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Resistance exercise to attenuate lean mass loss during tirzepatide therapy for obesity: a randomized controlled trial

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Incretin mimetics as obesity therapy induce substantial weight and fat loss but also decrease lean soft tissue mass, possibly impairing skeletal muscle function. Here, in this two-arm randomized controlled trial of adding resistance exercise (REx) to tirzepatide (T), 120 adults with overweight or obesity were treated with tirzepatide and randomized to thrice-weekly resistance exercise training or usual activities for 40 weeks. Tirzepatide was safe, and most participants tolerated up-titration to 15 mg weekly. Adherence to resistance exercise was 91%. Weight loss achieved was similar (T = −22.61 kg, T+REx = −22.28 kg, $P = 0.694$). For primary outcomes, loss of total fat mass was similar (T = −17.19 kg, T+REx = −17.98 kg, $P = 0.700$; between-group difference = −0.77 kg, 95% confidence interval (CI): −2.14 kg to 0.60 kg), but resistance exercise reduced loss of total lean soft tissue mass (T = −4.67 kg, T+REx = −3.57 kg, $P < 0.001$; between-group difference = 1.09 kg, 95% CI: 0.43–1.75 kg). For related endpoints, resistance exercise reduced loss of appendicular lean soft tissue mass (T = −3.55 kg, T+REx = −2.92 kg, $P < 0.001$). Upper and lower body muscle strength decreased with tirzepatide (bench press −4.09 kg, lat pulldown −4.42 kg, knee extension −4.42 kg) but increased with T+REx (+4.68 kg, +8.58 kg, +5.88 kg, respectively, all $P < 0.001$ versus tirzepatide). In conclusion, resistance exercise training attenuated loss of total lean soft tissue mass, representing an effective adjunct to tirzepatide anti-obesity therapy. Australian New Zealand Clinical Trials Registry identifier: ACTRN12623001236684.

The worldwide prevalence of obesity is a major public health challenge[1]. This is amplified by the role of excess adiposity as a gateway to multiple cardiometabolic complications[2]. Mimetics of endogenous nutrient-stimulated hormones released from the gut ('incretins') represent a novel strategy for the management of obesity[3,4]. Unsurprisingly, their use has accelerated, such that, in a sample of US adults, 11% reported taking these weight loss medications in 2026 (ref. 5), with expenditure on this drug class predicted to increase 10-fold from 2023 to 2033 (ref. 6). The scale of the underlying condition and this rapid uptake of anti-obesity therapies prompt careful consideration of their benefits but also their immediate and potential longer-term risks[7].

Studies of incretin mimetics in adults with obesity have reported total body weight reductions in the range of 15–24%[3,4,8], which is accompanied by 25–34% reductions in total body fat[3,4,9] and even greater reductions in visceral adipose tissue and in fat accumulated in ectopic depots such as the liver[10]. However, a focus on weight and fat loss masks

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impacts of these therapies on lean soft tissue mass, which includes skeletal muscle mass[11]. In studies assessing body composition using dual energy X-ray absorptiometry (DXA), incretin mimetic therapy for obesity resulted in 11–14% losses in total body lean soft tissue mass[3,4,9]. Skeletal muscle volume, assessed using magnetic resonance imaging (MRI), is also reduced by incretin mimetics, albeit with some reduction in muscle fat content[12]. That study did not assess the timecourse of body composition change or the effect of incretin mimetics on muscle function. Loss of skeletal muscle mass predisposes to sarcopenia and frailty in older adults, giving rise to concerns over potential risks posed by muscle loss in middle-aged and older individuals treated with incretin mimetics[9].

To mitigate skeletal muscle losses, the effects of muscle-preserving drugs are being tested in the setting of incretin mimetic therapy for obesity[13,14]. However, such approaches overlook a readily available non-pharmacological intervention, which is safe and potentially efficacious. Compared to other exercise modalities, resistance exercise training consistently results in greater gains in lean soft tissue mass and muscle strength while eliciting similar reductions in fat mass[15]. After weight loss induced by energy restriction, a combination of liraglutide and aerobic exercise training improved body composition[16], but the effect of combining resistance exercise training with newer and more potent incretin mimetics has not been tested as a primary strategy to optimize muscle mass and strength from the outset of weight loss. We aimed to test the hypothesis that, in adults with overweight or obesity, adding resistance exercise to tirzepatide treatment would attenuate losses in lean soft tissue mass compared to tirzepatide without resistance training, using DXA to assess changes in body composition. We also sought to test a second hypothesis: that this combination would improve regional muscle strength compared to tirzepatide without resistance exercise. Additional related secondary outcomes examined included changes in cardiovascular risk factors.

Results

Trial design

Participants who were obese, or overweight with ≥1 weight-related comorbidities, were randomized to resistance exercise training or usual activities in parallel groups with background tirzepatide therapy for 40 weeks. Co-primary endpoints were changes in fat mass and lean soft tissue mass. Secondary outcomes included regional muscle strength and cardiovascular risk factors (reported here) and cardiorespiratory fitness, vascular function and cardiac function (to be reported as distinct substudies).

Participant baseline characteristics

From 1,251 individuals screened, 121 were randomized between 6 March 2024 and 5 March 2025, with 120 entering the trial (Fig. 1). Baseline characteristics and medication usage of the 61 adults randomized to T and the 59 randomized to T+REx are shown (Table 1 and Extended Data Table 1a). Baseline differences between groups are shown as standardized mean differences, with the largest seen for body mass index (BMI) (Extended Data Table 2). Of the cohort, 50% were female, mean age was 57.7 years (range, 50.1–70.3), 13.3% were overweight, 86.7% were obese and 40% reported using any medication. The most common classes were non-steroidal anti-inflammatory drugs (7.5%), anti-reflux therapy (12.5%) and anti-depressants (10.8%) (Extended Data Table 1a). None of the participants was on anti-hypertensive medications or statins.

Attrition and adherence

In total, 111 (93%) participants completed the trial (T: 93%, T+REx: 92%; Fig. 1). The reasons for withdrawal were adverse events ($n = 6$), breast cancer diagnosis ($n = 2$) and personal reasons ($n = 1$). For tirzepatide dosage and adherence, 78 participants completed the study at the 15 mg dose of tirzepatide, six at 12.5 mg, 15 at 10 mg, nine at 7.5 mg and two at 5 mg. Dosing trajectories were similar for both groups (Extended Data Table 1b). One individual required dose de-escalation to 0 mg. Mean (±s.d.) total dose of tirzepatide was 407 ± 65 mg in the T group and 418 ± 54 mg in the T+REx group. Mean adherence to the thrice-weekly REx sessions was 91% across the 40-week intervention (range, 64–100%).

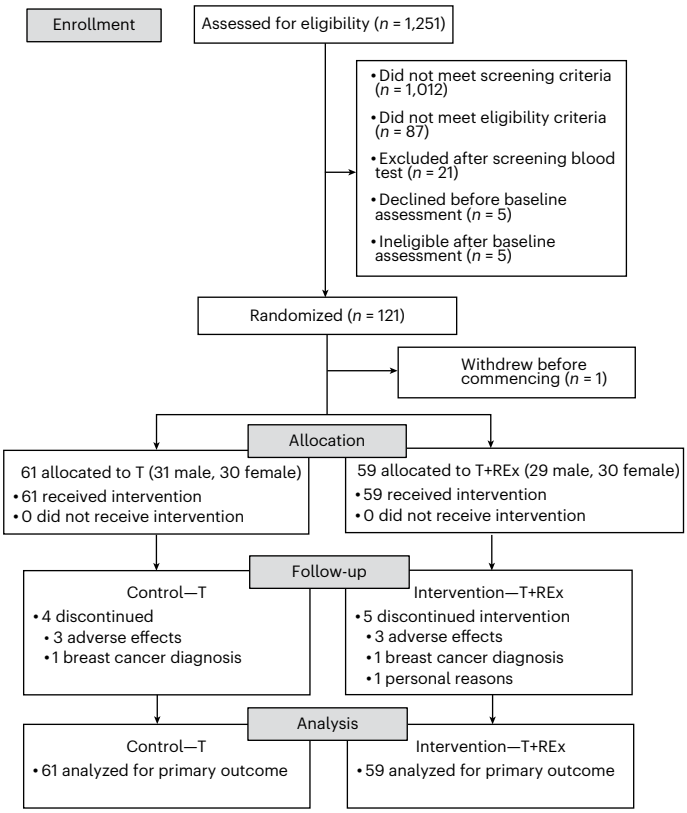

Fig. 1 | The T-REx trial CONSORT flow diagram. In total, 1,251 individuals completed an online screening questionnaire, of whom 1,012 were deemed ineligible. A total of 239 individuals attended an initial clinic visit and provided informed consent and then had screening blood tests. There were 131 individuals who were potentially eligible, of whom five declined to proceed with the study and did not undergo baseline assessments. Of 126 participants who underwent baseline assessments, three had abnormalities detected on transthoracic echocardiography, one could not complete the baseline exercise test and one had high blood pressure. All five were excluded from the study and advised to see their local doctor for follow-up. One participant was randomized but withdrew from the study before receiving any study injections or exercise intervention. A total of 120 participants were randomized into usual activities (T, $n = 61$) and exercise training (T+REx, $n = 59$) groups.

Primary outcomes: fat mass and total lean soft tissue mass

Serial DXA images illustrated dramatic changes from obese to non-obese phenotypes within individuals (Fig. 2). Body weight decreased similarly in both groups (Table 1 and Fig. 3). Total body fat mass decreased (effect of time: $P < 0.001$) to a similar extent in both T and T+REx groups (group × time interaction: $P = 0.700$) (Table 1, Fig. 3 and Extended Data Table 3). Individual changes in body weight and fat mass are shown (Extended Data Fig. 1a,b). In both groups, total body lean soft tissue mass decreased during the course of tirzepatide treatment (effect of time: $P < 0.001$) but to a lesser extent in the T+REx group compared to the T group (group × time interaction: $P < 0.001$) (Table 1 and Fig. 3). At week 40, the between-group difference in change in total body fat mass was −0.77 kg (97.5% CI: −2.14 to 0.60, Cohen's $d = -0.08$, Bonferroni-adjusted $P = 0.416$) (Extended Data Table 4), indicating no significant difference. By contrast, the T+REx group

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Table 1 | Baseline characteristics of the trial cohort and changes occurring over the 40-week intervention

	T	T+REx	*P* value[a]
	(31♂, 30♀)	(29♂, 30♀)	
Age, years	57.07±4.30	58.34±5.06	
Body weight, kg			
Baseline	98.41 (95.35, 101.46)	102.08 (98.98, 105.19)	
Δ 40 weeks	−22.61 (−23.80, −21.42)	−22.28 (−23.49, −21.07)	0.694
BMI, kg m^{-2}			
Baseline	33.08 (32.12, 34.03)	34.62 (33.65, 35.59)	
Δ 40 weeks	−7.62 (−8.01, −7.22)	−7.59 (−7.99, −7.19)	0.820
Waist circumference, cm			
Baseline	106.95 (104.19, 109.70)	109.88 (107.05, 112.71)	
Δ 40 weeks	−19.90 (−21.40, −18.41)	−19.20 (−20.71, −17.68)	0.146
DXA			
Total body fat mass, kg			
Baseline	41.44 (39.24, 43.65)	44.21 (41.97, 46.45)	
Δ 40 weeks	−17.19 (−18.16, −16.15)	−17.98 (−18.99, −16.97)	0.700
Total body lean soft tissue mass, kg			
Baseline	53.16 (51.92, 54.39)	54.03 (52.78, 55.28)	
Δ 40 weeks	−4.67 (−5.12, −4.22)	−3.57 (−4.02, −3.11)	<0.001
Appendicular lean soft tissue mass, kg			
Baseline	25.24 (24.56, 25.92)	25.90 (25.21, 26.59)	
Δ 40 weeks	−3.55 (−3.82, −3.29)	−2.92 (−3.19, −2.66)	<0.001
Strength measures, kg			
Bench press, kg			
Baseline	44.07 (41.92, 46.23)	46.95 (44.78, 49.12)	
Δ 40 weeks	−4.09 (−5.56, −2.62)	4.68 (3.22, 6.15)	<0.001
Lat pulldown, kg			
Baseline	55.37 (53.14, 57.60)	55.68 (53.42, 57.95)	
Δ 40 weeks	−4.42 (−6.54, −2.29)	8.58 (6.46, 10.70)	<0.001
Knee extension, kg			
Baseline	45.30 (42.44, 48.16)	44.45 (41.52, 47.38)	
Δ 40 weeks	−4.42 (−6.90, −1.93)	5.88 (3.35, 8.41)	<0.001
Knee extension/body weight			
Baseline	0.460 (0.422, 0.499)	0.442 (0.402, 0.481)	
Δ 40 weeks	0.073 (0.045, 0.101)	0.202 (0.173, 0.231)	<0.001
Cardiovascular risk factors			
Systolic blood pressure, mmHg			
Baseline	128.62 (125.58, 131.66)	130.41 (127.27, 133.55)	
Δ 40 weeks	−15.26 (−17.79, −12.74)	−16.56 (−19.15, −13.98)	0.493
Diastolic blood pressure, mmHg			
Baseline	75.68 (73.94, 77.42)	75.05 (73.27, 76.83)	
Δ 40 weeks	−6.28 (−7.93, −4.62)	−7.15 (−8.84, −5.46)	0.725
Heart rate, beats per minute			
Baseline	62.75 (60.79, 64.71)	63.21 (61.20, 65.22)	
Δ 40 weeks	2.96 (1.23, 4.70)	2.55 (0.77, 4.33)	0.752
Glucose, mmol l^{-1}			
Baseline	5.37 (5.14, 5.61)	5.20 (4.96, 5.43)	
Δ 40 weeks	−1.04 (−1.29, −0.79)	−0.91 (−1.16, −0.66)	0.708
Insulin, mIU l^{-1}			

