Effects of liraglutide on visceral and ectopic fat in adults with overweight and obesity at high cardiovascular risk: a randomised, double-blind, placebo-controlled, clinical trial

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Summary

Background Visceral and ectopic fat are key drivers of adverse cardiometabolic outcomes in obesity. We aimed to evaluate the effects of injectable liraglutide 3·0 mg daily on body fat distribution in adults with overweight or obesity without type 2 diabetes at high cardiovascular disease risk.

Methods In this randomised, double-blind, placebo-controlled, phase 4, single centre trial, we enrolled community-dwelling adults, recruited from the University of Texas Southwestern Medical Center, with BMI of at least 30 kg/m² or BMI of at least 27 kg/m² with metabolic syndrome but without diabetes and randomly assigned them, in a 1:1 ratio, to 40 weeks of treatment with once-daily subcutaneous liraglutide 3·0 mg or placebo, in addition to a 500 kcal deficient diet and guideline-recommended physical activity counselling. The primary endpoint was percentage reduction in visceral adipose tissue (VAT) measured with MRI. All randomly assigned participants with a follow-up imaging assessment were included in efficacy analyses and all participants who received at least one dose of study drug were included in the safety analyses. The trial is registered on ClinicalTrials.gov: NCT03038620.

Findings Between July 20, 2017 and Feb 21, 2020 from 235 participants assessed for eligibility, 185 participants were randomly assigned (n=92 liraglutide, n=93 placebo) and 128 (n=73 liraglutide, n=55 placebo) were included in the final analysis (92% female participants, 37% Black participants, 24% Hispanic participants, mean age 50·2 years (SD 9·4), mean BMI 37·7 kg/m²). Mean change in VAT over median 36·2 weeks was –12·49% (SD 9·3%) with liraglutide compared with –1·63% (SD 12·3%) with placebo, estimated treatment difference –10·86% (95% CI –6·97 to –14·75, p<0·0001). Effects seemed consistent across subgroups of age, sex, race–ethnicity, BMI, and baseline prediabetes. The most frequently reported adverse events were gastrointestinal-related (43 [47%] of 92 with liraglutide and 12 [13%] of 93 with placebo) and upper respiratory tract infections (10 [11%] of 92 with liraglutide and 14 [15%] of 93 with placebo).

Interpretation In adults with overweight or obesity at high cardiovascular disease risk, once-daily liraglutide 3·0 mg plus lifestyle intervention significantly lowered visceral adipose tissue over 40 weeks of treatment. Visceral fat reduction may be one mechanism to explain the benefits seen on cardiovascular outcomes in previous trials with liraglutide among patients with type 2 diabetes.

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Introduction

Obesity is a multifactorial disease affecting an estimated 42·4% of adults in the USA with substantial cardiovascular disease morbidity and mortality.[1–3] Although lifestyle modification is the cornerstone of treatment for overweight and obesity,[4] most individuals find it difficult to maintain the degree of intensive dietary modification and physical activity necessary to sustain long-term weight loss which leads to high rates of weight regain.[5] Furthermore, intensive lifestyle interventions aimed at lowering the BMI alone have not been proven to reduce the rates of cardiovascular events in high risk patients.[6] One reason for this might be that BMI alone does not sufficiently discriminate cardiovascular disease and diabetes risk among individuals with obesity.[7,8] Rather, it appears that risk for diabetes and cardiovascular disease varies substantially across different fat depots,[9–11] and that excess visceral adipose tissue (VAT), consisting of fat near the intra-abdominal organs, and ectopic (eg, liver) fat are central to the pathogenesis of type 2 diabetes and cardiovascular disease.[7,12]

Pharmacological therapy, as an adjunct to lifestyle modification, is effective for obesity, with placebo-adjusted weight reduction over 12 months ranging from 2·9 to 6·8%[13] in appropriate patients.[14,15] However, long-term treatment for obesity can be costly and patients might develop adverse effects related to the medication. Selecting individuals with excess visceral and ectopic fat at high cardiovascular disease risk with the greatest potential therapeutic benefit remains a challenge. Prospective, adequately powered studies designed to examine the effects of medications for chronic weight management on visceral and ectopic fat depots are

