# Tirzepatide and muscle composition changes in people with type 2 diabetes (SURPASS-3 MRI): a post-hoc analysis of a randomised, open-label, parallel-group, phase 3 trial

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## Summary

**Background** Substantial weight reduction is often associated with loss of muscle mass. Tirzepatide has been associated with significant reductions in body weight in type 2 diabetes trials and a beneficial effect on body fat distribution in the SURPASS-3 MRI substudy. This post-hoc exploratory analysis studied the association of tirzepatide treatment with changes in thigh muscle volume, muscle volume Z score, and muscle fat infiltration, and aimed to contextualise the results using longitudinal MRI data from UK Biobank participants.

**Methods** SURPASS-3 was a randomised, open-label, parallel-group, phase 3 trial. The multicentre (45 sites) and multinational (eight countries) MRI substudy of SURPASS-3 enrolled insulin-naive adults (aged ≥18 years) with type 2 diabetes who were on treatment with metformin with or without a sodium–glucose co-transporter-2 (SGLT-2) inhibitor, had an $HbA_{1c}$ of 7·0–10·5% (53–91 mmol/mol), a BMI of at least 25 kg/m², and a fatty liver index of at least 60. Participants were randomly assigned (1:1:1:1) to receive subcutaneous injection once per week of tirzepatide (5, 10, or 15 mg), or subcutaneous injection once per day of titrated insulin degludec. Thigh muscle fat infiltration, muscle volume, and muscle volume Z score (invariant to sex, height, weight, and BMI) were quantified by MRI at baseline and week 52. In this post-hoc analysis, we assessed the differences between mean baseline and week 52 muscle composition values in the tirzepatide groups (pooled 5 mg, 10 mg, and 15 mg group, and per dose group) and insulin degludec group using paired *t* tests, and the differences in muscle composition changes with pooled tirzepatide versus insulin degludec via adjusted ANCOVA models. Observed changes in muscle fat infiltration, muscle volume, and muscle volume Z scores were compared using paired *t* tests to population-based estimates calculated from multiple linear regression models fitted to UK Biobank data (n=2942), capturing associations with change in body weight. Analyses were done by modified intention to treat, in the participants enrolled in the MRI substudy with a valid MRI scan at week 52. The SURPASS-3 clinical trial is registered with ClinicalTrials.gov, NCT03882970, and is complete.

**Findings** Participants were assessed for eligibility and recruited from April 1, 2019, to Nov 15, 2019. Among 502 participants assessed for eligibility to participate in the MRI substudy, 296 were enrolled, and 246 had a valid week 52 MRI scan and were included in the post-hoc analyses (tirzepatide 5 mg, n=63; tirzepatide 10 mg, n=60; tirzepatide 15 mg, n=67; insulin degludec, n=56; 147 [59·8%] male participants and 99 [40·2%] female participants). At baseline, overall mean age was 56·0 years (SD 9·9), median duration of type 2 diabetes was 6·7 years (IQR 3·7 to 10·7), mean $HbA_{1c}$ was 8·3% (SD 0·9), mean BMI was 33·4 kg/m² (SD 4·8), and 76 (30·9%) were on an SGLT-2 inhibitor. Mean baseline muscle fat infiltration, muscle volume, and muscle volume Z scores were similar between the pooled tirzepatide group and insulin degludec group. For the pooled and individual tirzepatide dose groups, significant reductions were observed from baseline to week 52 in muscle fat infiltration (for pooled tirzepatide, mean change –0·36 percentage points [95% CI –0·48 to –0·25], p<0·0001), muscle volume (–0·64 L [95% CI –0·74 to –0·54], p<0·0001), and muscle volume Z score (–0·22 [95% CI –0·29 to –0·15], p<0·0001), which occurred in the context of significant weight reduction. Insulin degludec was associated with a modest and significant increase in bodyweight and muscle volume, but no significant change in the other variables. The changes in all three muscle composition variables with pooled tirzepatide were significantly different compared to those with insulin degludec. In tirzepatide-treated participants, observed muscle volume changes across all tirzepatide doses were similar to population-based estimated changes (for pooled tirzepatide, mean difference *vs* population-based estimate, –0·04 L [95% CI –0·11 to 0·03], p=0·22); whereas, observed reductions in muscle fat infiltration across all doses were significantly greater than population-based estimates (for pooled tirzepatide, mean difference –0·42 percentage points [95% CI –0·54 to –0·31], p<0·0001), and the observed reduction in muscle volume Z score with tirzepatide 15 mg was significantly greater than the population-based estimate (mean difference –0·18 [95% CI –0·29 to –0·07], p=0·0016).

**Interpretation** In the SURPASS-3 MRI substudy, in the context of significant improvements in bodyweight and fat distribution, tirzepatide treatment was associated with potentially favourable changes in muscle fat infiltration and reductions in muscle volume broadly in accordance with the general association between changes in muscle volume

**and bodyweight. The present findings provide additional information on the potential effect of tirzepatide on muscle health that might help health-care providers when deciding among treatment options for individual patients.**

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## Introduction

Weight management is considered a key component in the treatment of type 2 diabetes and related comorbidities, and current guidelines recommend it as part of a multifactorial approach.[1] Recent data have linked excess weight in type 2 diabetes to several other complications, especially at younger ages.[2] A sustained reduction of more than 10% of bodyweight might provide disease-modifying effects, possible remission of type 2 diabetes, and improve long-term cardiovascular outcomes and mortality.[1]

Muscle composition is affected by age and metabolic conditions such as type 2 diabetes.[3] In turn, muscle mass and myosteatosis independently predict muscle strength, physical performance, morbidity, and mortality.[4–7] Although substantial bodyweight reduction has been associated with improvements in myosteatosis, it is commonly accompanied by a decrease in muscle mass. Although the reduction in muscle mass during moderate and controlled weight reduction can be adaptive with maintained mobility and function, an excess decrease in muscle mass, particularly with greater weight reduction, might lead to reduced muscle strength, mobility, and physical performance in the long term. This is especially concerning in people at increased risk of sarcopenia, such as older people with chronic conditions.[5] As new and more effective therapeutic options become available for weight management in type 2 diabetes, it is important to obtain contemporary and accurate information about changes in muscle composition (eg, muscle mass and myosteatosis) associated with bodyweight reductions using the most accurate and precise diagnostic tools, such as MRI or CT scans.[8]

Tirzepatide is a once-weekly glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor

### Research in context

#### Evidence before this study

We searched PubMed on May 25, 2024, with no restrictions other than English language, using the terms "albiglutide", "dulaglutide", "exenatide", "liraglutide", "lixisenatide", "semaglutide", "tirzepatide", "glucagon-like peptide-1 receptor agonist (GLP-1 RA)", "glucose-dependent insulinotropic polypeptide (GIP)", "basal insulin", "insulin degludec", "type 2 diabetes", "muscle fat", "muscle fat infiltration", "muscle volume", "muscle mass", and "muscle composition". Clinically significant reductions in bodyweight are often associated with changes in muscle, including volume and fat infiltration. Tirzepatide is a once-weekly, dual GIP and GLP-1 receptor agonist representing a first-in-class drug for the treatment of type 2 diabetes and obesity. It has been associated with significant improvements in glycaemic control, bodyweight, and cardiometabolic parameters across the SURPASS and SURMOUNT clinical programmes when compared with placebo (SURPASS and SURMOUNT) or basal insulin or semaglutide (SURPASS). In addition, tirzepatide showed significant reductions in liver, visceral, and abdominal subcutaneous fat compared with once-daily insulin degludec in the SURPASS-3 MRI substudy. Although some data are available on muscle composition changes in individuals with overweight or obesity treated with GLP-1 receptor agonists, no such data are available in individuals with overweight or obesity and type 2 diabetes.