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Table 1 (continued) | Baseline characteristics of the trial cohort and changes occurring over the 40-week intervention

	T	T+REx	*P* value[a]
	(31♂, 30♀)	(29♂, 30♀)	
Baseline	11.96 (10.47, 13.46)	13.30 (11.79, 14.80)	
Δ 40 weeks	−4.70 (−6.35, −3.05)	−4.65 (−6.36, −2.94)	0.554
HbA1c, %			
Baseline	5.42 (5.34, 5.50)	5.43 (5.35, 5.51)	
Δ 40 weeks	−0.55 (−0.65, −0.45)	−0.55 (−0.65, −0.45)	0.720
Total cholesterol, mmol l^{-1}			
Baseline	5.52 (5.33, 5.74)	5.65 (5.44, 5.86)	
Δ 40 weeks	−0.66 (−0.90, −0.42)	−0.67 (−0.91, −0.43)	0.421
LDL cholesterol, mmol l^{-1}			
Baseline	3.33 (3.18, 3.50)	3.49 (3.32, 3.66)	
Δ 40 weeks	−0.23 (−0.41, −0.05)	−0.21 (−0.39, −0.03)	0.949
HDL cholesterol, mmol l^{-1}			
Baseline	1.46 (1.37, 1.54)	1.39 (1.32, 1.49)	
Δ 40 weeks	0.05 (−0.03, 0.13)	0.08 (0.00, 0.16)	0.899
Triglycerides, mmol l^{-1}			
Baseline	1.51 (1.34, 1.68)	1.63 (1.44, 1.79)	
Δ 40 weeks	−0.66 (−0.82, −0.50)	−0.63 (−0.79, −0.47)	0.961

Values are marginal means and 95% CIs based on prespecified LMM analysis, except for age where s.d. is shown. *P* values are for group×time interactions derived from these mixed-effects models adjusted for age and sex. [a]*P* values for group×time interactions are shown, based on LMM analysis.

demonstrated a smaller loss of total body lean soft tissue mass, with a between-group difference of 1.09 kg (97.5% CI: 0.43–1.75, Cohen's $d = 0.10$, Bonferroni-adjusted $P < 0.001$).

A similar result was seen with appendicular lean soft tissue mass (effect of time: $P < 0.001$; group × time interaction: $P < 0.001$; between-group difference: 0.63 kg; 95% CI: 0.30–0.96; Cohen's $d = 0.11$) (Table 1, Fig. 3 and Extended Data Table 4).

Mean changes at each assessment timepoint shown graphically (Fig. 3) are also tabulated for reference (Extended Data Table 3). At week 24, total lean soft tissue mass had declined in the T group by 4.97 kg compared to 3.64 kg in the T+REx group. After 24 weeks, changes in total lean soft tissue mass plateaued so that, at week 40, the decrease from baseline in the T group was 4.67 kg compared to 3.57 kg in the T+REx group. Appendicular lean soft tissue mass declined consistently in both groups and, at week 40, was 3.52 kg lower in the T group and 2.94 kg lower in the T+REx group relative to baseline. Individual changes in total and appendicular lean soft tissue mass are shown (Extended Data Fig. 1c,d).

Secondary outcomes: BMI, waist circumference, skeletal muscle strength and cardiovascular risk factors

BMI and waist circumference decreased with tirzepatide treatment (effect of time: both $P < 0.001$), similarly in both T and T+REx groups (group × time interaction: both $P > 0.05$) (Table 1 and Extended Data Table 3). Muscle strength changed during tirzepatide treatment for all measures (effect of time: all $P < 0.001$), with a marked divergence in responses between T and T+REx groups (group × time interaction: all $P < 0.001$) (Fig. 4). In the T group, bench press, lat pulldown and knee extension strength decreased by 4.09 kg, 4.42 kg and 4.42 kg (8.4%, 6.5% and 9.0%), respectively, whereas, in the T+REx group, these strength measures increased by 4.68 kg, 8.58 kg and 5.88 kg (10.7%, 15.7% and 17.5%), respectively (Table 1, Fig. 4 and Extended Data Table 3). Net differences in muscle strength change between T and T+REx groups for bench press, lat pulldown and knee extension were 8.59 kg, 12.97 kg and 9.78 kg (18.8%, 23.4% and 21.8%), respectively (Extended Data Table 4). Individual changes in regional muscle strength are shown (Extended Data Fig. 2). The ratio of knee extension/body weight was increased substantially with T+REx compared to T (group × time interaction: $P < 0.001$; Table 1 and Extended Data Table 3).

Both groups had similar reductions in systolic and diastolic blood pressure, fasting glucose, fasting insulin, glycated hemoglobin (HbA1c), total cholesterol and triglycerides (effect of time: all $P < 0.01$; Table 1, Fig. 5a–g and Extended Data Tables 3 and 4), with the exception that high-density lipoprotein (HDL) cholesterol did not change over time ($P = 0.217$; Table 1 and Fig. 5h). The mean decrease in systolic blood pressure at 40 weeks was 15.3 mmHg and 16.6 mmHg in T and T+REx groups, respectively (Table 1). There was no effect of REx on these outcomes (group × time interaction: all $P > 0.05$).

Safety

The most common gastrointestinal adverse events were nausea (occurring in approximately half of participants), vomiting, constipation, diarrhea and indigestion (each occurring in approximately one-third), which were self-reported in similar frequencies in T and T+REx groups (Extended Data Table 5a). Other adverse events included feeling lightheaded (approximately 20–30%), low mood (approximately 15–20%), lethargy/weakness (approximately 15%) and headache, insomnia, hypotension, injection site reactions and general pain (approximately 10–20%), which were all also self-reported at similar frequencies in both groups. In total, 89 participants self-reported any adverse events occurring over 5 weeks, 23 over 6–10 weeks and none for more than 16 weeks (Extended Data Table 6). Six serious adverse events occurred, five in the T group, which were assessed as being unrelated to T treatment, and one in the T+REx group, which was assessed as being unrelated to either T treatment or REx (Extended Data Table 5b).

Sensitivity analyses

For the outcomes of total and appendicular lean soft tissue mass and regional muscle strength (bench press, lat pulldown and knee

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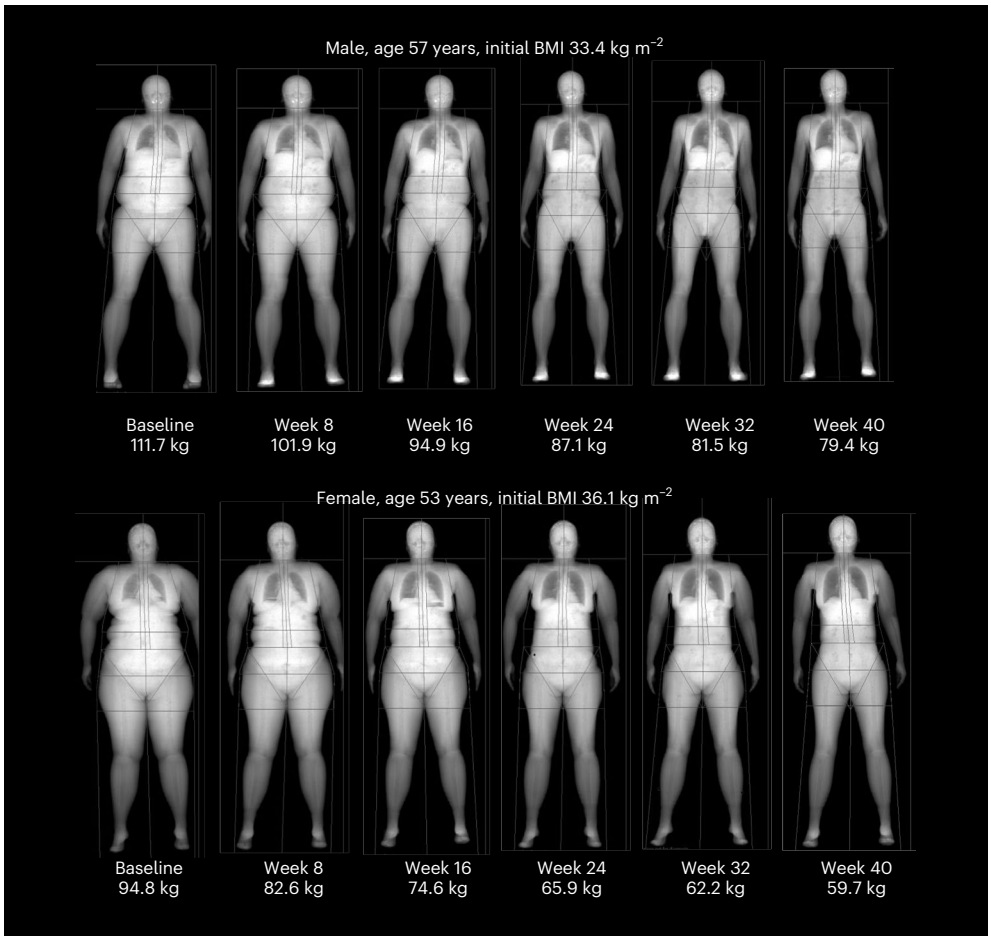

Fig. 2 | Changes in body size and shape over 40-weeks. Example of changes in DXA whole-body scans collected every 8 weeks across the 40-week tirzepatide administration period in one male (**a**) and one female (**b**) participant. Timing of the DXA imaging and the weight at the time of scanning are shown.

extension), adjustment for baseline BMI made no difference to the results (group × time interactions, all $P < 0.001$).

Post hoc analysis

In a subset of participants who completed 3-day food diaries, energy and protein intakes were similar in T and T+REx groups across baseline, week 24 and week 40 (Extended Data Table 7).

Discussion

To our knowledge, this is the first randomized trial to test resistance exercise training in combination with tirzepatide for treatment of overweight and obesity. In response to our 40-week tirzepatide intervention, total body lean soft tissue mass and appendicular lean soft tissue mass declined progressively over the 40-week intervention, and resistance exercise training attenuated these losses in both cases. Notably, in participants who received tirzepatide, both upper and lower body muscle strength was compromised, whereas those who received tirzepatide and contemporaneous resistance exercise training had substantially increased muscle strength. Both groups experienced similar progressive reductions in body weight, fat mass, waist circumference and BMI, with commensurate improvements in blood pressure, glycemia and lipids, with no added benefit of resistance exercise training on those outcomes.

In a previous trial in adults with obesity that included an initial 8-week energy restriction that resulted in a mean 13.1-kg decrease in weight, Lundgren et al.[16] found that a combination of liraglutide with twice-weekly, supervised, aerobic-based exercise for 12 months resulted in greater reductions body fat and a modest 0.5-kg increase in lean mass; liraglutide-only maintained lean mass (0.0 kg change). Our study used a more potent incretin mimetic that achieved considerably greater weight loss, combined personalized resistance exercise training with tirzepatide from the outset and tracked the timecourse of changes in body composition. Of note, the trajectory of loss of total body lean soft tissue mass in our study was not linear and appeared to plateau after 24 weeks. Although resistance exercise training did not completely prevent the reduction in lean soft tissue mass, it attenuated the loss, from 4.7 kg to 3.6 kg. Although lean soft tissue mass and skeletal muscle mass cannot be directly equated, when compared against assessment of skeletal muscle volume by whole-body MRI, skeletal muscle mass comprises approximately 50% of total body lean soft tissue mass and approximately 70% of appendicular lean soft tissue mass[17]. Participants who received tirzepatide had reduced appendicular lean soft tissue mass of 3.5 kg (14% of baseline value), which translates to approximately 2.5 kg of skeletal muscle mass, whereas those who received tirzepatide and resistance exercise training limited the loss to 2.9 kg (11% of baseline value), which corresponds to approximately 2 kg of muscle mass. Skeletal muscle mass has been estimated to decline by approximately 0.5–1% per year from middle to older ages[18], so, on this basis, the muscle loss observed over 40 weeks in our participants approximates changes that might occur over a decade or more of aging. Preserving skeletal muscle mass is important, as its loss is associated with poorer health outcomes, including higher risks of falls and fractures, and higher incidence of cardiovascular disease in middle-aged and older adults[19,20].