Research in context

Evidence before this study

We searched PubMed up to June 25, 2017 without any language restrictions for clinical trial studies evaluating the effects of liraglutide on visceral adipose tissue and liver fat assessed by imaging. The search terms were "visceral adipose tissue" OR "visceral fat" AND "liver fat" OR "hepatic steatosis" AND "computed tomography" OR "magnetic resonance imaging" OR "magnetic resonance spectroscopy" AND "liraglutide" OR "GLP-1 receptor agonist". Studies were of reasonable quality and modest generalisability to both European and North American populations. Studies included liraglutide at doses between 1·8 mg and 3·0 mg daily and participants with type 2 diabetes or prediabetes. Most showed a significant difference between visceral and liver fat reduction with liraglutide compared with placebo, although two smaller studies (n=50 and n=47) of the liraglutide 1·8 mg dose did not. Preliminary evidence from a small substudy (n=29) of the liraglutide 3·0 mg dose, which made use of computed axial tomography, suggested liraglutide recipients lost approximately 6% more visceral fat than those on placebo. However, this study was underpowered to definitively assess between group differences in the absolute or relative mean visceral fat lost and did not include other highly relevant fat distribution endpoints such as liver fat.

Added value of this study

Liraglutide at a once-daily dose of 3·0 mg, when used as an adjunct to a reduced-calorie diet and increased physical activity counselling, resulted in significantly lower visceral and ectopic fat over a median 36 weeks on treatment compared with placebo in a population of adults with overweight and obesity at high cardiovascular disease risk. The relative effects of liraglutide on fat reduction were two times greater in the abdominal viscera and six times greater in the liver than seen on overall bodyweight. The treatment effect was consistent across race–ethnicity and baseline BMI categories, and among those with or without baseline prediabetes. Liraglutide also reduced fasting blood glucose and C-reactive protein in the trial population without diabetes, the majority of whom had normoglycaemia at baseline.

Implications of all the available evidence

Taken together, although our study was not designed to directly examine the associations between liraglutide-mediated visceral adipose tissue loss, changes in biomarkers, and risk for cardiovascular disease events, our findings suggest that reductions in visceral fat and hepatic fat could be mechanisms underpinning the cardiovascular disease risk benefit that has been seen with liraglutide in patients with type 2 diabetes. Given the emerging recognition of visceral and ectopic fat as important cardiovascular risk factors, future pharmacological studies for weight loss should incorporate dedicated, gold-standard MRI imaging of visceral adipose tissue and liver fat as high-value, modifiable targets for obesity treatment.

rare.[16] Moreover, previous studies have focused almost exclusively on patients with pre-existing type 2 diabetes,[17–19] thereby limiting the generalisability of the findings to high-risk populations without type 2 diabetes.

GLP-1 is a polypeptide incretin hormone that induces glucose-dependent insulin secretion, reduces plasma glucagon concentrations, delays gastric emptying, and suppresses appetite.[20] Liraglutide is a GLP-1 receptor agonist approved at the 3·0 mg daily dose for chronic weight management in eligible patients with and without diabetes.[21–23] The LEADER trial showed cardiovascular disease benefit with liraglutide 1·8 mg daily treatment for patients with type 2 diabetes and high cardiovascular disease risk.[24] The mechanisms of benefit on cardiovascular disease risk reduction remain uncertain but might be mediated through metabolic modulation,[25] including, potentially, through modification of dysfunctional adiposity characterised by visceral and ectopic fat. Preliminary evidence from a small sub-study (n=29), which made use of computed axial tomography suggested liraglutide recipients lost approximately 6% more visceral fat than those on placebo.[26] However, this study was underpowered to definitively assess between group differences in the absolute or relative mean VAT lost and did not include other highly relevant fat distribution endpoints such as hepatic fat.

As of 2020, liraglutide was the most widely prescribed medication for obesity treatment, encompassing greater than 56% of the global market share.[27] Given its widespread use, proven cardiometabolic benefit, and potential effect on high-risk body fat depots, we did a randomised, placebo-controlled, clinical trial to assess the effects of liraglutide 3·0 mg daily on visceral and ectopic fat in adults with overweight or obesity without type 2 diabetes at high cardiovascular disease risk.