#### Added value of this study

To our knowledge, this is the first report to describe the associations between the use of an incretin-based medication and changes in muscle composition (muscle volume and muscle fat infiltration) in people with type 2 diabetes, using a gold-standard methodology (MRI). In the context of significant bodyweight loss and overall metabolic improvement, treatment with tirzepatide for 52 weeks was associated with significant reductions in muscle fat infiltration, muscle volume, and muscle volume Z score. When contextualised with longitudinal data from the UK Biobank, the results suggested that decreases in muscle volume with tirzepatide largely followed the general association between changes in muscle volume and bodyweight, whereas decreases in muscle fat infiltration appeared to be greater than the effect of the association with bodyweight. These data suggest an adaptive response to weight reduction for muscle volume and a potentially positive effect on muscle fat infiltration following tirzepatide treatment in this population.

#### Implications of all the available evidence

In people with type 2 diabetes and overweight or obesity, in the context of significant improvements in bodyweight and fat distribution, treatment with tirzepatide was associated with favourable changes in muscle fat infiltration and reductions in muscle volume that appeared to be broadly adaptive to the degree of weight reduction. These data support the clinical benefits observed in clinical trials with tirzepatide and provide additional evidence regarding the potential metabolic effects of this dual GIP and GLP-1 receptor agonist.

agonist approved for the treatment of type 2 diabetes and obesity, and is currently in development for the treatment of several obesity-related complications.[9,10] In people with type 2 diabetes, pooled tirzepatide 10 mg and 15 mg was associated with consistent and significant improvements in glycaemic control, weight-related measures, and multiple cardiometabolic parameters compared with various comparator treatments in the SURPASS programme.[11] Furthermore, in an MRI substudy of SURPASS-3, tirzepatide was associated with significant reductions in liver fat content and the volumes of visceral and abdominal subcutaneous adipose tissue compared with insulin degludec in a subpopulation of participants at high risk of hepatic steatosis.[12] In the current post-hoc exploratory analysis, we aimed to evaluate the association between the use of tirzepatide versus insulin degludec on thigh muscle composition (muscle volume and muscle fat infiltration) in participants in the SURPASS-3 MRI substudy. We also sought to place the results into context by comparing with changes in muscle volume and muscle fat infiltration associated with non-pharmacological weight change in a UK Biobank dataset.

## Methods

### Study design and participants

The SURPASS-3 MRI substudy was a randomised, open-label, parallel-group, phase 3 trial conducted at 45 medical research centres and hospitals in eight countries (Argentina, Austria, Greece, Hungary, Italy, Romania, Spain, and the USA). The design of the SURPASS-3 study and SURPASS-3 MRI substudy has been published previously and described in detail, including the study protocol.[10,13] The SURPASS-3 study enrolled insulin-naive adults (aged ≥18 years) with type 2 diabetes who had a $HbA_{1c}$ of 7·0–10·5% (53–91 mmol/mol), a BMI of at least 25 kg/m², and stable weight during the previous 3 months at baseline, and who were receiving metformin with or without a sodium–glucose co-transporter-2 (SGLT-2) inhibitor during the 3 months prior to screening. Full eligibility criteria were provided in the supplementary material of the primary publication.[13] Additional specific exclusion criteria for the SURPASS-3 MRI substudy were a fatty liver index value below 60 (to include patients with a high likelihood of hepatic steatosis[14]), contraindications to an MRI scan (such as the use of cardiac pacemakers and metal implants), claustrophobia precluding completion of an MRI scan, history of excessive alcohol intake (>21 units per week for male individuals and >14 units per week for female individuals), a BMI higher than 45 kg/m², and participation in the SURPASS-3 CGM (Continuous Glucose Monitoring) substudy.[12] This post-hoc exploratory analysis included participants who were considered to have a a valid MRI scan at week 52. Given that the MRI substudy assessed liver fat content and visceral and abdominal subcutaneous adipose tissue, an MRI scan was considered valid in the substudy if it provided data on one or more of these features.

Written informed consent to participate in the MRI substudy was obtained from all participants at the screening visit. The substudy protocol was approved by the ethical review board at each site (main site institutional review board approval number SSU00076754; National Research Institute, Los Angeles, CA, USA) and was followed according to local regulations and the principles of the Declaration of Helsinki, Council of International Organizations of Medical Sciences International Ethical Guidelines, and Good Clinical Practice guidelines. The SURPASS-3 trial is registered with ClinicalTrials.gov, NCT03882970.

### Randomisation and masking

Participants were randomly assigned (1:1:1:1) to receive tirzepatide (5 mg, 10 mg, or 15 mg) or insulin degludec by a computer-generated random sequence using an interactive web-response system. Stratification was done at randomisation on the basis of $HbA_{1c}$ (≤8·5% [≤69 mmol/mol] *vs* >8·5% [>69 mmol/mol]), country, and use of concomitant oral anti-hyperglycaemic medications (metformin alone or metformin plus an SGLT2 inhibitor). The study was open-label, owing to the different dosing frequencies, titration schemes, and injection devices of insulin degludec and tirzepatide.

### Procedures

Tirzepatide was administered once per week as a subcutaneous injection (5 mg, 10 mg, or 15 mg; Eli Lilly and Company, Indianapolis, IN, USA) with a single-dose pen. Tirzepatide was first given at a dose of 2·5 mg once per week for 4 weeks, which was escalated by 2·5 mg every 4 weeks until the assigned dose was reached. Insulin degludec (Novo Nordisk, Bagsvaerd, Denmark) was administered once per day as a subcutaneous injection with a prefilled pen containing 3 mL (U100/mL), ideally at bedtime. The initial dose of insulin degludec was 10 U/day, titrated weekly to a fasting blood glucose lower than 5·0 mmol/L (<90 mg/dL).[12]At baseline and at 52 weeks of treatment, study participants underwent MRI with the same machine) using a rapid (6–10 min) protocol in 1·5-T or 3-T MRI scanners (manufactured by Siemens, Munich, Germany; Philips, Amsterdam, Netherlands; or General Electric, Chicago, IL, USA).[12,15,16] The collected neck-to-knee images were analysed for quantification of thigh muscle volume and thigh muscle fat infiltration using AMRA Researcher (AMRA Medical AB, Linköping, Sweden) at the time of imaging and data collection. All AMRA personnel (including ODL and JL) were masked during the entire process of analysis and quality control of the images and resulting measurement values. Methods for image analysis and quantification have been described and validated elsewhere (including reproducibility, repeatability, interoperator and intra-operator variability, and sensitivity of the technique to

detect subtle changes in muscle volume and muscle fat infiltration).[16–18] Briefly, the process included (1) calibration of fat-water separated images, (2) automatic multiatlas segmentation of image volumes, (3) quality control (including potential corrections of segmentation) by two independent and trained operators with anatomical knowledge, and (4) quantification of muscle volume and muscle fat infiltration in the segmented regions.