Muscle strength is an important variable reflecting muscle quality, neuromuscular function and metabolic health in addition to muscle

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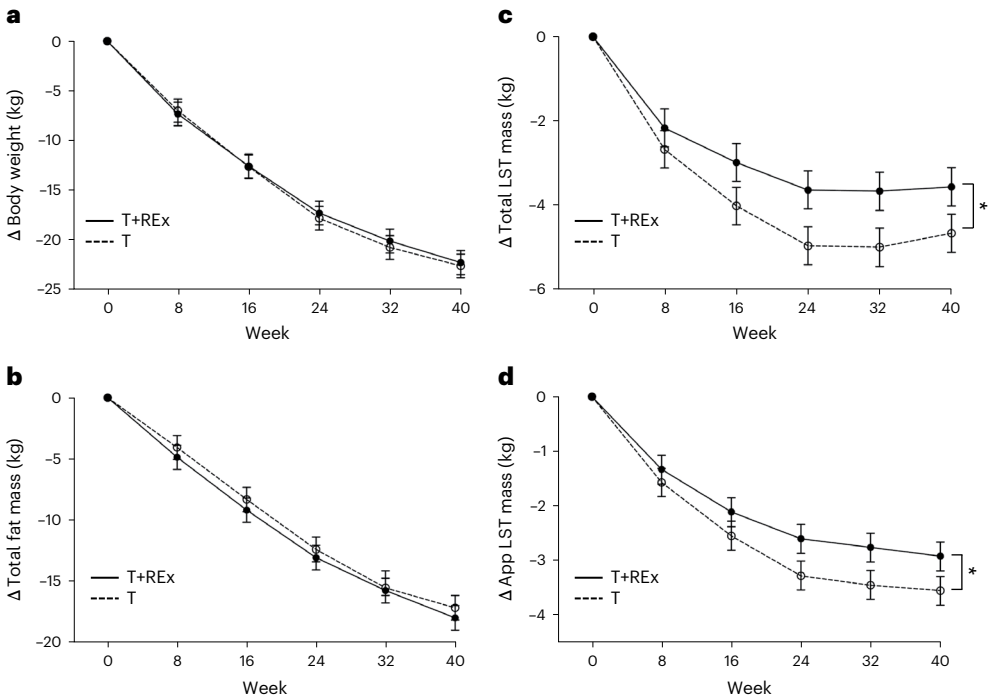

Fig. 3 | Changes in body weight, fat and lean soft tissue mass. Mean changes in body weight (**a**) and DXA-derived total fat mass (**b**), total body lean soft tissue mass (**c**) and appendicular lean soft tissue mass (**d**) in 60 male and 60 female participants with overweight and obesity who were randomized to receive tirzepatide (T) or tirzepatide alongside three supervised, center-based sessions of resistance exercise training (T+REx) weekly for 40 weeks. Error bars are 95% CIs. Statistical testing was performed using LMMs. Baseline value was the reference category, resulting in five degrees of freedom for the overall time effect and five corresponding treatment group × time interaction terms. All tests were two-sided. All four variables decreased over time in both groups (effect of time: all $P < 0.001$). Group × time interactions were present for total body and appendicular lean soft tissue mass (*$P < 0.001$), indicating an effect of resistance exercise training to reduce loss of lean soft tissue mass. LST, lean soft tissue.

quantity[21,22]. Data on the effects of incretin mimetics on regional muscle strength and its modulation by exercise are lacking[23–25]. In the trial by Lundgren et al.[16], perception of general health assessed by questionnaire improved, but muscle strength measured by isometric knee extension did not change significantly across groups[26]. In previous randomized, placebo-controlled trials of obesity, semaglutide and tirzepatide therapy resulted in substantial weight loss and modest improvements in questionnaire assessment of self-rated physical health[3,4]. In a prospective single-arm study of 106 adults with obesity, semaglutide 2.4 mg weekly reduced fat mass and lean mass over 7 months and 12 months, with an improvement in handgrip strength[25]. Handgrip strength is often used as a surrogate measure for overall body strength, but no previous studies have conducted serial assessments of change or regional changes in muscle strength (that is, upper and lower body muscle strength at regular timepoints to evaluate timecourse changes). Bariatric surgery can result in decreases in muscle strength, proportionate to weight loss[27]. We observed substantial reductions of 6–9% in upper and lower body muscle strength in the T group over 40 weeks. Notably, the T+REx group showed enhanced muscle strength with increases of 10–18% from baseline, a finding that was consistent across all muscle groups tested. After age 50, muscle strength declines at a rate of approximately 12–15% per decade[28]. Thus, the approximately 20% net gain in muscle strength with resistance exercise and tirzepatide, compared to tirzepatide alone, is substantial and likely to have longer-term functional implications. For improvements in function and quality of life, emphasis should be placed on increasing strength through resistance training rather than merely preventing muscle atrophy or inducing muscle hypertrophy in sedentary individuals[29].

Only a minority of participants self-reported symptoms of lethargy or weakness (14.8% in the T group and 16.9% in the T+REx group). Therefore, subjective impressions of weakness do not correlate with objective assessments of muscle strength. By performing serial measures every 8 weeks at the same timepoints, we familiarized both groups equally with the assessment procedures. The decline in upper and lower body muscle strength seen in the participants from the T group occurred in conjunction with a reduction in lean soft tissue mass. By contrast, participants in the T+REx group showed consistent, substantive increases in upper and lower body muscle strength, with a smaller reduction in total body and appendicular lean soft tissue mass. Gains in muscle strength in response to resistance exercise training arise from neuromuscular adaptation to achieve maximal or near-maximal recruitment of motor units as well as muscle hypertrophy[30,31]. We postulate that the extent of weight loss seen with tirzepatide treatment limited the ability of resistance exercise training to induce muscle hypertrophy, thus attenuating muscle loss while increasing muscle strength.

Outside the context of incretin-induced anti-obesity therapy, anabolic drugs can increase muscle mass and strength, but muscle quality and function are optimized with the addition of resistance exercise[32]. For example, testosterone treatment in overweight middle-to-older aged men is less effective at improving lean mass and strength compared to exercise training[33,34]. Bimagrumab and apitegromab are monoclonal antibodies targeting activin type II receptors and precursor forms of myostatin, a ligand for these receptors, respectively[13,14]. In a 24-week trial of bimagrumab to treat sarcopenia in community-dwelling older adults, treatment with bimagrumab increased lean body mass but did not improve physical performance assessed as Short Physical Performance Battery (SPPB) score, 6-minute walk test, gait speed and handgrip strength[35]. In another 24-week trial in older adults undergoing surgery for hip fracture repair, bimagrumab increased lean body mass but did not improve SPPB score or gait speed[36]. Recently, Heymsfield et al.[13] reported a 48-week trial in adults

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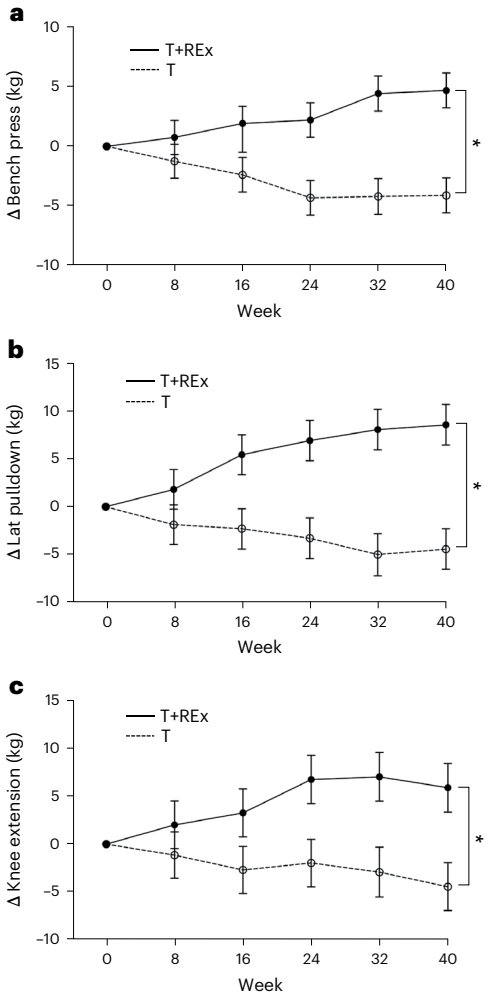

Fig. 4 | Changes in regional muscle strength. Mean changes in bench press (**a**), lat pulldown (**b**) and knee extension (**c**) strength measures, assessed using maximal strength testing (one-repetition maximum technique) in 60 male and 60 female participants with overweight and obesity who were randomized to receive tirzepatide (T) or tirzepatide alongside three supervised, center-based sessions of resistance exercise training (T+REx) weekly for 40 weeks. Error bars are 95% CIs. Statistical testing was performed using LMMs. Baseline value was the reference category, resulting in five degrees of freedom for the overall time effect and five corresponding treatment group × time interaction terms. All tests were two-sided. All variables changed in both groups over time (effect of time: all $P < 0.001$). Group × time interactions were present for all three strength measures (*$P < 0.001$). Strength decreased in participants receiving tirzepatide and increased in those receiving tirzepatide and resistance exercise training.

with overweight or obesity, finding an additive effect of bimagrumab and semaglutide at maximal doses on weight and fat loss. Bimagrumab increased total and appendicular lean soft tissue mass; semaglutide decreased both measures; and combinations of bimagrumab and semaglutide reduced the amount of lean soft tissue mass lost. Grip strength was presented as an exploratory outcome and increased in placebo, bimagrumab and semaglutide groups[13]. In a 24-week trial of adults with overweight or obesity, apitegromab combined with tirzepatide reduced loss of lean soft tissue mass compared to tirzepatide alone, with similar changes in body weight and fat[14]. In those studies, bimagrumab and apitegromab were given as intravenous infusions, which is a barrier to self-administration. The effects of these agents on regional muscle strength remain unclear, and side effects and likely expense may slow their wider clinical use. By contrast, resistance exercise training is safe, effective and readily available. Exercise may also help maintain body composition after an intervention is completed[37]. Future studies investigating the effect of combining muscle-preserving pharmacotherapy with resistance exercise training would be of interest.

Our serial DXA scans illustrate how rapidly and dramatically incretin mimetics can remodel the physical human body. Parallel improvements in lipid profiles and glucose metabolism occurred. We saw a marked reduction in systolic blood pressure, greater than previously reported with tirzepatide and similar to results with retatrutide[4,8], possibly because our cohort was naive to anti-hypertensive therapy. Of note, lightheadedness was reported in 31% of participants in the T group and in 24% of participants in the T+REx group, fainting in 5% and 2% and hypotension in 10% and 15%, respectively. Although systolic and diastolic blood pressure decreased over the course of 40 weeks, side effects, including lightheadedness, fainting and hypotension, commonly resolved over 8–10 weeks. Thus, these symptoms may have reflected a period of adjustment to changes in blood pressure, with lower blood pressure being part of the resultant less obese phenotype. These findings provide insight into modern human physiology when individuals are removed from the obesogenic environment.

In a previous study[38,39], we directly compared, within participants, the impacts of resistance versus endurance training and reported that, although large degrees of variation exist between individuals in terms of changes in traditional cardiovascular risk factors, the impacts of resistance training were, on average, modest. It is, therefore, likely that any effects of resistance exercise on blood pressure, glycemia and lipids were outweighed by the large tirzepatide-induced changes that we observed. Nevertheless, although resistance exercise did not provide any additional benefit for fat mass or cardiovascular risk factors, it contributed to a stronger and leaner physique.

Assessment by DXA partitions body composition into fat mass, lean soft tissue mass and bone mineral content, with overall high precision[40]. However, adipose tissue, in addition to fat, contains approximately 15% of lean mass in the form of protein and water[41,42]. Therefore, loss of substantial amounts of fat mass would be expected to also reduce some lean soft tissue mass via the loss of the non-fat component of adipose tissue[43]. In our trial, the amounts of body weight and total fat mass lost were similar in T and T+REx groups. Therefore, loss of fat-free adipose tissue mass would have been similar in both groups and, thus, would not have confounded the analysis of effects of resistance exercise training on lean soft tissue mass. It is possible that part of the reduction in lean soft tissue mass, including a component of skeletal muscle, may be adaptive in response to the degree of reduction in body weight. We found that the functionally relevant ratio of knee extension strength to body weight[44], reflecting the strength required to enable human movement, was largely stable over 40 weeks in the T group. However, this ratio was markedly enhanced in the T+REx group, suggesting an improvement in functional ability.