Methods

Study design

The study design is shown in figure 1. By means of a randomised, double-blind, placebo-controlled design, eligible community-dwelling adult participants recruited from the University of Texas Southwestern Medical Center with overweight or obesity at high risk for cardiovascular disease who completed a 2-week run-in phase consisting of a 500 kcal deficient diet and guide-line recommended physical activity were given daily liraglutide or placebo subcutaneous injection (Novo Nordisk, Bagsværd, Denmark) for 40 weeks. Study participation lasted approximately 46 weeks with 17 clinic visits. Participants desiring to complete their involvement in the study before the completion of the full trial protocol underwent an early termination visit. Medical

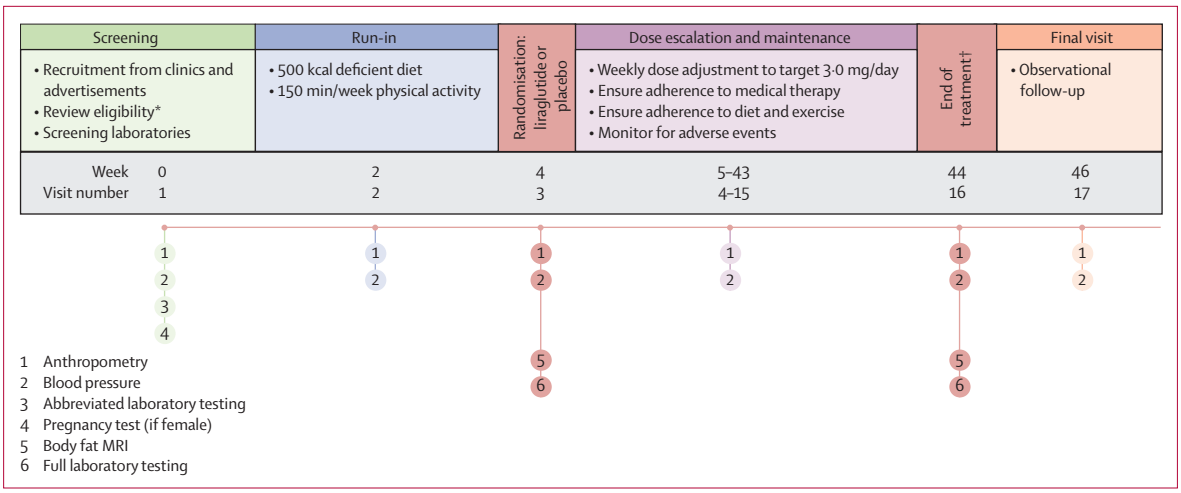

Figure 1: **Study design**
We did a randomised, double-blinded, placebo-controlled trial including adult participants with overweight or obesity at high risk for cardiovascular disease. Eligible participants who completed a 2-week run-in phase consisting of a 500 kcal deficient diet and guideline recommended physical activity were given daily liraglutide or placebo subcutaneous injection for 40 weeks. Study participation lasted approximately 46 weeks with 17 clinic visits. Participants desiring to complete their involvement in the study before the completion of the full trial protocol underwent an early termination visit. Medical history, anthropometry, body fat distribution imaging by MRI, plasma biomarkers, medication adherence, and adverse effects were assessed at various timepoints during the study. *Adults with overweight or obesity at high cardiovascular disease risk. †Completion of the full trial protocol or early termination visit at request of the participant.

history, anthropometry, body fat distribution imaging by magnetic resonance imaging, plasma biomarkers, medication adherence, and adverse effects were centrally assessed at various timepoints during the study (figure 1). The protocol is available from the corresponding author on reasonable request.

Participants

Community-dwelling individuals were screened and recruited from the University of Texas Southwestern Medical Center from 2017 to 2020. Adults aged 35 years and older with obesity (BMI ≥30 kg/m²) or with overweight (BMI ≥27 kg/m²) with prevalent metabolic syndrome were enrolled. Metabolic syndrome was defined by means of NCEP–ATP III criteria[28] as at least three of the following: waist circumference greater than 102 cm (40 in) in men or greater than 88 cm (35 in) in women, fasting triglyceride concentration of at least 150 mg/dL, blood pressure at least 130/85 mmHg, HDL cholesterol (HDL-C) concentration less than 40 mg/dL in men or less than 50 mg/dL in women, and fasting blood glucose concentration of at least 100 mg/dL. For inclusion, participants were required to be free from type 1 or type 2 diabetes (both by self-reported medical history and HbA1c measurement less than 6·5% at screening), and be able to undergo a neck-to-knee MRI scan for body fat assessment. Participants were excluded if they were currently taking or planned to take GLP-1 receptor agonists or other obesity treatments, had a history of contraindications or were at high risk for serious adverse effects from GLP-1 receptor agonist therapy (eg previous pancreatitis or gallbladder disease, personal or family history of familial medullary thyroid carcinoma or multiple endocrine neoplasia type 2), or were pregnant (by urine pregnancy test at the time of screening), or breastfeeding. A full list of inclusion and exclusion criteria is shown in the appendix (p 2). This clinical study was approved by the University of Texas Southwestern Medical Center Institutional Review Board and registered on ClinicalTrials.gov (NCT03038620). All participants provided written informed consent.