Thigh muscle volume was calculated as fat-free muscle volume, defined as the volume of all voxels with a fat fraction below 50% (sometimes called viable muscle tissue) in the anterior compartment (quadriceps femoris, sartorius, and tensor fascia latae) and posterior compartment (gluteus muscles, iliacus, adductor muscles, and hamstring muscles). If data were missing for one leg, thigh muscle volume was estimated by doubling the muscle volume for the other leg. Thigh muscle fat was calculated as muscle fat infiltration, defined as the mean fat fraction of viable muscle tissue (ie, the fat-free muscle volume) of the right and left anterior thighs, calculated by the sum of the fat fractions of the right and left anterior thigh divided by 2.[16,19] If data were missing for one leg, the mean muscle fat infiltration was estimated from the muscle fat infiltration of the other leg. In addition, muscle volume Z scores (unit SD) invariant to sex, height, weight, and BMI were calculated based on thigh fat-free muscle volume of each participant at baseline and week 52 according to previously published methodology.[5–7] The muscle volume Z score describes how much the muscle volume in each study participant deviates from the mean muscle volume among sex-matched and BMI-matched individuals.[5] For Z score calculation, at least 150 matched controls from approximately the first 40 000 participants scanned in the UK Biobank imaging study were used.[7]

Subsequently, to provide a population-based reference for how changes in muscle composition relate to weight change, we used data from the longitudinal UK Biobank imaging study. Data from 2942 UK Biobank participants with two imaging assessments performed (mean 2·2 [SD 0·1] years apart) and muscle composition values (muscle volume, muscle volume Z score, and muscle fat infiltration) were used. The UK Biobank is a large long-term study that enrolled 500 000 participants from the general population of the UK, who were aged 40–69 years at the time of recruitment in 2006–10. As a substudy, 100 000 of the original 500 000 participants are being re-enrolled for a detailed imaging assessment and repeat of the original baseline assessment (including detailed questionnaires, interviews by trained nurses, physical measurements, and sample collections of blood, urine, and saliva).[20] At the time of this analysis, 2942 participants had been rescanned and analysed for muscle composition, which provided the reference data in a general UK population used in this analysis. The UK Biobank data were accessed via the UK Biobank Access Management System under project ID 6569. The same scanning procedure, image analyses, and methods of quantification for muscle volume and muscle fat infiltration were used in the SURPASS-3 MRI substudy as in the UK Biobank.[15,16] Previous validation has shown high reproducibility and repeatability across manufacturers and field strengths, allowing for cross-study comparisons.[16]

### Outcomes

This post-hoc analysis evaluated the association of tirzepatide versus insulin degludec with changes in thigh muscle fat infiltration, muscle volume, and muscle volume Z score invariant to sex, height, weight, and BMI. Additional endpoints were comparisons with population-based estimated changes in muscle fat infiltration, muscle volume, and muscle volume Z score from calculations of models fitted to longitudinal MRI data of UK Biobank participants.

### Statistical analysis

All analyses were done by modified intention to treat, in all randomly assigned participants who received at least one dose of study drug, in participants enrolled in the MRI substudy with a valid MRI scan at week 52. Baseline demographics, clinical characteristics, and summaries of muscle composition were provided for study groups overall and by sex. Baseline muscle composition was described as mean (SD) in the tirzepatide groups (pooled 5 mg, 10 mg, and 15 mg groups, and per dose group) and insulin degludec group. To assess whether treatment with tirzepatide (pooled dose groups and per dose group) or insulin degludec was associated with significant changes in muscle fat infiltration, muscle volume, and muscle volume Z score, the baseline values were compared with corresponding week 52 values using a paired *t* test. Changes were assessed as mean absolute change and mean relative (%) change. Mean changes in weight and BMI, as well as participant-level relative changes in muscle fat infiltration, were also assessed. The difference in the change from baseline to week 52, comparing tirzepatide (pooled dose groups) and insulin degludec, was tested with an ANCOVA model adjusted for baseline values of the change variable, baseline $HbA_{1c}$, use of SGLT-2 inhibitor, and country. 95% CIs for mean absolute change and mean relative change within the tirzepatide pooled and insulin degludec groups were calculated as *t*-intervals of the change values and the relative change values, respectively. Associations of participant-level absolute change in muscle volume, muscle volume Z score, and muscle fat infiltration in relation to absolute change in body weight, as well as absolute change in muscle fat infiltration in relation to muscle volume Z score, were assessed using scatter plots (tirzepatide 5 mg, 10 mg, and 15 mg groups *vs* insulin degludec) and Pearson correlation coefficients (for the pooled tirzepatide and insulin degludec groups). The same assessments were done for relative change in body weight.

We also did subgroup analyses to assess potential differential changes in muscle composition by important baseline characteristics, in which participants treated with tirzepatide (pooled) were partitioned according to sex, age (<60 years *vs* ≥60 years), muscle volume Z score (low *vs* normal or high), and muscle fat infiltration (high *vs* normal or low). To partition on low versus normal or high muscle volume Z score and high versus normal or low muscle fat infiltration, previously published thresholds to identify adverse muscle composition (muscle volume Z score: –0·68 SD, muscle fat infiltration: 8·82% [women] and 7·69% [men]) were used.[6,7] Differences in the mean absolute and relative changes in bodyweight, BMI, and muscle composition from baseline to week 52 between the subgroups were tested with ANCOVA models adjusted for baseline values of the change variable, baseline $HbA_{1c}$, use of SGLT-2 inhibitor, and country.

In addition, associations of baseline muscle composition with baseline values for body composition and several biomarkers (including glycaemia, lipids, and surrogates of adipose tissue function), and associations of absolute changes in muscle composition with changes in body composition and biomarkers, were assessed with Spearman correlation coefficients in the whole study and separately in the tirzepatide (pooled) and insulin degludec groups.

To calculate population-based estimates of change for comparison with the observed changes, three multiple linear regression models for absolute changes in muscle fat infiltration, muscle volume, and muscle volume Z score were fitted to data from the 2942 UK Biobank participants. To capture the overall association between absolute changes in muscle composition and bodyweight, participants were included in the modelling regardless of disease status and whether they had stable weight, lost weight, or gained weight between the first and second imaging assessments. In addition to bodyweight change, the models included basic characteristics associated with change in muscle composition: sex, baseline age (at first imaging assessment), change in age (between the first and second imaging assessment; to account for study duration), type 2 diabetes status, the interaction between type 2 diabetes status and weight change, and baseline values of either muscle fat infiltration, muscle volume, or muscle volume Z score as predictors. Modelling outputs from the fitted changes in muscle volume, muscle volume Z score, and muscle fat infiltration in the UK Biobank dataset are provided in the appendix (p 12).