Strengths of this study include the prospective, randomized controlled trial design and the repeat 8-weekly measures of body composition to monitor timecourse changes. Two-thirds of participants up-titrated to the maximum dose of tirzepatide. We used contact-matched controls to address the Hawthorne effect, applied block randomization with sex stratification and provide a detailed, replicable periodized training prescription. Our intervention was 40 weeks in duration, which is substantially longer than most exercise trials, and enabled major changes in body composition to be analyzed. The exercise training intervention was center based, personalized, progressive and closely supervised by accredited exercise physiologists. Providing group sessions was logistically advantageous and allowed participants to coalesce into mutually supportive, collegiate groups, a virtuous phenomenon that we have observed in previous studies[33,38,39]. This likely contributed to a supportive environment and, thereby, the high retention and adherence rates. This intervention can be translated into community settings where group exercise sessions are feasible. DXA assessments were performed at the same time of day,

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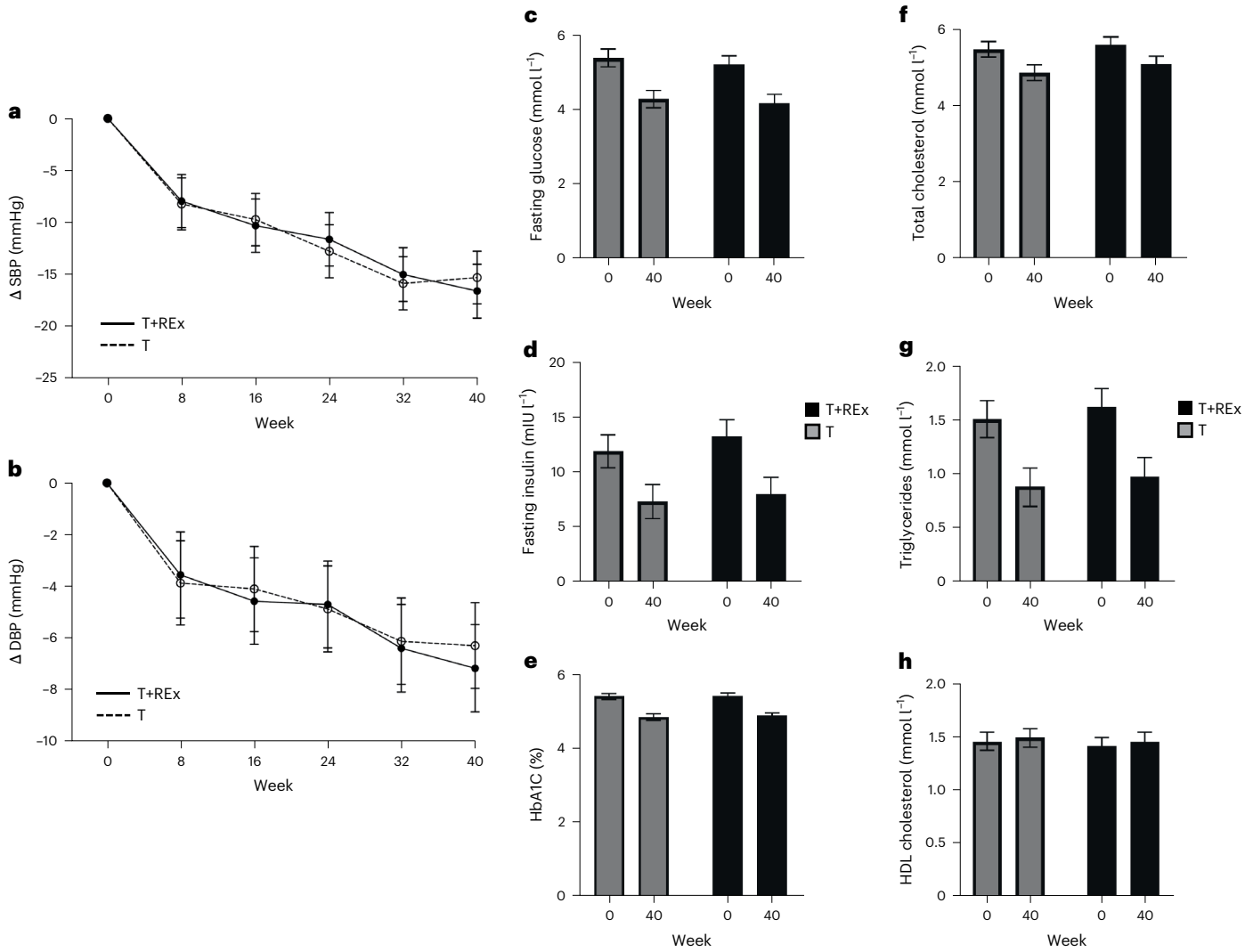

Fig. 5 | Changes in blood pressure, glycemia and lipids. Mean changes in systolic blood pressure (SBP) (**a**), diastolic blood pressure (DBP) (**b**), fasting blood glucose (**c**), insulin (**d**), HbA1c (**e**), total cholesterol (**f**), triglyceride (**g**) and HDL cholesterol (**h**) levels in 60 male and 60 female participants with overweight and obesity who were randomized to receive tirzepatide (T, $n = 61$) or tirzepatide alongside three supervised, center-based sessions of resistance exercise training (T+REx, $n = 59$) weekly for 40 weeks. Gray columns represent the T group at baseline (left) and week 40 (right); black columns represent the T+REx group at baseline (left) and week 40 (right). Error bars are 95% CIs; the measure of center for these are the dot points in **a** and **b** and the height of the bars in **c**–**h**. Statistical testing was performed using LMMs. Baseline value was the reference category, resulting in five degrees of freedom for the overall time effect and five corresponding treatment group × time interaction terms. All tests were two-sided. Time-related reductions were observed in blood pressures, fasting glucose, fasting insulin, HbA1c, total cholesterol and triglycerides (effect of time: all $P < 0.01$) but not for HDL cholesterol. No group × time interactions were observed (all $P > 0.05$), indicating that resistance exercise did not materially alter the cardiometabolic benefits associated with tirzepatide.

after an overnight fast with participants instructed to maintain normal hydration, with the analyst blinded to group allocations.

We acknowledge limitations of this trial. We chose DXA to assess total body and appendicular lean soft tissue mass because DXA is widely available and validated for body composition assessment. MRI assessment of skeletal muscle volume remains time-consuming and expensive, and repeated computed tomography scans were not considered owing to the radiation exposure. Estimation of muscle mass based on dilution of stable isotope-labeled creatine, although holding promise, is technically demanding and not regionally specific[45]. We did not include a non-incretin mimetic placebo arm in this study, as previous multicenter trials have established the large impacts of therapy over placebo in terms of body composition change[3,4]. Similarly, we previously showed, in male and female middle-aged and older-aged participants, that non-participation in exercise does not typically improve body composition outcomes over time[46,47], nor would non-participation in an exercise intervention, in the absence of weight loss, be expected to change muscle strength[48]. All participants were instructed to maintain protein intake, but no specific dietary intervention was provided. We enrolled middle-aged to older-aged adults, without diabetes or cardiovascular disease, not taking cardiovascular medications and initially sedentary; thus, our findings may not be generalizable to all individuals receiving tirzepatide anti-obesity therapy. The feasibility of the resistance training intervention needs to be established in routine clinical practice. Additional studies would be needed to determine how differences in lean soft tissue mass affect long-term outcomes. Finally, we acknowledge the lack of blinding in a trial with an open-label intervention such as exercise training. The accredited clinical exercise physiologists who performed the strength assessments used standardized operating procedures so that strength testing and exercise sessions were consistent for all participants, including levels of encouragement and motivation. The differences in muscle strength that emerged between the groups were large and consistent. Randomization and masking of allocations occurred, and DXA results are produced by software that is objective.

In conclusion, during tirzepatide therapy for obesity, decreases in lean soft tissue mass were attenuated by resistance training, which also abolished the compromising impact of weight loss on muscle strength. Resistance exercise training is an effective strategy to manage adverse impacts of incretin mimetic therapies and should be considered when prescribing incretin mimetics as anti-obesity therapy.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-026-04752-5.

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Methods

Trial design and oversight

The Tirzepatide and Resistance Exercise (T-REx) study was a phase 3 single-center trial comparing the impacts of tirzepatide (T) versus the combination of tirzepatide and resistance exercise (T+REx) training on lean and fat mass, muscle strength and cardiovascular risk factors in community-dwelling overweight or obese middle-aged and older men and postmenopausal women. Participants were randomized (1:1) into two parallel groups. Participants received weekly supervised tirzepatide injections for 40 weeks or tirzepatide injections alongside three sessions per week of center-based, supervised and monitored progressive resistance exercise training aimed at enhancing skeletal muscle mass and strength (Extended Data Table 8). The protocol was pre-registered in the Australian New Zealand Clinical Trials Registry as ACTRN12623001236684 on 30 November 2023. The trial was approved by the University of Western Australia Human Research Ethics Committee and adhered to the Declaration of Helsinki, and all participants provided written informed consent. Eli Lilly reviewed the trial protocol and provided tirzepatide for the study via an investigator-initiated trial program. Eli Lilly did not provide any other funding and had no role in the conduct of the trial. The trial was led by the investigators, who independently organized all staffing, participant recruitment, procedures, data collection, analysis and report writing. Eli Lilly reviewed a draft of the manuscript to ensure that there were no identifiable intellectual property or new safety issues identified, with no changes made to its content.

Adverse events were ascertained throughout the duration of the 40-week intervention phase. Participants were asked to self-report adverse events during each weekly visit when they attended for their tirzepatide injections. Adverse events were assessed by a research nurse, and events of concern were referred to medically qualified study investigators (B.B.Y. or P.G.F.) who reviewed participants in person where required. Where appropriate and with permission, additional information was collected from participants and their local doctors. Adverse events were reported to an independent monitoring committee comprising an endocrinologist, a pharmacist and an exercise physiologist. Serious adverse events were also reported to the University of Western Australia Human Research Ethics Committee and to Eli Lilly.

Participants

We recruited community-dwelling adult men and postmenopausal women aged 50–70 years with BMI ≥30 kg m^{-2} or ≥27 kg m^{-2} with at least one weight-related comorbidity (for example, hypertension, dyslipidemia or obstructive sleep apnea). All participants reported their gender as the same as their sex assigned at birth. Participants had to self-report less than 60 minutes of moderate or higher intensity exercise per week over the previous 3 months prior to entering the study. Participants also had to be willing to undertake up to 150 minutes per week of exercise for 6 months in a center-based program.

Exclusion criteria were as follows: known pregnancy or premenopausal status; history of cardiovascular disease or diabetes mellitus; any history of pancreatitis; any history of multiple endocrine neoplasia (MEN) type 2 or medullary thyroid carcinoma; previous or planned bariatric surgery; any prior use of incretin-based therapies; use of non-incretin-based anti-obesity or cardiovascular medications (for example, statins and anti-hypertensive drugs) within 3 months of enrollment; and any other clinically significant illnesses (for example, cancer and severe respiratory disease).

Potential participants completed an online screening questionnaire. Those who met the inclusion and exclusion criteria above were invited to attend a clinic visit at the study center, where the study was explained, informed consent was obtained and a medical history and examination were conducted (Fig. 1). Participants were then provided with a phlebotomy form to complete screening blood tests at an accredited pathology provider (Western Diagnostic Pathology, Australia). Further exclusion criteria were applied after the initial visit and screening blood test as follows: blood pressure higher than 160/100 mmHg during the first study visit, total cholesterol >7.0 mmol l^{-1}, low-density lipoprotein (LDL) cholesterol >4.0 mmol l^{-1}, estimated glomerular filtration rate (eGFR) <45 ml min^{-1}, HbA1c >7.0% or biochemical evidence of significant liver disease.

List of amendments according to date approved by the ethics committee

Approved 20 September 2023

- Drug delivery method changed from self-administered pre-filled subcutaneous injector pens to allow administration of subcutaneous injection from single-dose vials.
- Age inclusion criteria changed from 45–70 years to 50–70 years to reduce the risk of enrolling premenopausal women.
- Withdrawal criteria amended, such that participants who cannot tolerate a minimum dose of 5 mg tirzepatide will be withdrawn from the study.
- Exclusion criteria amended from excluding a history of chronic pancreatitis to excluding a history of any pancreatitis.
- Exclusion criteria amended to exclude those with of any history of MEN type 2 or medullary thyroid carcinoma.
- The power test section of the application amended to focus on lean mass as the principal outcome measure. This did not change the number of participants to be recruited ($n = 120$).
- Two of the assessments moved to different sessions for smoother flow through the study: the blood pressure screening now occurs prior to blood tests, and the echocardiogram has been moved from visit 2 to visit 1.

Approved 26 February 2024

- Addition that should participants be unable to attend the campus for injections (for example, because they are on holidays), then they will, on these occasions, be able to self-administer the drug off-site. It is noted that tirzepatide is designed to be self-administered, and participants will receive training from a healthcare professional (for example, a nurse) to appropriately self-administer tirzepatide.
- Change to one of the study exclusion criteria: participants will now be excluded if their LDL cholesterol measures above 4.5 mmol l^{-1} (changed from 4 mmol l^{-1}).

Approved 7 January 2025

- Diet assessment will now take place over a 3-day period rather than a 7-day period.