See Online for appendix

Randomisation and masking

Participants were randomly assigned to liraglutide subcutaneous injection 3·0 mg once daily or matching placebo (in a 1:1 ratio) to be taken for the duration of the study. Randomisation was done by means of a computerised randomisation code generated by a statistician at UT Southwestern Medical Center not involved in the conduct of the study. All participants, study personnel, and outcome adjudicators were masked to the treatment assignment until the completion of all study procedures. Pen-injectors used to administer liraglutide and placebo were identical in appearance. Guideline recommended diet and physical activity counselling was provided for all participants at each study visit for the duration of the trial.

Procedures

After the initial screening visit, participants who met eligibility criteria underwent a 2-week run-in phase of dietary and physical activity counselling. Dietary counselling consisted of calculation of total energy expenditure by means of published equations[29] and prescription of a hypocaloric diet containing approximately 30% of energy from fat, 20% of energy from

protein, 50% of energy from carbohydrates, and an energy deficit of approximately 500 kcal/day compared with the participant's baseline estimated total energy expenditure. Three-day food diaries were used during the run-in phase and periodically during the study to assess participant adherence to dietary counselling. Counselling on guideline recommended physical activity included initial assessment of baseline physical activity and then counselling to increase physical activity (at the participant's discretion) to a recommended minimum of at least 150 min/week of moderate-intensity activity. Continued adherence to dietary and physical activity counselling were encouraged and assessed throughout the study treatment phase. Participants who were unable to maintain adherence to the dietary or physical activity, or both, recommendations during the run-in phase were removed from the study before random assignment.

After randomisation, participants were started on 0·6 mg once daily of subcutaneous injection liraglutide or matching placebo by means of a 6·0 mg/mL, 3 mL pen injector. Dosing with the liraglutide–placebo pen injector was controlled by turning the dose selector until the dose indicator showed the relevant dose (0·6, 1·2, 1·8, 2·4, or 3·0 mg). The dose was titrated up on a weekly basis by 0·6 mg increments to a target dose of 3·0 mg. Participants unable to tolerate an initial dose increase were allowed to wait an additional week before re-attempting dose titration.

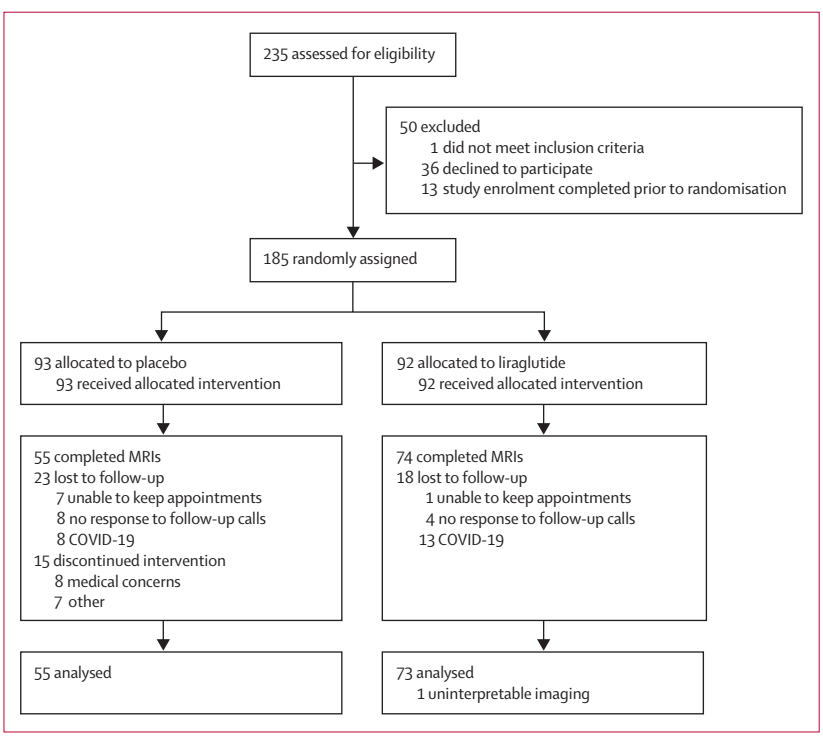

Figure 2: **Trial profile**
Participants with overweight or obesity without type 2 diabetes at high cardiovascular risk were screened for eligibility in the trial and 185 were randomly assigned to liraglutide or matching placebo. 30·8% of participants withdrew or were lost to follow-up, most commonly because of COVID-19. 128 participants (73 liraglutide and 55 placebo) were included in the final analysis. The medical concerns leading to study discontinuation (n=8) were musculoskeletal (2), diabetes (1), cough/headache (1), inflammatory condition (1), cardiac (1), visual changes (1), infection (1); other (n=7), family emergency, car accident, extenuating circumstances, no weight loss (2), personal reasons (2).