See Online for appendix

Population-based estimates of individual-level absolute changes in muscle fat infiltration, muscle volume, and muscle volume Z score for the SURPASS-3 MRI substudy participants were then calculated based on the models fitted to the UK Biobank data. Paired *t* tests were used to compare absolute changes in the SURPASS-3 MRI study across the tirzepatide (pooled dose groups and per dose group) and insulin degludec treatment arms with the population-based estimated changes. 95% CIs of the mean difference between observed and population-based estimates of changes were calculated as *t*-intervals of the pairwise differences.

Missing values were handled separately for each analysis using a complete-case analysis approach. Model assumptions for the ANCOVA and multiple linear regression models were checked with residual plots and scatter plots. Normality of differences in paired t-tests were assessed with density plots and Q–Q plots. R (version 4.4.0) was used for analyses and a p value threshold of 0.05 was used to define significance in the analyses.

### Role of the funding source

The funder of the study was involved in study design, data collection, data analysis, data interpretation, and writing of the report.

## Results

SURPASS-3 screened and recruited participants between April 1, 2019 and Nov 15, 2019. Among 502 participants assessed for eligibility to participate in the MRI substudy, 296 were enrolled. Of these 296 participants, 246 had a valid week 52 MRI scan and were included in the post-hoc analyses (tirzepatide 5 mg, n=63; tirzepatide 10 mg, n=60; tirzepatide 15 mg, n=67; insulin degludec, n=56; appendix p 14). Of these 246 participants, 227 (tirzepatide 5 mg, n=58; tirzepatide 10 mg, n=53; tirzepatide 15 mg, n=61; insulin degludec, n=55) had complete muscle composition data at baseline, and 206 (tirzepatide 5 mg, n=50; tirzepatide 10 mg, n=50; tirzepatide 15 mg, n=56; insulin degludec, n=50) had complete muscle composition data at both baseline and week 52. The table summarises baseline muscle composition measurements in the pooled tirzepatide group and insulin degludec group, as well as demographic and clinical characteristics of participants, which have been previously described in detail.[12] 147 (59·8%) participants were male and 99 (40·2%) were female. At baseline, overall mean age was 56·0 years (SD 9·9), median type 2 diabetes duration was 6·7 years (IQR 3·7–10·7), mean $HbA_{1c}$ was 8·3% (SD 0·9), and mean BMI was 33·4 kg/m² (SD 4·8). 76 (30·9%) participants were on an SGLT-2 inhibitor. Mean baseline thigh muscle fat infiltration, muscle volume, and muscle volume Z score did not statistically differ between the pooled tirzepatide group and insulin degludec group. There were clinically modest but statistically significant differences between the groups in baseline bodyweight and fatty liver index. Baseline demographics, clinical characteristics, and summaries of muscle composition by sex are included in the appendix (p 3).

For pooled tirzepatide, significant reductions were observed from baseline to week 52 in muscle fat infiltration (mean change –0·36 percentage points [95% CI –0·48 to –0·25], p<0·0001), muscle volume (–0·64 L [95% CI –0·74 to –0·54], p<0·0001), and muscle

volume Z score (–0·22 [95% CI –0·29 to –0·15], p<0·0001; appendix p 4). Changes in muscle fat infiltration, muscle volume, and muscle volume Z score from baseline were significant across all doses of tirzepatide (figure 1A, appendix p 4). With insulin degludec, muscle volume was modestly but significantly increased from baseline (mean change 0·16 L [0·01 to 0·31], p=0·043), whereas no significant change was observed for muscle volume Z score (0·06 [–0·06 to 0·18], p=0·35) or muscle fat infiltration (0·03 percentage points [–0·09 to 0·14], p=0·62; figure 1A, appendix p 4). Participant-level relative change in muscle fat infiltration is shown in the appendix (p 15). Observed changes with pooled tirzepatide in all three variables were significantly different compared to those with insulin degludec (all p<0·01; appendix p 4). Changes in muscle composition were observed in the context of significant weight reduction across doses of tirzepatide (for pooled tirzepatide, mean relative weight change –10·1% [95% CI –11·2 to –9·0], p<0·0001) and significant weight gain for insulin degludec (mean relative weight change 3·3% [95% CI 1·8 to 4·9], p=0·0001; appendix p 4). Absolute changes in weight and BMI are included in the appendix (p 4).

Participant-level results indicated a heterogeneous response to both treatments with regard to change in muscle composition in relation to the amount of weight lost (figure 2). Correlation statistics for pooled tirzepatide showed that changes in muscle volume were strongly and significantly correlated with weight change (figure 2A), whereas the correlations of change in muscle volume Z score and muscle fat infiltration with weight change were weaker, albeit also significant (figure 2B, C). Correlation statistics for insulin degludec similarly showed significant correlations of changes in body weight with changes in muscle volume and muscle fat infiltration (figure 2A, C), but no significant correlation with changes in muscle volume Z score (figure 2B). No correlation between changes in muscle volume Z score and muscle fat infiltration was observed for tirzepatide or insulin degludec (figure 2D). Analyses by percentage change in bodyweight are included in the appendix (p 16).

Figure 3 presents results from the subgroup analysis for the effect of pooled tirzepatide on bodyweight and muscle composition. Female participants had a significantly greater decrease in bodyweight with tirzepatide than male participants, and older participants (≥60 years) had a significantly greater decrease in bodyweight with tirzepatide than younger participants. No significant differences in bodyweight decreases were observed by baseline muscle volume Z score or muscle fat infiltration categories. There was no significant difference in the change in muscle composition with tirzepatide between female and male participants, between participants with a low versus normal or high muscle volume Z score at baseline, or between participants with high versus normal or low muscle fat

| | Pooled tirzepatide group (n=190) | Insulin degludec group (n=56) | p value |
|---|---|---|---|
| Age, years | 56·0 (9·8) | 56·1 (10·2) | 0·95 |
| Sex | | | |
| Male | 116 (61·1%) | 31 (55·4%) | .. |
| Female | 74 (38·9%) | 25 (44·6%) | 0·54 |
| Duration of diabetes, years | 6·8 (3·8–11·8) | 5·6 (3·7–8·7) | 0·061 |
| $HbA_{1c}$, mmol/mol | 67·3 (9·8) | 65·6 (11·9) | 0·33 |
| $HbA_{1c}$, % | 8·3 (0·9) | 8·2 (1·1) | 0·33 |
| BMI, kg/m² | 33·7 (4·8) | 32·7 (4·5) | 0·16 |
| Bodyweight, kg | 95·8 (16·5) | 90·7 (16·2) | 0·039 |
| Waist circumference, cm | 111·2 (11·4) | 108·9 (11·5) | 0·18 |
| Fatty liver index | 85·8 (13·0) | 80·8 (17·4) | 0·048 |
| Visceral adipose tissue volume, L | 6·7 (2·0) | 6·2 (1·8) | 0·14 |
| Abdominal subcutaneous adipose tissue volume, L | 10·5 (4·1) | 9·8 (4·0) | 0·28 |
| Liver fat content, % | 14·3 (9·3–21·3) | 15·0 (9·5–23·1) | 0·69 |
| Thigh muscle fat infiltration*, % | 8·1 (2·3) | 7·6 (2·7) | 0·30 |
| Thigh muscle volume*, L | 10·8 (2·6) | 10·7 (3·1) | 0·91 |
| Thigh muscle volume Z score* | –0·48 (1·07) | –0·25 (1·07) | 0·17 |
| Sodium–glucose co-transporter-2 inhibitor use | 64 (33·7%) | 12 (21·4%) | 0·11 |

Data are mean (SD), n (%), or median (IQR). p values are from two-sample *t* tests for all continuous variables except for duration of diabetes and liver fat content, for which the p values are from two-sample Wilcoxon rank-sum tests; p values for categorical variables are from two-proportions *z* tests. *n=18 in the pooled tirzepatide group and n=1 in the insulin degludec group were missing data on baseline muscle volume, muscle volume Z score, and muscle fat infiltration.