Randomization

Computer-based randomization was used to generate concealed envelopes. Personnel enrolling participants had no access to the sequence. Participants were block randomized to ensure similar numbers and sex matching of participants in each group. A bespoke 'ralloc' package was used (Stata software; StataCorp); blocks of four or eight were randomly selected, and block randomization was stratified for gender. Participants were block randomized between March 2024 and May 2025. One participant withdrew from the study after randomization but before receiving any study intervention and was replaced by recruitment of a new participant. As a result, a total of 120 participants were recruited into the trial, comprising 60 men and 60 postmenopausal women, of whom 61 were randomly allocated to tirzepatide (T) without resistance exercise training and 59 to tirzepatide and resistance exercise training (T+REx).

Procedures

Open-label tirzepatide treatment was administered as once-weekly subcutaneous injections supervised by a research nurse at the study

center. Treatment was initiated at 2.5 mg and increased by 2.5 mg every 4 weeks during the dose-escalation period, aiming to reach a maintenance dose of 15 mg at week 20. Therapy was maintained for a further 20 weeks (total, 40 weeks). Delayed dose escalation, down-titration (minimum dose of 5 mg) and/or maintenance at maximum tolerated dose <15 mg were permitted to manage side effects. Decisions regarding dose modification were made by medically qualified study investigators (B.B.Y. and P.G.F.) considering the circumstances of each participant. All participants were instructed to maintain hydration status, protein intake and fiber intake (fruit and vegetables) across the 40-week intervention period and to report any side effects at their weekly check-ins with the nursing staff.

Participants randomized to the exercise group attended three 1-hour group sessions per week for 40 weeks in a dedicated gymnasium. The program focused on increasing muscle mass, strength and function, with progressive overload, and comprised five specified training phases (mesocycles), each of 8-week duration (Extended Data Table 8). The first 8-week mesocycle included light to moderate intensity exercises, focused on developing correct technique and neuromuscular adaptation, accustoming participants to exercise. Over the course of 40 weeks, intensity gradually increased to moderate to vigorous intensity, focusing on muscle strength and hypertrophy adaptation. The second mesocycle provided two sessions per week focused on hypertrophy and one on strength. The following three mesocycles covering the remainder of the 40-week intervention and provided two hypertrophy and one strength session per week for mesocycle 3, one hypertrophy and two strength sessions per week for mesocycle 4 and alternating hypertrophy and strength sessions for mesocycle 5 (Extended Data Table 8). Each 1-hour session alternated between upper and lower body strength exercises, supervised by qualified accredited exercise physiologists. A general whole-body warmup including approximately 5 minutes of light to moderate intensity aerobic activity (for example, cycling or rowing ergometry) and dynamic stretches was followed by resistance-based exercises involving major muscle groups using a variety of apparatuses, including body weight exercises, bands, cables, machines and free weights. Example exercises are squats, deadlifts, leg press, leg extension, lat pulldowns, shoulder press, bicep curls and chest press. Borg's rating of perceived exertion (RPE 1–10) scale was used for each exercise during each session to ensure that exercise intensity followed the training protocol. During the exercise sessions, each participant was monitored to ensure that RPE targets were achieved for each exercise, and exercise intensity was increased accordingly to maintain their progression during the intervention phase.

The non-training (tirzepatide-only) group attended once per week across the 40-week intervention phase for tirzepatide injections and was assessed at the same timepoints as the exercise training group.

Endpoints and assessments

The primary endpoints of interest were changes in whole-body lean soft tissue mass and fat mass measured using DXA (GE Healthcare, Lunar iDXA), assessed at baseline (week 0) and at weeks 8, 16, 24, 32 and 40. We also assessed changes in appendicular lean soft tissue mass, which better represents upper limb and lower limb skeletal muscle mass than total lean soft tissue mass[17]. Standard DXA calibration and quality assurance procedures were used (https://www.gehealthcare.com). Changes in body weight are presented to provide context for changes in fat mass and lean soft tissue mass.

Key secondary outcomes collected at the same timepoints included changes in regional muscle strength, to accompany the analysis of changes in lean soft tissue mass. Muscle strength was assessed using the one-repetition maximum technique for three distinct assessments (bench press, lat pulldown and single knee extension). The strength testing session commenced with a similar warmup as the regular gym sessions (approximately 5 minutes of light to moderate intensity aerobic activity and dynamic stretches) prior to performing one warmup set at a light intensity for 10 repetitions and one warmup set at a moderate intensity for five repetitions, with 2-minute recovery between sets. Exercise order was standardized as bench press, leg press and then lat pulldown. After the two warmup sets, participants completed one repetition for each subsequent set, with 3-minute recovery between sets. RPE was documented after each one-repetition set and would help guide the subsequent weight increment. One-repetition sets were conducted until the final maximum strength was recorded. As the researcher(s) administering the strength tests were exercise physiologists who could also be involved in supervising the regular training sessions, it was not possible to ensure that researcher(s) administering the test were blinded to group allocation. Methods to reduce the risk of bias in the strength testing protocol included the researcher following the identical protocol for all participants and not being aware of the participants' previous performance during strength tests conducted after week 1.

Prior to the completion of the study, we decided to analyze BMI as a secondary outcome and to present both BMI and waist circumference results to provide added context for the primary outcomes. In addition to these and muscle strength, we reported changes in cardiovascular risk factors, which are part of routine clinical assessments in the obesity setting. During each assessment, resting blood pressure was averaged from six readings after 20 minutes of quiet supine rest in a darkened room using an automated oscillometric device (GE Healthcare, Dinamap V100). At pre-intervention (week 0) and week 40, fasting blood glucose, insulin, HbA1c and lipids were measured by a nationally accredited pathology provider (Western Diagnostic Pathology, Australia).

Thus, the secondary endpoints included in this analysis are those immediately relevant to appreciating changes in fat and total lean soft tissue mass, namely changes in weight, BMI, waist circumference, appendicular lean soft tissue mass, regional muscle strength and cardiometabolic parameters. Other distinct secondary endpoints assessed during the study, including cardiorespiratory fitness, vascular function and cardiac function (using transthoracic echocardiography), are still in the process of being analyzed and will be reported as separate substudies.

DXA. Participants arrived at the laboratory at the same time of day for each of the six measurement timepoints after an overnight fast and were instructed to maintain normal hydration. DXA measurements were performed on a Lunar iDXA densitometer (GE Healthcare). iDXA outcomes are highly reproducible (intra-class correlation >0.99). All DXA data were analyzed by an expert who was independent of the study design and data collection team (R.M.D.) and was blinded to group allocation. Half-body scans were performed on those unable to fit within scan lines, with the body composition from the scanned side doubled. This is a valid and accurate approach to DXA scanning in obese individuals[49]. DXA scans are painless, non-invasive and associated with low-dose X-ray exposure; the radiation dose from a single GE Lunar iDXA scan is 6 µSv (or 0.006 mSv). To provide a comparison with other radiation sources, background radiation levels in Australia approximate 1.5 mSv per year, equivalent to approximately 250 DXA scans annually. An airline flight from Perth to the UK results in exposure to 60 µSv (that is, 0.06 mSv), equivalent to 10 DXA scans. To determine scan–rescan repeatability of DXA at our center, 32 participants (16 male and 16 female) received two full-body DXA scans in succession by a single trained operator. The participants were instructed to remain in the same position throughout both scans. A single trained researcher defined regions of interest using participant-specific anatomical landmarks for the assessment of total fat mass, total lean soft tissue mass and appendicular lean soft tissue mass. These data were used to calculate percent coefficient of variation (CV%) for these three variables between the two scans, indicating a CV% of 1.08% for total fat

mass, 0.49% for total lean soft tissue mass and 1.23% for appendicular lean soft tissue mass.

Power calculation. The power calculation was based on a conservative estimate of the difference that we expect to observe in the change in lean soft tissue mass, assessed using DXA, between groups. Because no previous trials tested the effects of exercise training in conjunction with initial incretin-induced weight loss, our estimate of effect size was based on a 12-week 2 × 2 factorial randomized controlled trial involving combined aerobic and resistance exercise training that we undertook in men aged 50–70 years with central adiposity[33]. In that study, exercise training induced a change in lean soft tissue mass from 65.0 kg to 65.7 kg, a delta of 0.7 kg (±1.7). A larger effect size was anticipated in the T-REx trial given the more intensive resistance-focused exercise component of the intervention and the much longer intervention period. Assuming a difference between groups (exercise training versus usual activities) in lean soft tissue mass of 1.0 kg, s.d. of 1.7, for 80% power, we would need 47 completers in each group. We had previously recorded 85% or greater completion rates in our studies, so, using a conservative 80% adherence rate, we aimed to recruit 60 participants in each group, $N = 120$ in total.

We consider the effect size estimate to be conservative because our previous study was only 12 weeks in duration and involved exercise that was not specifically designed to maximize lean mass changes. The present study was powered based on differences between groups for changes in total body lean soft tissue mass measured by DXA (from baseline and throughout the 40-week intervention). Based on our calculations above, our sample size of 60 participants per group possessed greater than 80% power (at $\alpha = 0.05$) to detect a difference in total body soft tissue lean mass of more than 1.0 kg.

Data cleaning procedures

Data cleaning procedures were conducted prior to analysis to identify implausible observations, statistical outliers and potential data entry errors across repeated measurement timepoints. Data cleaning was conducted algorithmically without regard to group allocation. For each participant, a linear regression model was fitted in Stata using all available observations across timepoints to estimate the expected trajectory of the measured variable over time. Standardized residuals from these models were calculated, and observations with residuals exceeding predetermined statistical thresholds were flagged as potential outliers for further review. In addition, changes between consecutive timepoints were assessed using sample means and standard deviations. Observations demonstrating changes greater than a specified threshold relative to the distribution of within-person changes were flagged as potentially anomalous. Directionality checks were also performed to identify values that violated expected temporal trends or biologically plausible patterns (for example, unexpected reversals in trajectory). These observations were flagged for manual inspection.

To complement statistical screening procedures, longitudinal graphs were generated for each participant to visually inspect trajectories over time and identify unusual patterns, abrupt deviations or potential outliers not detected through automated methods. Flagged observations were reviewed individually and retained, corrected or excluded based on source verification to correct transposition or data entry errors. All data cleaning procedures, including flagged observations, corrections and exclusions, were systematically recorded in an audit trail to maintain transparency and reproducibility.

Statistical analysis

Data were analyzed according to the intention-to-treat principle by an independent professional statistician (L.L.) who was not involved in the study design or data collection. All participants who received at least one dose or session of the intervention were included in the intention-to-treat analysis. Statistical analyses was performed using SPSS version 31 and Stata version 19 software. All data were reported as group-adjusted estimated marginal means and 95% CIs. Baseline was denoted as week 0 and end-of-study as week 40. Response to each intervention is the difference between end-of-study and baseline assessments, and the study is powered based on differences between groups. Data were included for any participant who has received at least one dose of tirzepatide or one exercise training session. For each of the prespecified outcomes, linear mixed-effect models (LMMs) were used to investigate the relationship among variables, exercise and time. A random intercept was included in each model to account for the repeated nature of the data. The model included terms for age, sex, exercise training, time and the interaction of exercise training with time. Thus, the model examined differences between groups at baseline, effects of time (changes between baseline and week 40 in either group, resulting from tirzepatide treatment of all participants) and group × time interactions (the effect of randomization to the resistance exercise training intervention over the 40-week duration of the study), adjusting for age and sex. Time was modeled as a categorical factor with six levels (baseline and weeks 8, 16, 24, 32 and 40) rather than as a continuous linear trend. Baseline was the reference category, resulting in five degrees of freedom for the overall time effect and five corresponding treatment group × time interaction terms. Models included a participant-specific random intercept. No additional residual covariance structure was specified; therefore, observations were assumed conditionally independent given the participant-specific random intercept, with the random intercept inducing a constant covariance between repeated observations within participants. Models were estimated using maximum likelihood and incorporated all available repeated outcome measurements. Inference from these likelihood-based models assumes that missing outcome data are missing at random (MAR), conditional on the variables and observed outcomes included in the model. The LMM is the preferred statistical test for repeated-measures datasets. For all analyses, effects of time and group × time interactions were estimated and reported. All tests were two-sided with default statistical significance specified at $P < 0.05$.

Testing the hypothesis that, in adults with overweight or obesity, combining tirzepatide treatment with resistance exercise training would maintain or attenuate losses in muscle mass, compared to tirzepatide without resistance training, required the finding of a significant group × time interaction for the outcome of total body lean soft tissue mass. Similarly, the second hypothesis, that this combination would improve muscle strength compared to tirzepatide without resistance training, required the finding of significant group × time interactions for measures of muscle strength. Total body fat mass and total lean soft tissue mass were analyzed as co-primary outcomes, with a Bonferroni correction: $\alpha = 0.05 / 2 = 0.025$. Thus, each co-primary outcome is judged against $P < 0.025$, with corresponding 97.5% CIs. For all other endpoints, individual P values and 95% CIs for the estimated effects are reported to allow readers to judge the weight (strength) of any intervention effects.