Age, sex, and race–ethnicity were self-reported. Weight and height were measured by means of a standard scale wearing loose fitting clothing and without shoes. BMI was calculated as weight in kg divided by height in m². Waist circumference was measured 1 cm above the iliac crest and hip circumference at the widest circumference of the buttocks at the area of the greater trochanters. Pulse and blood pressure were measured by means of an Omron 5 series upper arm blood pressure monitor (Omron Healthcare, Lake Forest, IL, USA). At various timepoints during the 46 weeks anthropometry, blood pressure, body fat, and full laboratory testing measurements were taken (figure 1).

Outcomes

The primary outcome, investigating the efficacy of liraglutide compared to placebo in reducing VAT, and secondary outcomes including changes in abdominal subcutaneous adipose tissue volume, total fat tissue volume, fat-free tissue volume, lower body adipose tissue volume, and hepatic fat content were all measured by MRI. Participants underwent MRI scanning on either a Philips Achieva 3-T MRI scanner (Philips Healthcare, Amsterdam, Netherlands) or a General Electric 750w (wide bore) 3-T MRI scanner (GE Healthcare, Chicago, IL, USA) by means of a 6-min dual-echo Dixon Vibe protocol, providing a water and fat separated volumetric data set covering neck to knees, and a single-slice multiecho Dixon acquisition for proton density fat fraction assessment in the liver. Images of the liver were acquired by means of a 16-channel SENSE XL torso coil and images from the rest of the body were acquired by means of the body coil. For body composition, acquired image data were analysed for total adipose tissue volume, VAT, abdominal subcutaneous adipose (SAT) tissue, lower body subcutaneous fat (consisting of adipose tissue in the hips and buttocks), and liver fat proton density fat fraction. Briefly, the image analysis consisted of image calibration, fusion of image stacks, image segmentation, and quantification of fat and muscle volumes and included manual quality control by an analysis engineer.[30–33] Body composition analyses were done by means of AMRA Profiler Research (AMRA Medical AB, Linköping, Sweden). The coefficients of variation for the various measurements are 4·4% for visceral adipose tissue, 3·2% for abdominal SAT, and 28·7% for, liver fat.[34] Participants were scanned on the same model scanner both at baseline and follow-up. By means of a test set of participants (n=3) who were imaged on both scanners, the inter-scanner differences for visceral adipose tissue measurement between the Philips and General Electric scanners were seen to range between 0·03% and 1·7%. Additional secondary outcomes were analysed including changes in circulating

	Placebo (n=55)	Liraglutide (n=73)
Age, years	50·9 (8·8)	49·6 (9·8)
Female	51 (93%)	67 (92%)
Male	4 (7%)	7 (8%)
Race		
White	35 (64%)	43 (59%)
Black	19 (35%)	28 (38%)
Other	1 (2%)	2 (3%)
Ethnicity		
Hispanic	12 (22%)	18 (25%)
On-treatment time, weeks	36·1 (8·2)	36·2 (8·6)
Systolic blood pressure, mm Hg	125·8 (13·9)	130·3 (14·9)
Diastolic blood pressure, mm Hg	78·5 (8·3)	80·9 (7·8)
Weight, kg	102·3 (17·9)	101·0 (17·9)
Height, m	1·6 (0·1)	1·6 (0·1)
BMI, kg/m²	38·1 (6·1)	37·2 (6·0)
Waist circumference, cm	104·8 (10·6)	105·5 (12·2)
Hip circumference, cm	122·1 (13·0)	119·8 (11·6)
Baseline, kcal/day	2196 (189)	2177 (195)
Medical history		
Hypertension,	20 (36%)	30 (41%)
Hyperlipidaemia	16 (29%)	15 (20%)
Prediabetes	3 (5%)	2 (3%)
Lab Values		
Fasting blood glucose, mg/dL	99·1 (14·4)	100·6 (12·9)
Fasting insulin, mIU/L	18·0 (17)	16·3 (10·8)
HOMA-IR	4·85 (7·01)	4·22 (3·56)
Triglycerides, mg/dL	118·3 (50·6)	109·4 (49·7)
HDL-C, mg/dL	54·6 (11·8)	58·6 (11·9)
C-reactive protein, mg/L	7·8 (6·8)	8·0 (4·3)
NT-proBNP, pg/mL	63·2 (44·7)	59·6 (44·1)
Body fat–composition		
Total body adipose tissue, L	40·9 (9·8)	39·6 (8·9)
Visceral adipose tissue, L	4·5 (1·7)	4·5 (2·1)
Abdominal subcutaneous adipose tissue, L	16·2 (4·2)	15·6 (4·3)
Lower body adipose tissue, L	15·6 (5·0)	14·7 (4·3)
Liver fat	6·1% (6·1)	7·6% (7·9)
Total body lean tissue, L	21·5 (3·5)	21·6 (3·8)