***Table:*** **Baseline demographic and clinical characteristics of the analysed SURPASS-3 MRI substudy population**

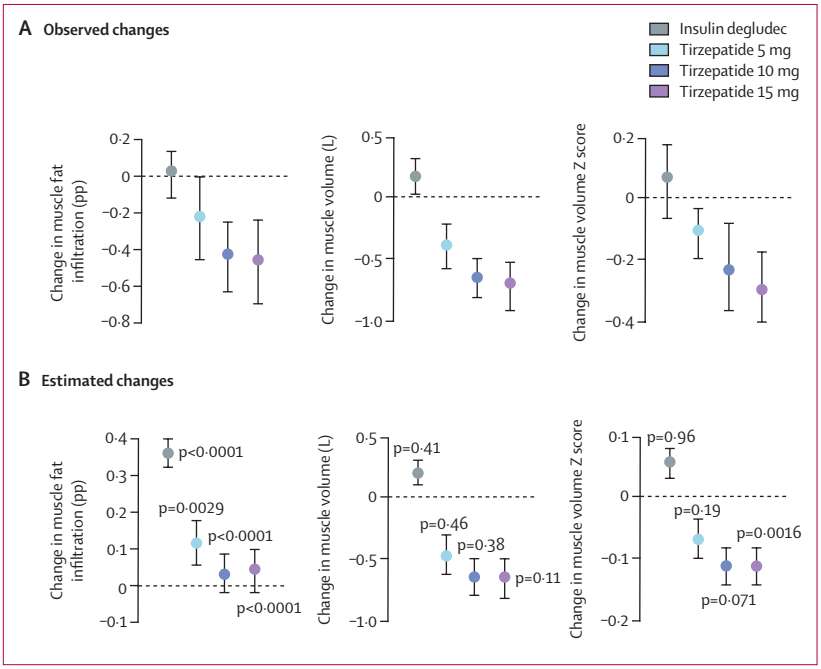



***Figure 1:*** **Changes in muscle composition for insulin degludec and tirzepatide 5 mg, 10 mg, and 15 mg as observed changes (A) and population-based estimated changes (B)**

Values represented are mean and 95% CIs (error bars); p values are from paired t-tests comparing observed changes (panel A) to population-based estimates (panel B). Note that scales on y axes differ between plots for the same measure. pp=percentage points.

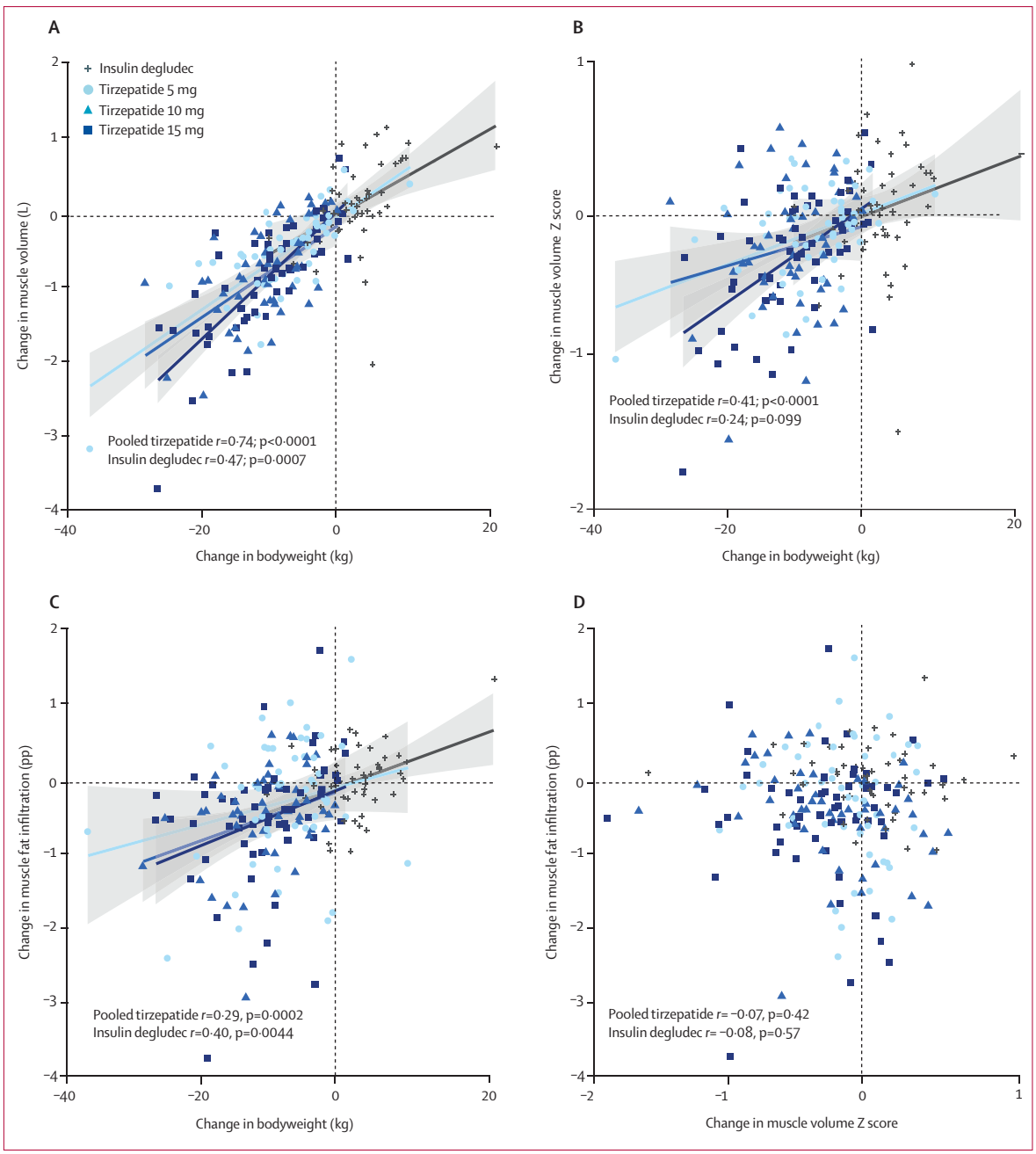
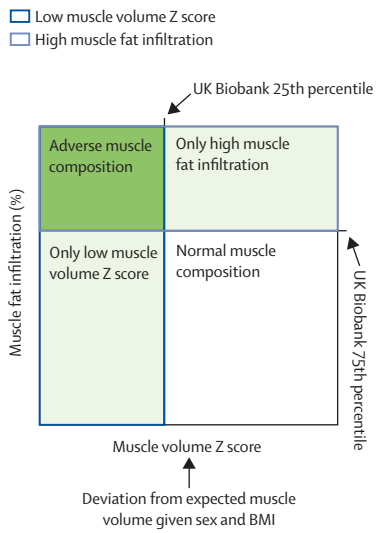



***Figure 2:*** **Participant-level change in muscle composition and its relation to weight change**
Plots show the change in muscle volume (A), muscle volume Z score (B), and muscle fat infiltration (C) in relation to weight change, and the change in muscle fat infiltration in relation to muscle volume Z score (D) in participants treated with tirzepatide and insulin degludec. Associations were assessed with Pearson correlation coefficients for the pooled tirzepatide groups (5 mg, 10 mg, and 15 mg) and the insulin degludec group; shaded areas show 95% confidence bands. pp=percentage points.

infiltration at baseline. Older participants (≥60 years) had a significantly larger decrease in muscle volume Z score with tirzepatide than younger participants. However, there were no significant differences in the reductions in muscle volume or muscle fat infiltration by age group. The appendix (pp 5–6) reports full results including baseline values for each variable and subgroup.