After identification of a significant group × time interaction, the individual time × treatment interaction coefficients from the fitted LMMs were examined to identify the earliest follow-up visit at which the change from baseline differed significantly between treatment groups. These exploratory analyses were derived from the fitted models, and no additional models were fitted. As BMI was examined as an outcome, it was not included as a covariable in the LMMs. We performed sensitivity analyses to test the effect of adding BMI as a covariable to LMMs where a significant group × time interaction was present.

Post hoc dietary analysis

The second 60 participants enrolled were invited to complete 3-day food diaries, and 95% ($n = 57$) responded. Three-day food diaries were collected using an app (Easy Diet Diary) that linked to Foodworks Online and was analyzed using Xyris software[50]. Each participant's

mean daily food intake across the 3 days was used in the analyses. Energy misreporting was addressed by excluding implausible reported energy intakes using sex-specific cutoffs (females, <500 or >3,500 kcal per day; males, <800 or >4,200 kcal per day)[51]. Across all timepoints, nine observations were excluded due to implausible energy intakes, including under-reporting ($n = 7$) and over-reporting ($n = 2$). Protein intake as a percentage of total energy intake was calculated as follows: (protein intake (g per day) × 4 kcal per g / total energy intake (kcal per day)) × 100. Changes in energy intake and protein intake as a percentage of total energy over time were assessed using LMMs. Estimated marginal means with 95% CIs were reported for each treatment group at each timepoint. Model-estimated between-group differences were also calculated at each timepoint and reported as mean differences with 95% CIs. All tests were two-sided, with statistical significance set at $P < 0.05$. Statistical analyses were performed using Stata version 18.0 software.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

To protect participant confidentiality, no data will be deposited in a public-facing repository. Individual participant data are not available for sharing. Source data are provided with this paper.

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Author contributions

D.J.G. and B.B.Y. conceptualized the study. D.J.G. developed assessment techniques and analytical procedures and recruited and supervised graduate students. D.J.G., A.H., D.R.U., E.R.W., A.A.G., E.S.G., P.G.F. and B.B.Y. collected data. D.J.G., A.A.G., R.M.D., E.S.G. and L.L. analyzed data, and L.L. conducted the statistical analysis. D.J.G. and B.B.Y. drafted the manuscript. All authors contributed to the interpretation of results, participated in preparing the final manuscript and approved its submission. All authors were academic authors. D.J.G. and B.B.Y. are the guarantors of this work and, as such, have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the analysis.

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Competing interests

D.J.G. has received speaker honoraria from Eli Lilly. P.G.F. has received speaker honoraria from Novo Nordisk, Eli Lilly and Boehringer Ingelheim. B.B.Y. has received speaker honoraria from Eli Lilly and Boehringer Ingelheim and participated in an advisory role for Eli Lilly (all honoraria were paid to the University of Western Australia) and is a shareholder and clinical advisor to ProGenis Pharmaceuticals. R.M.D. has received speaker honoraria from Abbott, Fresenius Kabi and Nutricia Australia and educational grants from Abbott. The other authors declare no competing interests.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-026-04752-5.

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Extended Data Table 1 | (A) Medications use self-reported by participants at baseline, shown as N (%). (B) Final tirzepatide doses at week 40 for numbers of participants in T and T+REx groups

A	All participants (N=120)	T group (N=61)	T+REx group (N=59)
Medications use (all)	48 (40.0)	25 (41.0)	23 (39.0)
Non-steroidal anti-inflammatory drugs	9 (7.5)	4 (6.6)	5 (8.5)
Reflux/ulcer therapy	15 (12.5)	10 (16.4)	5 (8.5)
Anti-depressant	13 (10.8)	6 (9.8)	7 (11.9)
Menopausal hormone therapy	8 (6.6)	5 (8.2)	3 (5.1)
Thyroxine	6 (5.0)	3 (4.9)	3 (5.1)
Metformin	3 (2.5)	2 (3.3)	1 (1.2)
Other[§]	13 (10.8)	7 (11.5)	6 (10.2)
B **Final dose of tirzepatide at week 40 (mg)**	**All participants (N)**	**T group (N)**	**T+REx group (N)**
0	1*	1*	0
2.5	0	0	0
5	2	1	1
7.5	9	5	4
10	15	9	6
12.5	6	3	3
15	78	38	40

[§]Other medications: asthma inhaler (three participants), minoxidil (two participants), baclofen, mirabegron, topical steroid, allopurinol, fish oil and glucosamine (same participant), citrulline, iron, sildenafil (voluntarily discontinued for duration of study). *one participant in the T group uptitrated on schedule to 12.5 mg by week 18, but was subsequently downtitrated to 10 mg at week 19, then to 5 mg at week 25, and 0 mg at week 29.

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Extended Data Table 2 | Differences in characteristics and outcome variables at baseline between T and T+REx groups, expressed as standardized mean differences

Baseline variable	Standardized Mean Difference between T and T+REx groups
Age, years	0.27
Body weight, kg	0.25
BMI, kg/m^2	0.40
Waist circumference, cm	0.22
Total body fat mass, kg	0.33
Total body lean soft tissue mass, kg	0.09
Appendicular lean soft tissue mass, kg	0.13
Bench press, kg	0.17
Lat pulldown, kg	0.11
Knee extension, kg	0.07
Knee extension/body weight	0.13
SBP, mmHg	0.19
DBP, mmHg	0.04
Heart rate, bpm	0.03
Glucose, mmol/L	0.17
Insulin, mIU/L	0.21
HbA1c, %	0.02
Total cholesterol, mmol/L	0.15
LDL cholesterol, mmol/L	0.26
HDL cholesterol, mmol/L	0.12
Triglycerides, mmol/L	0.12

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Extended Data Table 3 | Baseline values and changes for body composition, muscle strength and cardiovascular risk factors at each assessment timepoint are shown, for the Tirzepatide only (T) and Tirzepatide and Resistance Exercise (T+REx) groups

	T (31♂, 30♀)	T+REx (29♂, 30♀)
Age, years	57.07 ± 4.30	58.34 ± 5.06
Body weight (kg)		
Baseline	98.41 (95.35, 101.46)	102.08 (98.98, 105.19)
Δ 8 weeks	−6.99 (−8.16, −5.82)	−7.33 (−8.52, −6.13)
Δ 16 weeks	−12.63 (−13.82, −11.45)	−12.58 (−13.78, −11.37)
Δ 24 weeks	−17.82 (−19.01, −16.63)	−17.30 (−18.50, −16.09)
Δ 32 weeks	−20.77 (−21.96, −19.57)	−20.11 (−21.33, −18.90)
Δ 40 weeks	−22.61 (−23.80, −21.42)	−22.28 (−23.49, −21.07)
Body mass index (kg/m^2)		
Baseline	33.08 (32.12, 34.03)	34.62 (33.65, 35.59)
Δ 8 weeks	−2.32 (−2.71, −1.94)	−2.48 −2.87, −2.09)
Δ 16 weeks	−4.27 (−4.66, −3.88)	−4.26 (−4.65, −3.86)
Δ 24 weeks	−6.00 (−6.40, −5.61)	−5.85 (−6.25, −5.46)
Δ 32 weeks	−7.02 (−7.41, −6.63)	−6.85 (−7.25, −6.45)
Δ 40 weeks	−7.62 (−8.01, −7.22)	−7.59 (−7.99, −7.19)
Waist circumference (cm)		
Baseline	106.95 (104.19, 109.70)	109.88 (107.05, 112.71)
Δ 8 weeks	−5.24 (−6.73, −3.75)	−5.50 (−6.99, −4.01)
Δ 16 weeks	−10.77 (−12.27, −9.27)	−10.29 (−11.79, −8.79)
Δ 24 weeks	−15.74 (−17.24, −14.24)	−14.50 (−16.00, −12.99)
Δ 32 weeks	−17.82 (−19.32, −16.32)	−17.84 (−19.37, −16.30)
Δ 40 weeks	−19.90 (−21.40, −18.41)	−19.20 (−20.71, −17.68)
DUAL ENERGY X-RAY ABSORPTIOMETRY		
Total body fat mass (kg)		
Baseline	41.44 (39.24, 43.65)	44.21 (41.97, 46.45)
Δ 8 weeks	−4.06 (−5.04, −3.07)	−4.86 (−5.86, −3.87)
Δ 16 weeks	−8.31 (−9.31, −7.32)	−9.17 (−10.18, −8.17)
Δ 24 weeks	−12.39 (−13.39, −11.38)	−13.05 (−14.05, −12.04)
Δ 32 weeks	−15.13 (−16.14, −14.13)	−15.75 (−16.76, −14.74)
Δ 40 weeks	−17.19 (−18.16, −16.15)	−17.98 (−18.99, −16.97)
Total body lean soft tissue mass (kg)		
Baseline	53.16 (51.92, 54.39)	54.03 (52.78, 55.28)
Δ 8 weeks	−2.68 (−3.12, −2.23)	−2.17 (−2.62, −1.72)
Δ 16 weeks	−4.02 (−4.47, −3.58)	−2.99 (−3.44, −2.54)
Δ 24 weeks	−4.97 (−5.42, −4.52)	−3.64 (−4.09, −3.19)
Δ 32 weeks	−5.00 (−5.46, −4.55)	−3.67 (−4.13, −3.22)
Δ 40 weeks	−4.67 (−5.12, −4.22)	−3.57 (−4.02, −3.11)
Appendicular lean soft tissue mass (kg)		
Baseline	25.24 (24.56, 25.92)	25.90 (25.21, 26.59)
Δ 8 weeks	−1.57 (−1.83, −1.31)	−1.33 (−1.60, −1.07)
Δ 16 weeks	−2.55 (−2.81, −2.28)	−2.11 (−2.38, −1.85)
Δ 24 weeks	−3.28 (−3.54, −3.01)	−2.60 (−2.87, −2.34)
Δ 32 weeks	−3.45 (−3.71, −3.18)	−2.76 (−3.03, −2.50)
Δ 40 weeks	−3.55 (−3.82, −3.29)	−2.92 (−3.19, −2.66)
STRENGTH MEASURES		
Bench press (kg)		
Baseline	44.07 (41.92, 46.23)	46.95 (44.78, 49.12)

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Extended Data Table 3 (continued) | Baseline values and changes for body composition, muscle strength and cardiovascular risk factors at each assessment timepoint are shown, for the Tirzepatide only (T) and Tirzepatide and Resistance Exercise (T+REx) groups

	T (31♂, 30♀)	T+REx (29♂, 30♀)
Δ 8 weeks	−1.25 (−2.66, 0.17)	0.75 (−0.67, 2.17)
Δ 16 weeks	−2.37 (−3.81, −0.93)	1.92 (0.48, 3.36)
Δ 24 weeks	−4.29 (−5.74, −2.84)	2.21 (0.75, 3.66)
Δ 32 weeks	−4.18 (−5.67, −2.70)	4.42 (2.95, 5.89)
Δ 40 weeks	−4.09 (−5.56, −2.62)	4.68 (3.22, 6.15)
Lat pulldown (kg)		
Baseline	55.37 (53.14, 57.60)	55.68 (53.42, 57.95)
Δ 8 weeks	−1.87 (−3.94, 0.20)	1.82 (−0.25, 3.88)
Δ 16 weeks	−2.29 (−4.40, −0.19)	5.45 (3.37, 7.53)
Δ 24 weeks	−3.28 (−5.40, −1.15)	6.93 (4.82, 9.04)
Δ 32 weeks	−5.00 (−7.19, −2.82)	8.07 (5.95, 10.19)
Δ 40 weeks	−4.42 (−6.54, −2.29)	8.58 (6.46, 10.70)
Knee extension (kg)		
Baseline	45.30 (42.44, 48.16)	44.45 (41.52, 47.38)
Δ 8 weeks	−1.13 (−3.54, 1.28)	2.01 (−0.45, 4.48)
Δ 16 weeks	−2.67 (−5.11, −0.23)	3.25 (0.75, 5.75)
Δ 24 weeks	−1.95 (−4.42, 0.52)	6.73 (4.23, 9.23)
Δ 32 weeks	−2.90 (−5.49, −0.31)	7.01 (4.47, 9.55)
Δ 40 weeks	−4.42 (−6.90, −1.93)	5.88 (3.35, 8.41)
Knee extension/Body weight		
Baseline	0.460 (0.422, 0.499)	0.442 (0.402, 0.481)
Δ 8 weeks	0.021 (−0.006, 0.048)	0.059 (0.031, 0.087)
Δ 16 weeks	0.036 (0.009, 0.064)	0.101 (0.072, 0.129)
Δ 24 weeks	0.074 (0.046, 0.103)	0.173 (0.145, 0.202)
Δ 32 weeks	0.083 (0.053, 0.112)	0.198 (0.169, 0.227)
Δ 40 weeks	0.073 (0.045, 0.101)	0.202 (0.173, 0.231)
CARDIOVASCULAR RISK FACTORS		
Systolic blood pressure (mmHg)		
Baseline	128.62 (125.58, 131.66)	130.41 (127.27, 133.55)
Δ 8 weeks	−8.19 (−10.68, −5.69)	−7.92 (−10.46, −5.39)
Δ 16 weeks	−9.70 (−12.21, −7.20)	−10.28 (−12.84, −7.72)
Δ 24 weeks	−12.74 (−15.29, −10.20)	−11.59 (−14.15, −9.03)
Δ 32 weeks	−15.82 (−18.36, −13.27)	−14.97 (−17.56, −12.39)
Δ 40 weeks	−15.26 (−17.79, −12.74)	−16.56 (−19.15, −13.98)
Diastolic blood pressure (mmHg)		
Baseline	75.68 (73.94, 77.42)	75.05 (73.27, 76.83)
Δ 8 weeks	−3.86 (−5.48, −2.23)	−3.55 (−5.21, −1.89)
Δ 16 weeks	−4.09 (−5.74, −2.45)	−4.56 (−6.23, −2.89)
Δ 24 weeks	−4.86 (−6.52, −3.20)	−4.69 (−6.36, −3.01)
Δ 32 weeks	−6.11 (−7.77, −4.44)	−6.38 (−8.07, −4.69)
Δ 40 weeks	−6.28 (−7.93, −4.62)	−7.15 (−8.84, −5.46)

Values are marginal means and 95% confidence intervals (95% CI) based on pre-specified linear mixed models analysis, except for age where SD are shown.