Data presented as n (%), mean (SD), or proportion as appropriate. HOMA-IR=homoeostasis model assessment-insulin resistance. NT-proBNP=NT-proB-type natriuretic peptide.

Table 1: **Baseline characteristics**

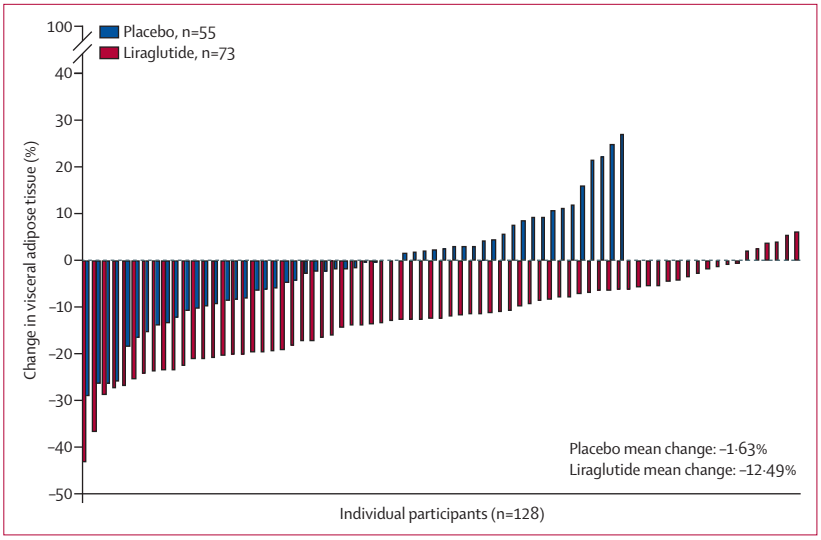

Figure 3: **Participant-level relative changes in visceral adipose tissue**
Individual, participant-level relative changes in VAT are shown in this waterfall plot. Participants assigned to liraglutide are in red and those assigned to placebo are in blue.

blood biomarkers of cardiometabolic risk by blood being drawn after an 8 h fast for analysis of plasma glucose, insulin, triglycerides, HDL-C, C-reactive protein (CRP), and NT-proB-type natriuretic peptide (NT-proBNP). Samples were analysed by UT Southwestern Laboratories (Dallas, TX, USA) by means of standard assays. A post-hoc analysis of weight loss was done. At each visit, safety was assessed by collection of self-reported adverse events and serious adverse events and investigator-adjudicated attribution of adverse events related or not to study drug.

Statistical analysis

The trial was powered to detect the primary outcome of percentage reduction in VAT. The estimates used in the sample size calculations were derived from previous data from the SCALE programme.[26] Assuming an expected mean 8% reduction of VAT among placebo treated participants and a 16% reduction of VAT among liraglutide treated participants (SD 16%), we expected to require 128 total participants (in a 1:1 trial drug:placebo randomisation scheme) to achieve 80% power to detect an 8% difference between groups at an α level of 0·05. Assuming an estimated 28% of participants would withdraw study medication during the trial (on the basis of previous clinical trial experience[21,23] with liraglutide 3·0 mg), we expected a planned total of 178 patients would be randomly assigned in order to achieve at least 128 participants with baseline and follow-up assessments of the primary and secondary imaging outcomes.