Correlations of baseline muscle composition and changes in muscle composition with body composition and biomarkers are reported in the appendix (pp 7–10). In the tirzepatide (pooled) group, both baseline muscle fat infiltration and the absolute change in muscle fat infiltration with tirzepatide treatment were significantly correlated with triglycerides, HDL cholesterol,




| Subgroups | | Change in bodyweight | | Change in muscle volume | | | Change in muscle fat infiltration | |
|---|---|---|---|---|---|---|---|---|
| | | Absolute (kg) | Relative (%) | Absolute (L) | Relative (%) | Z score | Absolute (pp) | Relative (%) |
| Sex | Females (n=74) | −10·4 (−12·2 to −8·6) | −11·7 (−13·8 to −9·7) | −0·6 (−0·7 to −0·5) | −6·9 (−8·4 to −5·3) | −0·24 (−0·35 to −0·13) | −0·3 (−0·5 to −0·2) | −3·5 (−5·4 to −1·7) |
| | Males (n=116) | −9·0 (−10·4 to −7·7) | −9·0 (−10·3 to −7·8) | −0·7 (−0·8 to −0·5) | −5·5 (−6·6 to −4·3) | −0·20 (−0·29 to −0·11) | −0·4 (−0·5 to −0·2) | −5·1 (−7·1 to −3·1) |
| | p value | 0·015 | | 0·35 | | 0·76 | 0·87 | |
| Age | <60 years (n=118) | −9·0 (−10·3 to −7·6) | −8·9 (−10·2 to −7·7) | −0·6 (−0·8 to −0·5) | −5·3 (−6·4 to −4·1) | −0·19 (−0·28 to −0·09) | −0·3 (−0·5 to −0·2) | −4·6 (−6·4 to −2·9) |
| | ≥60 years (n=72) | −10·5 (−12·3 to −8·8) | −11·9 (−13·9 to −9·9) | −0·7 (−0·8 to −0·5) | −7·3 (−8·8 to −5·8) | −0·27 (−0·37 to −0·17) | −0·4 (−0·6 to −0·2) | −4·2 (−6·5 to −1·9) |
| | p value | 0·029 | | 0·11 | | 0·016 | 0·51 | |
| Baseline muscle volume Z score* | Low (n=65) | −9·8 (−11·8 to −7·8) | −10·8 (−13·0 to −8·7) | −0·5 (−0·6 to −0·4) | −5·5 (−7·0 to −4·1) | −0·10 (−0·19 to −0·01) | −0·5 (−0·6 to −0·3) | −4·8 (−6·9 to −2·6) |
| | Normal or high (n=107) | −9·1 (−10·5 to −7·8) | −9·4 (−10·8 to −8·1) | −0·7 (−0·9 to −0·6) | −6·3 (−7·5 to −5·1) | −0·29 (−0·38 to −0·20) | −0·3 (−0·5 to −0·2) | −4·3 (−6·1 to −2·5) |
| | p value | 0·19 | | 0·38 | | 0·51 | 0·45 | |
| Baseline muscle fat infiltration* | High (n=50) | −9·9 (−11·9 to −7·9) | −10·5 (−12·6 to −8·4) | −0·6 (−0·8 to −0·4) | −6·4 (−8·2 to −4·7) | −0·24 (−0·37 to −0·11) | −0·6 (−0·9 to −0·3) | −5·5 (−8·3 to −2·7) |
| | Normal or low (n=122) | −9·2 (−10·6 to −7·8) | −9·7 (−11·1 to −8·3) | −0·6 (−0·8 to −0·5) | −5·9 (−7·0 to −4·8) | −0·21 (−0·29 to −0·13) | −0·3 (−0·4 to −0·2) | −4·1 (−5·7 to −2·5) |
| | p value | 0·72 | | 0·92 | | 0·24 | 0·46 | |

***Figure 3:*** **Subgroup analysis of participants treated with tirzepatide (pooled dose groups) stratified by sex, age, baseline muscle volume Z score, and baseline muscle fat infiltration**
Participants were stratified by baseline muscle composition according to the left diagram, by applying previously published thresholds for adverse muscle composition (ie, low muscle volume Z score combined with high muscle fat infiltration).[6,7] Participants with adverse muscle composition at baseline were included both among those with low muscle volume Z score (blue group) and among those with high muscle fat infiltration (yellow group). Values are mean (95% CI). p values are from ANCOVA comparing each set of groups and variable. As the ANCOVA models included the baseline value of each variable tested, p values for absolute changes and relative changes are the same. *n=18 missing data on muscle composition at baseline.

adiponectin, and free fatty acids. Among these, only adiponectin at baseline and change in HDL cholesterol were significantly correlated with muscle fat infiltration in the insulin degludec group.

The UK Biobank participants (n=2942), used to calculate population-based estimates for the SURPASS-3 MRI substudy participants, comprised 1471 (50·0%) female participants and 1471 (50·0%) male participants, with a mean age of 63·4 years (SD 7·2), mean BMI of 26·2 kg/m² (SD 4·1), and a type 2 diabetes prevalence of 4·2% (n=124). Compared with the SURPASS-3 MRI study participants, the 124 participants in the UK Biobank with type 2 diabetes were older (mean age 56·0 years [SD 9·9] *vs* 65·0 years [7·2]), had lower weight, BMI, and waist circumference (mean: 94·7 kg [SD 16·5] *vs* 83·8 kg [15·9], 33·4 kg/m² [SD 4·8] *vs* 28·5 kg/m² [4·6], and 110·7 cm [SD 11·4] *vs* 97·2 cm [12·9], respectively), but similar muscle composition (mean muscle volume 10·8 L [SD 2·7] *vs* 10·8 L [2·4], muscle volume Z score –0·43 [SD 1·07] *vs* –0·32 [1·01], and muscle fat infiltration 8·0 L [SD 2·4] *vs* 7·8% [2·1]). Further demographic and clinical characteristics of the UK Biobank participants are provided in the appendix (p 11). A summary of model outputs including proportion of missing data on the predictors for the SURPASS-3 MRI study participants is also provided in the appendix (p 12).

