*) indicates statistically significant for FDR-adjusted p -value <0.05 . Significant associations are shown in bold. Abbreviations: BMI: body mass index; WHR: waist-to-hip ratio; MET: metabolic equivalent task; HGS: hand grip strength; T2D: type-2 diabetes; CVD: cardiovascular disease; GM: gluteus maximus; IMAT: intermuscular adipose tissue. **Table S5:** Significance areas for covariates of the mass univariate linear mixed-effect models for the anthropometric variables of the left GM S2S distances (mm) by gender (1362 men and 1358 women). The total area has been split into positive and negative association areas. The standardised regression coefficients ($\hat{\beta}$) are presented as medians (interquartile ranges [IQR]), and the significance areas are expressed as percentages (%) of the vertices with statistically significant associations. Abbreviations: BMI: body mass index, WHR: waist-to-hip ratio; MET: metabolic equivalent task; HGS: hand grip strength; T2D: type-2 diabetes; GM: gluteus maximus; IMAT: intermuscular adipose tissue. **Table S6:** Significance areas for covariates of the mass univariate linear mixed-effect models for the anthropometric variables of the right GM S2S distances (mm) by gender (1362 men and 1358 women). The total area has been split into positive and negative association areas. The standardised regression coefficients ($\hat{\beta}$) are presented as median (interquartile ranges [IQR]) and the significance areas as a percentage (%) of the vertices with statistically significant associations. All continuous variables used as fixed effects were standardised before analysis. Abbreviations: BMI: body mass index, WHR: waist-to-hip ratio; MET: metabolic equivalent task; HGS: hand grip strength; T2D: type-2 diabetes; GM: gluteus maximus. **Video S1a:** Three-dimensional sex-specific SPMs of GM morphology, showing the rendering from posterior and anterior views for both left (L) and right (R) GM. The SPMs show the local strength of association for each disease (T2D, frailty, osteoporosis and CVD) in the model with S2S distances in men ($N=23,364$) and women ($N=24,670$). White contour lines indicate the boundary between statistically significant regions ($p < 0.05$) after correction for multiple testing, with bright red showing an outward deformation (fatty hypertrophy) and bright blue showing inward deformation (atrophy). The standardised regression coefficients ($\hat{\beta}$) are shown with units in standard deviations for each covariate. Abbreviations: SPM: statistical parametric map; GM: gluteus maximus; S2S: surface-to-surface; T2D: type-2 diabetes; CVD: cardiovascular disease. **Video S1b:** Three-dimensional sex-specific SPMs of GM morphology, showing the rendering from posterior and anterior views for both left (L) and right (R) GM. The SPMs show the local strength of association for each disease (T2D, frailty, osteoporosis and CVD) in the model with S2S distances in men ($N=23,364$) and women ($N=24,670$). White contour lines indicate the boundary between statistically significant regions ($p < 0.05$) after correction for multiple testing, with bright red showing an outward deformation (fatty hypertrophy) and bright blue showing inward deformation (atrophy). The standardised regression coefficients ($\hat{\beta}$) are shown with units in standard deviations for each covariate. Abbreviations: SPM: statistical parametric map; GM: gluteus maximus; S2S: surface-to-surface; T2D: type-2 diabetes; CVD: cardiovascular disease. **Video S2a:** The first 10 modes of shape variation for the GM S2S distances, showing posterior views for both left and right GMs in men ($N=23,364$) and women ($N=24,670$). The mean shape and the shape at the ± 3 standard deviations are displayed for each mode, showing the GM S2S distances change in mm. For visualisation purposes, SPCA was applied jointly to two complementary representations of shape: the 3D coordinates, capturing physical shape variation, and the S2S distances, capturing computational shape differences relative to a reference surface. Together, these two components allow the modes to reflect both the physical deformation of the structure and the surface-level morphological variation. Abbreviations: SPM: statistical parametric map; GM: gluteus maximus; S2S: surface-to-surface; SPCA: sparse principal component analysis. **Video S2b:** The first 10 modes of shape variation for the GM S2S distances, showing posterior views for both left and right GMs in men ($N=23,364$) and women ($N=24,670$). The mean shape and the shape at the ± 3 standard deviations are displayed for each mode, showing the GM S2S distances change in mm. For visualisation purposes, SPCA was applied jointly to two complementary representations of shape: the 3D coordinates, capturing physical shape variation, and the

S2S distances, capturing computational shape differences relative to a reference surface. Together, these two components allow the modes to reflect both the physical deformation of the structure and the surface-level morphological variation. Abbreviations: SPM: statistical parametric map; GM: gluteus maximus; S2S: surface-to-surface; SPCA: sparse principal component analysis. **Data S1:** Supporting information.