Baseline characteristics of the study population stratified by treatment assignment were compared by means of the Kruskal-Wallis test for continuous variables or Fisher's Exact test for categorical variables. Visit-by-visit changes in bodyweight, BMI, and waist circumference over the treatment period for both liraglutide and placebo were plotted by means of the available data with missing values for the interim visits imputed with the Monte Carlo Markov Chain method by means of n=10 imputations. All participants had weight, BMI, and waist circumference measurements at the baseline and follow-up imaging visits. Imputation was only done for bodyweight, BMI, and waist circumference owing to missing data for these measures during interim visits as a consequence of the COVID-19 pandemic in-person research visit restrictions. The primary (relative percentage change in VAT) and

	Placebo (n=55)	Liraglutide (n=73)	Estimated treatment difference for liraglutide vs placebo (95% CI)	p value
Primary outcome				
Visceral adipose tissue change	−1·63% (12·3%)	−12·49% (9·3%)	−10·86% (−6·97 to −14·75)	<0·0001
Secondary outcomes				
Percentage changes				
Weight	−1·19% (4·68)	−6·59% (4·80)	−5·40% (−3·74 to −7·01)	<0·0001
BMI	−1·08% (4·88)	−6·53% (4·84)	−5·45% (−3·75 to −7·15)	<0·0001
Waist circumference	−4·16% (6·06)	−6·90% (6·43)	−2·74% (−0·56 to −4·92)	0·021
Total body adipose tissue	−0·95% (7·80)	−9·59% (7·15)	−8·64% (−6·00 to −11·27)	<0·0001
Abdominal subcutaneous adipose tissue	−0·77% (8·40)	−9·87% (8·23)	−9·10% (−6·18 to −12·01)	<0·0001
Lower body adipose tissue	−1·29% (8·57)	−9·95% (7·61)	−8·66% (−5·80 to −11·52)	<0·0001
Liver fat	20·63% (104·92)	−12·37% (61·43)	−33·00% (−1·90 to −64·10)	0·025
Total body lean tissue	−0·90% (3·66)	−2·47% (4·04)	−1·57% (−0·23 to −2·91)	0·029
Total body fat/total body lean tissue	0·01% (7·83)	−7·23% (7·25)	−7·24% (−4·58 to −9·89)	<0·0001
Absolute changes				
Visceral adipose tissue, L	−0·10 (0·53)	−0·53 (0·43)	−0·43 (−0·26 to −0·60)	<0·0001
Weight, kg	−1·30 (4·79)	−6·75 (5·35)	−5·45 (−3·69 to −7·21)	<0·0001
BMI, kg/m²	−0·43 (1·86)	−2·46 (2·01)	−2·46 (−1·36 to −2·70)	<0·0001
Waist circumference, cm	−4·60 (6·69)	−7·40 (6·82)	−2·80 (−0·44 to −5·16)	0·019
Total body adipose tissue, L	−0·42 (2·92)	−3·76 (2·87)	−3·34 (−2·32 to −4·35)	<0·0001
Abdominal subcutaneous adipose tissue, L	−0·15 (1·24)	−1·52 (1·31)	−1·37 (−0·92 to −1·81)	<0·0001
Lower body adipose tissue, L	−0·19 (1·19)	−1·51 (1·34)	−1·32 (−0·88 to −1·76)	<0·0001
Liver fat, %	0·01% (3·24)	−2·35% (5·35)	−2·36% (−0·86 to −3·86)	0·0044
Total body lean tissue, L	−0·17 (0·80)	−0·54 (0·88)	−0·37 (−0·08 to −0·66)	0·022
Visceral adipose tissue:subcutaneous adipose tissue ratio	0 (0·02)	−0·01 (0·03)	−0·01 (−0·001 to −0·02)	0·19
Post-hoc outcomes				
Weight loss ≥5%	21·8%	63·0%	..	<0·0001
Weight loss ≥10%	3·6%	19·2%	..	<0·0001

Data are mean % (SD). Value for primary outcome is mean percentage (SD). Values for secondary outcome are mean percentages (SD) or means (SD). Values for post-hoc outcomes are proportions. Estimated treatment differences are calculated using analysis of covariance without imputation.

Table 2: **Body composition and fat distribution outcomes stratified by treatment assignment**

secondary outcomes (absolute change in VAT, relative and absolute changes in all other anthropometric, imaging, and biomarker outcomes) were analysed in all randomly assigned participants with a follow-up imaging assessment for efficacy analyses (including both per-protocol completers and participants who stopped participation early, but underwent early termination imaging assessment), and all participants who received at least one dose of study drug for the safety analyses. No imputation of imaging outcomes was done for these analyses. Placebo-adjusted estimated treatment effects and 95% CIs were calculated by means of generalised linear mixed models with random effects for participants. Treatment effects were also analysed by subgroups of age (median), sex, race–ethnicity, BMI categories, and baseline prediabetes status. Spearman correlation coefficients were calculated between changes in weight and fat distribution phenotypes and biomarkers. A completers (ie, per-protocol) analysis was also done for primary and secondary outcomes in participants who underwent random assignment and had a follow-up imaging endpoint assessment after completing the full 40-week on-treatment protocol. For all statistical testing (including interaction testing), a 2-sided p value of less than 0·05 was considered significant. All statistical analyses were done by means of SAS version 9.4 software (SAS Corporation, Cary, NC). A Data and Safety Monitoring Committee was used. The trial is registered on ClinicalTrials.gov, NCT03038620 where the full statistical analysis plan has been published.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, in the writing of the report, or in the decision to submit the paper for publication.