For pooled tirzepatide, the differences between observed changes and population-based estimated changes were significant for muscle fat infiltration (mean difference –0·42 percentage points [95% CI –0·54 to –0·31], p<0·0001) and muscle volume Z score (–0·12 [–0·18 to –0·06], p=0·0002), but not for muscle volume (–0·04 L [–0·11 to –0·03], p=0·22; appendix p 13), indicating that muscle fat infiltration and muscle volume Z score were reduced beyond the effect of the association with bodyweight change, whereas reductions in muscle volume with tirzepatide largely followed the overall association between changes in muscle volume and bodyweight.

The observed reductions in muscle fat infiltration across all tirzepatide doses were significantly larger than population-based estimated changes (mean difference between observed *vs* estimated change: –0·34 percentage points [95% CI –0·55 to –0·12], p=0·0029, for 5 mg

tirzepatide; –0·45 percentage points [–0·61 to –0·28], p<0·0001, for 10 mg tirzepatide; and –0·48 percentage points [–0·69 to –0·26], p<0·0001, for 15 mg tirzepatide), whereas observed reductions in muscle volume did not significantly differ from population-based estimates (mean difference: 0·04 L [95% CI –0·06 to 0·13], p=0·46, for 5 mg tirzepatide; –0·06 L [–0·19 to 0·07], p=0·38, for 10 mg tirzepatide; and –0·10 L [–0·22 to 0·02], p=0·11, for 15 mg tirzepatide; figure 1A, B, appendix p 13). Decreases in muscle volume Z score were somewhat larger than the population-based estimate across tirzepatide doses, albeit with the difference between the observed change and population-based estimate only reaching statistical significance for the 15 mg dose (mean difference: –0·05 [95% CI –0·13 to 0·03], p=0·19, for 5 mg tirzepatide; –0·11 [–0·24 to 0·01], p=0·071, for 10 mg tirzepatide; and –0·18 [–0·29 to –0·07], p=0·0016, for 15 mg tirzepatide). For insulin degludec, the observed increase in muscle fat infiltration was smaller than the model-predicted change, resulting in a negative significant difference when comparing observed change with the population-based estimated change (–0·33 percentage points [95% CI –0·43 to –0·23], p<0·0001); whereas, increases in muscle volume and muscle volume Z score were in accordance with population-based estimates (figure 1A, B, appendix p 13).

## Discussion

These post-hoc analyses of the SURPASS-3 MRI substudy are, to our knowledge, the first to assess the association of an incretin-based therapy with changes in muscle composition assessed by MRI in people with type 2 diabetes and overweight or obesity. Overall, tirzepatide treatment was associated with significant reductions in muscle fat infiltration, muscle volume, and muscle volume Z score, whereas treatment with insulin degludec was associated with a small but significant increase in muscle volume, and no significant changes in muscle fat infiltration and muscle volume Z score. These observations with tirzepatide occurred in the context of significant bodyweight reduction together with improvements in multiple cardiometabolic risk factors, such as lipoproteins and glycaemic control, which were previously reported.[12] In addition, significant improvements were observed for visceral adipose tissue and abdominal subcutaneous adipose tissue and for liver fat content in the previous analysis.[12] When comparing observed changes in muscle composition with population-based estimates derived from UK Biobank data, we identified significantly larger reductions in muscle fat infiltration across all doses of tirzepatide, which potentially suggests a targeted, positive effect of this treatment on muscle fat infiltration. The reductions in muscle volume largely followed the overall association between population-based model-predicted changes in muscle volume and bodyweight (accounting for basic characteristics such as type 2 diabetes status and study duration), indicating that tirzepatide did not seem to be associated with accelerated muscle loss in this population (at least based on the metric of muscle volume). Notably, we also did not observe evidence of a heterogeneous effect on muscle volume or muscle fat infiltration in participants aged 60 years or older, or in participants with low muscle volume Z score or high muscle fat infiltration at baseline, as subgroups at increased risk of multiple complications. There was a small but significant difference in the effect of tirzepatide on muscle volume Z score when comparing older participants (aged ≥60 years) and younger participants. Although exploratory in nature, we believe these data are informative and might serve as an additional reference for future studies evaluating the effect of pharmacological interventions on muscle mass and myosteatosis, especially in the context of marked bodyweight reduction.

In this analysis, we observed significant correlations between change in weight and change in muscle volume, muscle volume Z score, and muscle fat infiltration among tirzepatide-treated participants. It is still unclear if the effects of incretin-based therapies on muscle metabolism are mainly due to the significant bodyweight and fat mass reduction, or also due to specific effects on muscle. Moderate weight reduction with a hypocaloric diet can significantly improve subcutaneous adipose tissue and muscle fat content in people with obesity.[21] However, low or very low calorie diets can also lead to muscle loss due to downregulation of muscle protein synthesis and increased proteolysis.[22] Observations from studies in rodents indicate a potential effect of GLP-1 receptor stimulation on microvascular blood flow and glucose transport in skeletal myocytes, with increased supply of oxygen and nutrients, as well as insulin.[23] There are conflicting preclinical reports about the potential role of GIP in muscle metabolism, and further research is needed to fully elucidate its contribution.[24] No direct comparisons have been reported between a selective GLP-1 receptor agonist and tirzepatide with regard to their effects on muscle composition; therefore, we cannot determine whether GIP receptor stimulation leads to any effects beyond those likely associated with weight reduction.

There are some important aspects to consider when interpreting the results of this analysis. There is a paucity of research on the change in muscle mass and myosteatosis with pharmacological interventions, particularly those that induce large weight reductions, and often an absence of standardisation on the type of techniques and measurements used for the assessment. For example, body composition was evaluated with dual-energy x-ray absorptiometry in a subgroup of participants in the SURMOUNT-1 and STEP-1 studies, and both studies showed a reduction in total fat mass with a relatively lower reduction in lean mass with tirzepatide (SURMOUNT-1) and semaglutide (STEP-1).[25,26] However, these studies did not report the proportion of muscle mass loss out of total lean mass loss, or change in

myosteatosis. Both dual-energy x-ray absorptiometry and bioelectrical impedance provide an estimate of the amount of lean (fat-free) mass, which includes not only muscle mass but also organs, bone, fluids, and hydration in fat tissue. Because lean mass composition varies with bodyweight among individuals, interpretation of how changes in lean mass relate to changes in muscle mass is especially challenging during weight reduction.[27,28] Conversely, gold-standard techniques for muscle composition assessment such as MRI or CT provide accurate measures of muscle volume or mass and myosteatosis—a strength of our study—as these parameters have been associated with function and mortality.[4–7] However, the use of these technologies to evaluate muscle composition changes in clinical trials is uncommon mainly due to cost and availability. These factors likely contribute to the absence of a clear standard consensus on how to measure and interpret the clinical significance and implications of changes in body and muscle composition.