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Extended Data Table 4 | Between-group differences in change from baseline to Week 40 for body composition, strength and cardiometabolic parameters

Variable	
Co-primary endpoints	
Total body fat mass, kg	−0.77 kg (97.5% CI −2.14 to 0.60), Cohen's *d* = −0.08, Bonferroni-adjusted *P* = 0.416
Total body lean soft tissue mass, kg	1.09 kg (97.5% CI 0.43 to 1.75), Cohen's *d* = 0.10, Bonferroni-adjusted *P* < 0.001
Other endpoints	
Appendicular lean soft tissue mass, kg	0.63 kg (95% CI 0.30 to 0.96), Cohen's *d* = 0.11
Bench press, kg	8.59 kg (95% CI 6.69 to 10.50), Cohen's *d* = 0.49
Lat pulldown, kg	12.97 kg (95% CI 10.21 to 15.74), Cohen's *d* = 0.60
Knee extension, kg	9.78 kg (95% CI 6.38 to 13.18), Cohen's *d* = 0.48
Knee extension/body weight	0.118 (95% CI 0.077 to 0.159), Cohen's *d* = 0.72
Systolic BP, mmHg	−1.34 mmHg (95% CI −4.60 to 1.91), Cohen's *d* = −0.10
Diastolic BP, mmHg	−0.74 mmHg (95% CI −2.82 to 1.35), Cohen's *d* = −0.09
Heart rate, bpm	−0.20 bpm (95% CI −2.60 to 2.20), Cohen's *d* = −0.02
Glucose, mmol/L	0.06 mmol/L (95% CI −0.26 to 0.38), Cohen's *d* = 0.06
Insulin, mIU/L	−0.66 mIU/L (95% CI −2.85 to 1.53), Cohen's *d* = −0.10
HbA1c, %	0.03% (95% CI −0.11 to 0.17), Cohen's *d* = 0.07
Total cholesterol, mmol/L	0.11 mmol/L (95% CI −0.15 to 0.36), Cohen's *d* = 0.14
LDL cholesterol, mmol/L	0.01 mmol/L (95% CI −0.24 to 0.26), Cohen's *d* = 0.01
HDL cholesterol, mmol/L	0.01 mmol/L (95% CI −0.10 to 0.11), Cohen's *d* = 0.02
Triglycerides, mmol/L	−0.01 mmol/L (95% CI −0.22 to 0.21), Cohen's *d* = −0.01

Cohen's d was calculated by standardising the model-estimated between-group difference in change from baseline to Week 40 by the pooled baseline SD. For the two co-primary outcomes, 97.5% CIs and Bonferroni-adjusted P values are reported to account for multiplicity.

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Extended Data Table 5 | Self-reported adverse events occurring during the T-REx trial

	All participants (N=120)	T (N=61)	T+REx (N=59)
A: Adverse Events			
Gastrointestinal			
Nausea	66 (55.0)	32 (52.5)	34 (57.6)
Vomiting	27 (22.5)	10 (16.4)	17 (28.8)
Constipation	38 (31.7)	17 (27.9)	21 (35.6)
Diarrhoea	35 (29.2)	15 (24.6)	20 (33.9)
Indigestion	43 (35.8)	19 (31.1)	24 (40.7)
Gastroenteritis	19 (15.8)	8 (13.1)	11 (18.6)
Abdominal pain	12 (10.0)	5 (8.2)	7 (11.9)
Bloating	10 (8.3)	5 (8.2)	5 (8.5)
Dry/metallic taste	4 (3.3)	1 (1.6)	3 (5.1)
Neurological			
Lightheaded[c]	33 (27.5)	19 (31.1)	14 (23.7)
Low mood	21 (17.5)	9 (14.8)	12 (20.3)
Lethargy/weakness	19 (15.8)	9 (14.8)	10 (16.9)
Headache	14 (11.7)	8 (13.1)	6 (10.2)
Insomnia	10 (8.3)	3 (4.9)	7 (11.9)
Fainting	4 (3.3)	3 (4.9)	1 (1.7)
Anxiety	3 (2.5)	2 (3.3)	1 (1.7)
Other			
Hypotension	15 (12.5)	6 (9.8)	9 (15.3)
Injection site reaction	22 (18.3)	9 (14.8)	13 (22.0)
Skin reactions	7 (5.8)	1 (1.6)	6 (10.2)
Itching/dry skin	4 (3.3)	1 (1.6)	3 (5.1)
General pain	17 (14.2)	7 (11.5)	10 (16.9)
Hair loss	5 (4.2)	3 (4.9)	2 (3.4)
COVID-19	10 (8.3)	5 (8.2)	5 (8.5)
Flu/respiratory infection	54 (45.0)	21 (34.4)	33 (55.9)
Viral/throat infection	5 (4.2)	3 (4.9)	2 (3.3)
Urinary infection	9 (7.5)	8 (13.1)	1 (1.7)
Fracture injury	7 (5.8)	2 (3.3)	5 (8.5)
B: Serious Adverse Events			
Retropharyngeal abscess	1	1[d]	0
Renal calculus	1	1[e]	0
Blood in stool	1	1[f]	0
Prostate cancer	1	1[g]	0
Breast cancer	2	1[i]	1[h]

Events self-reported by three or more participants (>2% of the study cohort) at any time during the course of the 40-week intervention phase are shown.[a,b] [a]Participants reporting more than one type of adverse event are counted in each category of adverse event (total event numbers >120/100%). On average, participants who reported adverse events reported 7.7 different types of adverse events over the course of 40 weeks. [b]Adverse events reported by any two participants: paraesthesia, visual disturbance, sweats, gout, anal fissure and tendinitis. Adverse events reported by single participants: loss of appetite, brain fog, tinnitus, bloodshot eyes, anaemia, haemorrhoids, psoriasis flare, shingles, cataract and lymphadenopathy. One participant was inadvertently provided with a tirzepatide pen containing the incorrect dose, and self-administered that dose. [c]Includes symptoms of dizziness and vertigo. [d]Presented with neck pain, hospitalised for antibiotic therapy, continued tirzepatide on advice of treating physicians to reduce risk of concomitant dexamethasone-induced hyperglycemia. [e]Presented with pain, hospitalised for stent and stone removal, continued tirzepatide. [f]Underwent gastroscopy and colonoscopy with no malignancy detected, had already down-titrated to 0 mg dose of tirzepatide due to side effects. [g]Elevated PSA on screening, underwent MRI, biopsy, curative prostatectomy, continued tirzepatide on advice of surgeon for pre-operative weight loss. [h]Detected on routine screening, planned for surgery and radiotherapy therefore withdrawn from study to avoid interference with treatment. [i]Detected on routine screening, planned for surgery, chemo and radiotherapy therefore withdrawn from study to avoid interference with treatment.

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Extended Data Table 6 | Length of time participants self-reported experiencing adverse events during the T-REx trial, shown as the number of weeks during the 40-week intervention phase in which any adverse event was self-reported by an individual participant[a]

	All participants	T	T+REx
	(N=120)	(N=61)	(N=59)
Number of weeks			
0	7 (5.8)	4 (6.6)	3 (5.1)
1	17 (14.2)	12 (19.7)	5 (8.5)
2	16 (13.3)	7 (11.5)	9 (15.3)
3	15 (12.5)	8 (13.1)	7 (11.9)
4	20 (16.7)	11 (18.0)	9 (15.3)
5	14 (11.7)	6 (9.8)	8 (13.6)
6	8 (6.7)	4 (6.6)	4 (6.8)
7	3 (2.5)	1 (1.6)	2 (3.4)
8	4 (3.3)	0 (0.0)	4 (6.8)
9	3 (2.5)	3 (4.9)	0 (0.0)
10	5 (4.2)	2 (3.3)	3 (5.1)
11	2 (1.7)	0 (0.0)	2 (3.4)
12	2 (1.7)	2 (3.3)	0 (0.0)
13	2 (1.7)	1 (1.6)	1 (1.7)
14	1 (0.8)	0 (0.0)	1 (1.7)
15	0 (0.0)	0 (0.0)	0 (0.0)
16	1 (0.8)	0 (0.0)	1 (1.7)

[a]No participant self-reported experiencing any adverse event for more than 16 weeks during the 40-week intervention phase.

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Extended Data Table 7 | Estimated energy and protein intake and between group differences over course of the T-REx trial

Time	Group	Energy (kcal/day) Mean (95% CI)	Protein (% energy) Mean (95% CI)
Baseline	T	1,864 (1,686, 2,042)	19.5 (17.2, 21.8)
	T+REx	1,847 (1,677, 2,018)	20.6 (18.4, 22.9)
	Between-group diff.	−16 (−263, 230)	1.2 (−2.1, 4.4)
	P value*	0.896	0.482
24 weeks	T	1,377 (1,190, 1,564)	23.0 (20.6, 25.5)
	T+REx	1,316 (1,132, 1,501)	22.6 (20.1, 25.0)
	Between-group diff.	−61 (−324, 202)	−0.4 (−3.9, 3.0)
	P value*	0.650	0.799
40 weeks	T	1,493 (1,313, 1,674)	24.5 (22.1, 26.8)
	T+REx	1,268 (1,084, 1,453)	22.6 (20.2, 25.1)
	Between-group diff.	−225 (−484, 34)	−1.8 (−5.2, 1.6)
	P value*	0.088	0.292
Overall *P*-value	Group×time	0.299	0.318

The second 60 participants enrolled into the T-REx trial were invited to complete three-day food diaries at baseline, week 24 and week 40. Of these, 57 participants responded. Energy intake (kcal/d) and protein intake (%kcal) are shown as estimated marginal means from linear mixed effect models, with 95% confidence intervals (CI). Energy intake changed over time in both T and T+REx groups (effect of time: $P<0.001$). There was no group×time interaction ($P=0.299$). Protein intake as a percentage of total energy changed over time in both groups (effect of time: $P=0.001$). There was no group×time interaction ($P=0.318$). Overall, energy intake and protein intake as a percentage of total energy changed significantly over time; however, changes in energy intake and protein intake (% energy) did not differ significantly between the T and T+REx groups. There were no significant between-group differences in energy intake or protein intake (% energy) at any time point. *between group comparison at each time point