To further contextualise our observations with tirzepatide, we looked at other datasets that used the same quantification technique as in the SURPASS-3 MRI substudy. Preliminary data on annualised changes in weight-stable UK Biobank participants without type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), or cardiovascular disease showed a mean increase in muscle fat infiltration of 0·11 (SD 0·17) percentage points,[29] indicating that the reduction in muscle fat infiltration across the tirzepatide doses in our population would be 2–4 times greater than the mean increase seen with 1 year of ageing. In the UK Biobank, the mean annualised change in muscle volume Z score was –0·07 (SD 0·12) in participants without type 2 diabetes, NAFLD, or cardiovascular disease. In weight-stable participants with type 2 diabetes, in whom muscle wasting with age is intensified, the change in muscle volume Z score was –0·10 (0·13), which is similar to what was observed with the 5 mg dose of tirzepatide in our analysis (–0·12 [95% CI –0·21 to –0·03]).[29,30] In a recently reported trial of individuals with overweight or obesity without diabetes, once-daily subcutaneous liraglutide plus a lifestyle intervention was associated with a mean weight reduction of 6·59% (SD 4·80), with a concurrent absolute mean change in muscle fat infiltration of –0·26 percentage points (SD 0·43) and a significant decrease in muscle volume Z score (–0·11 [SD 0·31]).[8,31] Although the study populations were different, both the magnitude of weight reduction and changes in muscle volume Z score and muscle fat infiltration with liraglutide were similar to those observed in the present analysis for the 5 mg dose of tirzepatide (appendix p 4). Notably, our results showed that reductions in bodyweight, muscle fat infiltration, and muscle volume Z score were greater with the 10 mg and 15 mg doses of tirzepatide. In our study, the observed reduction in muscle volume Z score with tirzepatide 15 mg was significantly greater than a population-based estimate (mean difference –0·18 [95% CI –0·29 to –0·07]). This additional reduction in muscle volume Z score with the 15 mg dose was balanced by a significant additional reduction in muscle fat infiltration (–0·48 percentage points [–0·69 to –0·26]), suggesting a potentially neutral effect on strength and physical performance based on previous research.[32]

As the study was not specifically designed to evaluate muscle-related changes, assessments of strength, mobility, and physical performance are not available. Although changes in these parameters might occur without changes in muscle composition, MRI-based muscle volume and muscle fat infiltration assessments have shown strong correlations with these outcomes. For example, in study populations representative of a general population, both MRI-based muscle volume and muscle fat infiltration have been shown to significantly and independently associate with muscle strength, mobility, and physical performance.[5,6,33] In neuromuscular disorders, changes in muscle fat infiltration have been shown to precede changes in function (with increases associated with worsening function), supporting the potential to use muscle fat infiltration as a surrogate endpoint for muscle function.[34,35] Notably, the use of muscle volume Z score (instead of muscle volume) has a stronger association to muscle strength, mobility, and physical performance and potentially allows comparison of muscle volume changes independent of the magnitude of weight reduction in different trials.[5,6] In contrast to MRI-based assessment of muscle volume and muscle fat infiltration, tests of strength, mobility, and physical performance can be highly variable, challenging to standardise (especially in a multisite setting), and are affected by other factors besides muscle status (eg, motivation, fitness, and pain).[34]

There were no specific instructions in our study about dietary changes or exercise training beyond the standard of care at each site and region, and we cannot exclude the influence that individual differences in lifestyle management might have had on the results. It has been reported that resistance exercise training or dietary supplements might exert a positive effect on muscle composition[36,37] and are recommended when substantial weight reduction is achieved or expected (eg, after bariatric surgery).[38] With the advent of new medications capable of inducing bodyweight reduction that are closing the gap with bariatric surgery procedures, there is a need to evaluate and incorporate detailed information in guidelines and clinical recommendations about patient education, lifestyle management, healthy diet, protein supplements, and regular physical exercise as part of a holistic approach.[3]

This study has several limitations. As previously stated, it was not specifically designed for the assessment of muscle composition and it didn't account for the influence of dietary changes or exercise, and therefore the results of this exploratory post-hoc analysis must be

considered hypothesis-generating and interpreted with caution. A commonly highlighted limitation of MRI is variability introduced by the use of scanners from different manufacturers and field strengths. The repeatability of AMRA Researcher has been assessed in previous validation studies, including a comparison of results from five scanners of different brands (Siemens, General Electric, and Philips) and field strength (1·5 T and 3 T), which yielded repeatability coefficients of 1·44 percentage points (muscle fat infiltration) and 0·311 L (thigh muscle volume).[16]

The participants in SURPASS-3 MRI had type 2 diabetes, were on treatment with metformin with or without an SGLT-2 inhibitor, had a high likelihood of steatotic liver disease, and were mostly White.[12] Additional studies might need to be done in other populations to establish if the results are generalisable, given that different ethnic groups might have different body compositions.[39] Because MRI scans were obtained at baseline and at 52 weeks, we cannot speculate about the changes over time in muscle fat infiltration or muscle volume between these two timepoints. We included an indirect comparison using population-based estimates from UK Biobank due to the absence of available data for comparison, even indirectly, with other therapeutic agents or dietary-based interventions for weight reduction. Additional MRI-based clinical trial data are needed to better contextualise our findings. There was no direct comparison with a selective GLP-1 receptor agonist, and therefore conclusions cannot be drawn about the potential advantages or disadvantages of dual GIP and GLP-1 receptor agonism with respect to the measured variables. Finally, the study does not provide information about long-term outcomes, and we cannot formulate any conclusion in that regard from our observations.

In this post-hoc exploratory analysis in people with type 2 diabetes on metformin with or without SGLT-2 inhibition and with overweight or obesity, treatment with tirzepatide was associated with significant reductions in muscle fat infiltration, muscle volume, and muscle volume Z score, in the context of meaningful weight reduction and improvements in multiple cardiometabolic parameters.[12] When contextualised with longitudinal data from the UK Biobank, the results indicate that decreases in muscle volume with tirzepatide largely followed the overall association between changes in muscle volume and bodyweight, whereas decreases in muscle fat infiltration appear to be greater than the effect of the association with body weight. Overall, the data suggest an adaptive response to weight reduction for muscle volume and a potentially positive effect on muscle fat infiltration following tirzepatide treatment in this population. Additional studies with more specific designs are needed to further investigate how these MRI data translate into long-term changes in muscle strength, mobility, and physical performance in people treated with tirzepatide.

**Contributors**
JL and AR wrote the first draft with input from NS and IJN. JL and AR contributed equally to the manuscript. RB was responsible for the statistical analyses. All authors participated in interpretation of the data and critical review of the manuscript, had full access to all the data in the study, and had final responsibility for the decision to submit for publication. NS, IJN, RB, JL, and AR accessed and verified the data.

**Declaration of interests**
JL and ODL are employees and shareholders of AMRA Medical and have received consulting fees from Eli Lilly and Company. IJN has received institutional grants from the US National Institutes of Health and consulting fees, honoraria, or travel support from Bayer Pharmaceuticals, Boehringer Ingelheim, Eli Lilly and Company, and Novo Nordisk. NS has received institutional grants or contracts from AstraZeneca, Boehringer Ingelheim, Novartis, and Roche Diagnostics and consulting fees or honoraria from Abbott Laboratories, AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Hanmi Pharmaceuticals, Janssen, Menarini Ricerche, Novartis, Novo Nordisk, Pfizer, Roche Diagnostics, and Sanofi. LFL, RB, and AR are employees and shareholders of Eli Lilly and Company.

**Data sharing**
Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymisation, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has received first regulatory authorisation and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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