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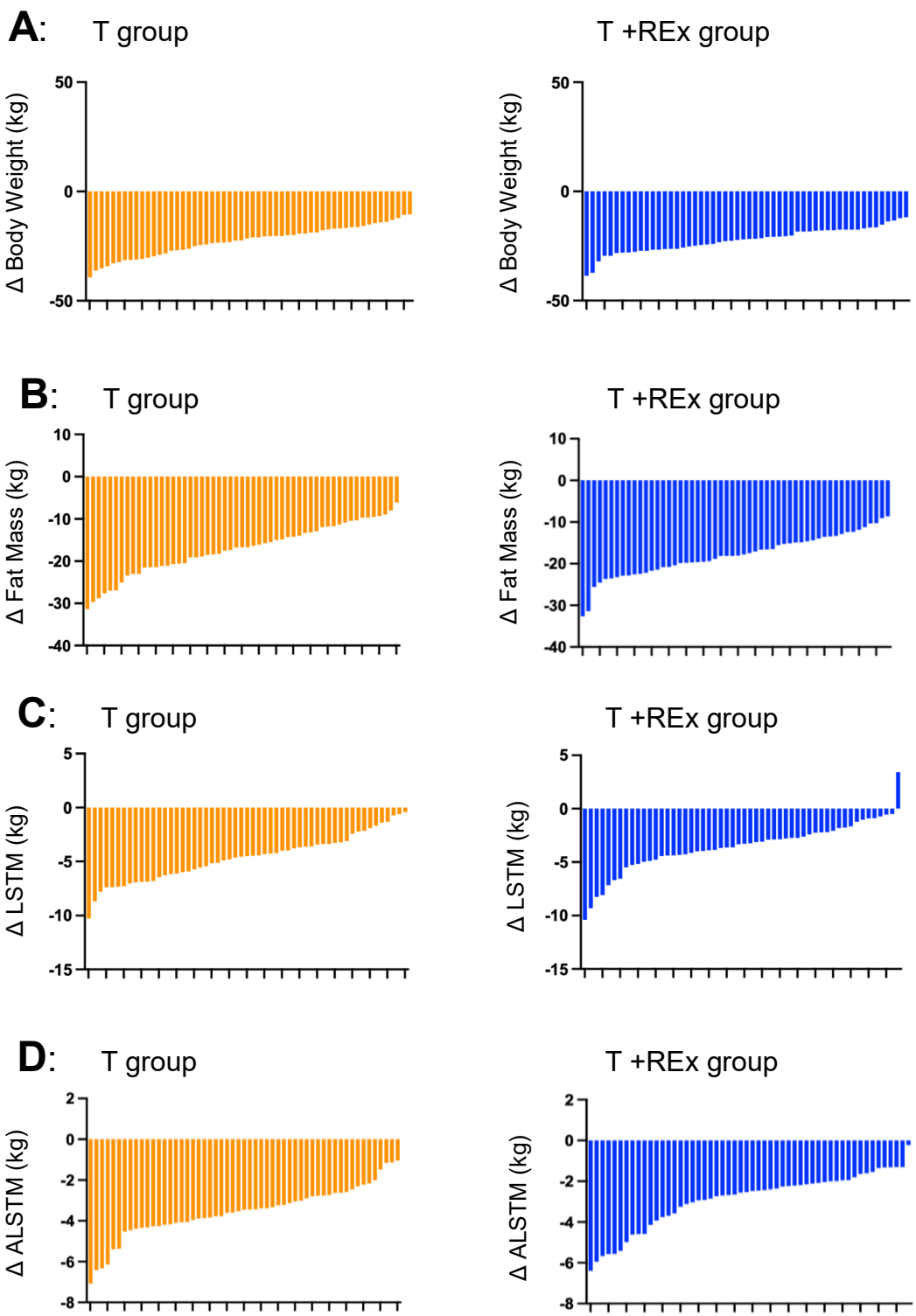
Extended Data Table 8 | Detailed schematic of the T-REx trial resistance exercise training intervention

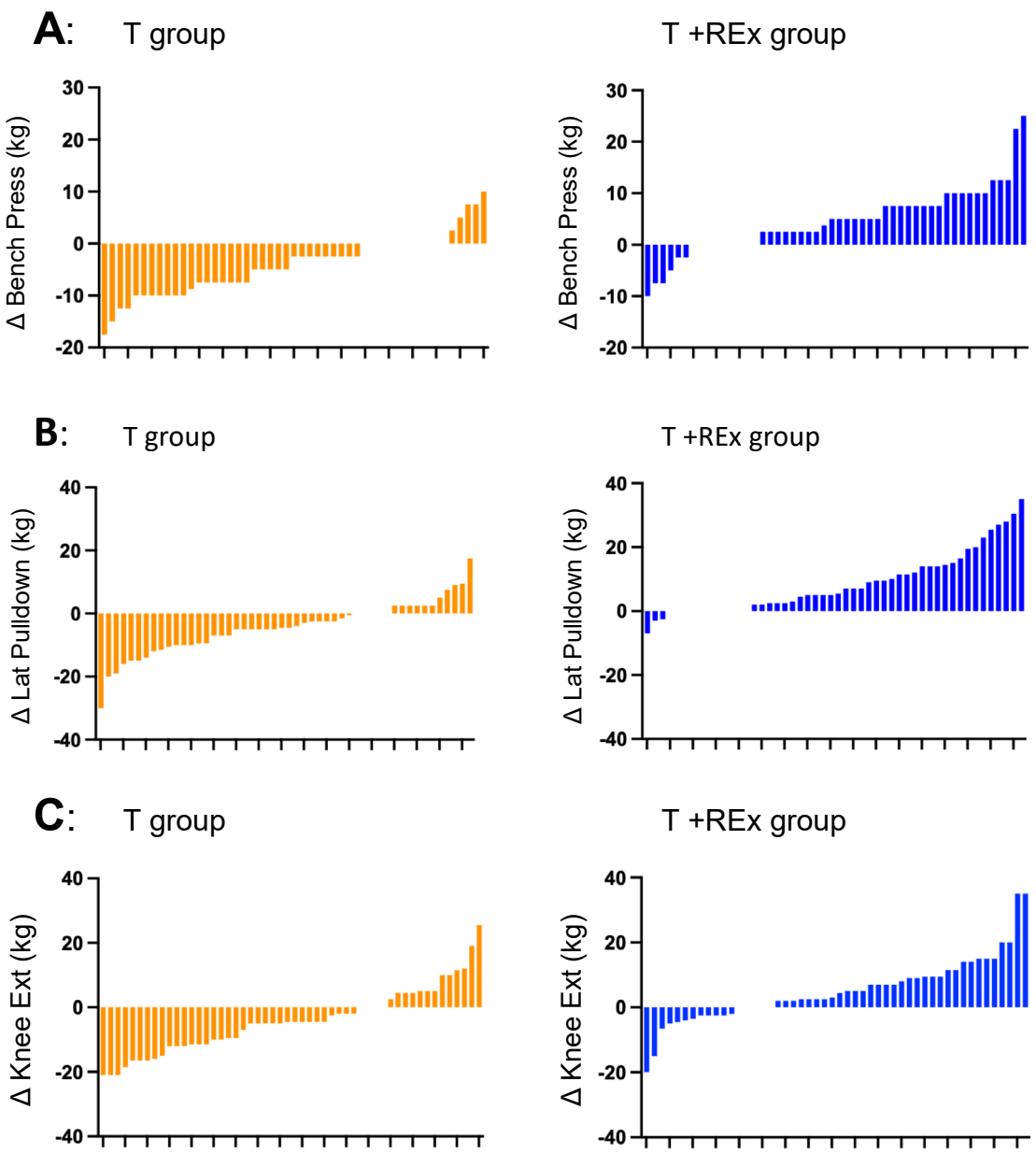
40-week Resistance Training Intervention **5 x 8-week mesocycles (3 exercise bouts per week)**						
Mesocycle	1		2	3	4	5
Week	1-4	5-8	9-16	17-24	25-32	33-40
Training Goals	Skill acquisition & Neuromuscular adaptation		Hypertrophy & Strength			
Exercise Information e.g. sets, reps & intensity (rating of perceived exertion RPE 1-10 scale)	**Week 1-4** 12 foundational exercises per session at low to moderate intensity (RPE <5) to develop correct technique and neuromuscular adaptation. 2 sets of 12-15 reps per exercise. 4 lower body (e.g. bodyweight squat, glute bridge, calf raise) + 6 upper body (e.g. incline push-up, lat pulldown) + 2 trunk (e.g. dead bug, bird dog) **Week 5-8** 7 exercises per session, 2 sets x 12 reps per exercise ar RPE 6-7		**Hypertrophy 2 x sessions per week** 8 exercises, 2-3 sets of 10-15 reps at 7-8 RPE per exercise **Strength 1 x session per week** 7 exercises, 2-3 sets of 6-8 reps at 7-8 RPE per exercise	**Hypertrophy and Strength sessions per mesocycle** Mesocycle 3: 2 hypertrophy and 1 strength session per week Mesocycle 4: 1 hypertrophy and 2 strength sessions per week Mesocycle 5: Alternating hypertrophy and strength sessions **Hypertrophy sessions** 3 sets of 8-10 reps at 7-9 RPE for each exercise: 3 lower body (e.g. lunges, hamstring curl, leg extension) + 4 upper body (e.g. cable fly's, cable row, shoulder press) + 1 trunk/core (e.g. side plank) **Strength sessions** 6 strength exercises + 1 trunk, 3 sets of 6-8 reps at 8-10 RPE for each exercise: 2-3 lower body (e.g. leg extension, leg press) + 2-3 upper body (e.g. chest press, lat pulldown) + 1 trunk/core (e.g. hanging knee raises)		

https://doi.org/10.1038/s41591-026-04752-5



Extended Data Fig. 1 | Changes in body weight, fat mass and lean soft tissue mass in individual participants. Waterfall plots showing changes at week 40 in (**a**) body weight, (**b**) total fat mass, (**c**) total lean soft tissue mass, LSTM, and (**d**) appendicular lean soft tissue mass, ALSTM, in participants receiving tirzepatide alone (T) versus those receiving tirzepatide and resistance exercise training (T+REx). Data are shown for individual participants in each group who completed the study with both baseline and week 40 results.

https://doi.org/10.1038/s41591-026-04752-5



Extended Data Fig. 2 | Changes in regional muscle strength in individual participants. Waterfall plots showing changes at week 40 in (**a**) bench press, (**b**) lat pulldown and (**c**) knee extension strength in participants receiving tirzepatide alone (T) and those receiving tirzepatide and resistance exercise training (T+REx). Data are shown for individual participants in each group who completed the study with both baseline and week 40 results.

nature portfolio

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For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

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☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Data was collected on RedCap.
Data analysis	Data was analyzed using SPSS v31 and STATA v19.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

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To protect participant confidentiality no data will be deposited in a public-facing repository. Individual participant data is not available for sharing.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	All participants reported their gender as the same as their sex assigned at birth.
Reporting on race, ethnicity, or other socially relevant groupings	Participants were not categorized on the basis of race, ethnicity or social grouping.
Population characteristics	We recruited community-dwelling adult men and post-menopausal women aged 50-70 years with body mass index (BMI) ≥30 kg/m², or ≥27 kg/m² with at least one weight-related comorbidity. Participants had to self-report <60 minutes of moderate or higher intensity exercise per week over the previous 3 months prior to entering the study. Participants also had to be willing to undertake up to 150 minutes per week of exercise for 6 months in a center-based program.
Recruitment	Participants were recruited via advertisements on social and local print media, and email. Information posters and flyers were distributed around the campus of the University of Western Australia and to provided to local general practices. Participants were pre-screened via an on-line questionnaire, those meeting the selection criteria were provided with the participant information form and invited to attend the study center for an in person visit. At this visit participants were informed of the study, and consent sought. Participants had to be willing to attend the study center three times a week for the duration of the study (required should they be randomized to the exercise training group). For these reasons, the cohort might contain more motivated persons living closer to the University of Western Australia (a generally affluent part of the metropolitan area of Perth, Western Australia).
Ethics oversight	University of Western Australia Human Research Ethics Committee (reference 2022/ET000666). All participants provided written informed consent.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Assuming a difference between groups (exercise training vs usual activities) in lean soft tissue mass of 1.0 kg, SD of 1.7, for 80% power we would need 47 completers in each group. We had previously recorded 85% or greater completion rates in our studies, so using a conservative 80% adherence rate, we aimed to recruit 60 participants in each group, N=120 in total.
Data exclusions	Data cleaning procedures were conducted prior to analysis to identify implausible observations, statistical outliers, and potential data entry errors across repeated measurement time points. Data cleaning was conducted algorithmically without regard to group allocation. To complement statistical screening procedures, longitudinal graphs were generated for each participant to visually inspect trajectories over time and identify unusual patterns, abrupt deviations, or potential outliers not detected through automated methods. Flagged observations were reviewed individually and retained, corrected, or excluded based on source verification to correct transposition or data entry errors.
Replication	This was a randomized controlled trial, and no replication was planned.
Randomization	Computer-based randomization was used to generate concealed envelopes. Participants were block-randomized to ensure similar numbers and sex-matching of participants in each group. A bespoke 'ralloc' package was used (Stata software, StataCorp, College Station, TX): blocks of 4 or 8 were randomly selected and block randomization was stratified for gender.
Blinding	Randomization and masking of allocations occurred, and personnel enrolling participants had no access to the sequence. It was not possible to blind the exercise training intervention. Body composition was assessed using dual energy X-ray absorptiometry (DXA) and the investigator analyzing the DXA data was blinded to group allocation. Strength testing was conducted using standardized operating procedures to be consistent for all participants. Statistical analyses were conducted by an independent professional statistician who was not involved in the study design or data collection.

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Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	ACTRN12623001236684
Study protocol	https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=385806&isReview=true
Data collection	Data were collected at the study center, within the School of Exercise and Sport Science at the University of Western Australia. Participants were randomized between 6 March 2024 and 5 March 2025. The last participant received their last dose of study medication on 6 March 2026. Of 120 participants in the study, 50% were female.
Outcomes	Pre-defined primary outcomes collected during this study were total body fat mass and total lean soft tissue mass, assessed using dual energy X-ray absorptiometry (DXA). Secondary outcomes reported in this manuscript are: appendicular lean soft tissue mass assessed by DXA, regional muscle strength (bench press, lat pulldown and knee extension) assessed using 1 repetition maximum (1RM) strength testing, body mass index, waist circumference, systolic and diastolic blood pressure measured using an automated oscillometric device, and fasting blood glucose, insulin, HbA1c, and lipid profile measured at a nationally accredited pathology laboratory.

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A