Results

Between July 20, 2017 and Feb 21, 2020, from 235 participants assessed for eligibility, a total of 185 participants underwent random assignment; 92 received study drug and 93 received placebo. 129 participants completed follow-up until Oct 13, 2020 (n=74 study drug and n=55 placebo) but one participant allocated to study drug had uninterpretable follow-up imaging; therefore, 128 participants (n=73 study drug and n=55 placebo) were included in the final analysis (figure 2).

The study cohort was 92% female with 37% Black participants and with 24% of participants reporting Hispanic ethnicity. The mean (SD) age was 50·2 years (9·4) and mean (SD) BMI was 37·7 (6·1) kg/m². Baseline characteristics of the study population stratified by treatment assignment are shown in table 1. Mean drug compliance (defined as proportion of all drug taken or dispensed across all visits) was 98% (98% for liraglutide and 98% for placebo). The mean (SD)

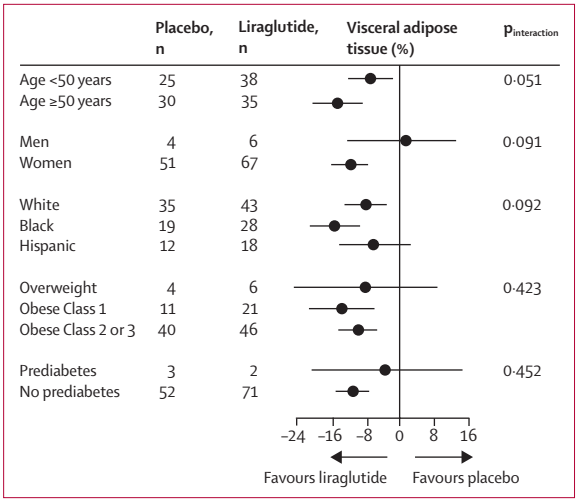

Figure 4: **Effect of liraglutide on visceral adipose tissue by key subgroups**
Effect of liraglutide compared with placebo on visceral adipose tissue by subgroups of age, sex, race–ethnicity, BMI classification, and prediabetes status at baseline. Liraglutide showed consistent effects on VAT across all subgroups with no significant (p<0·05) interactions observed.

achieved liraglutide dose was 2·49 (0·82) mg/day. 96% of participants achieved the 3·0 mg dose with a mean (SD) time on that dose of 28·2 (10·9) weeks. Individual, participant-level relative changes in VAT are shown in figure 3. Liraglutide significantly reduced the primary endpoint of relative percentage change in VAT compared with placebo (mean VAT change with placebo –1·63% (SD 12·3%), mean VAT change with liraglutide –12·49% (SD 9·3%), placebo-adjusted estimated treatment difference –10·86%, 95% CI –6·97 to –14·75, p<0·0001; table 2). Liraglutide effects on VAT seemed consistent across subgroups of age, sex, race–ethnicity, BMI, and baseline prediabetes status; no statistical interactions by subgroup were observed (figure 4). Compared with placebo, liraglutide treatment also significantly reduced the secondary endpoints of total body fat, abdominal SAT, lower body SAT, liver fat, and total body lean tissue (table 2). Similar findings were seen when absolute changes in body composition and fat distribution were examined (table 2). Changes in weight were most highly correlated with changes in total body fat and abdominal SAT, and less so with VAT and liver fat (appendix p 4). Liraglutide also significantly reduced fasting blood glucose and CRP compared with placebo, but there were no significant differences in fasting insulin, triglyceride:HDL-C ratio, or NT-proBNP concentrations between the liraglutide and placebo treated groups (table 3). Weight loss and reduction in all fat depots were significantly correlated with reductions in fasting blood glucose and CRP, but not with fasting insulin or NT-proBNP. Reduction in CRP was most highly correlated with VAT loss. Only reduction in hepatic fat was significantly correlated with reduction in triglyceride:HDL-C ratio (appendix p 5).

	Placebo (n=55)	Liraglutide (n=73)	Estimated treatment difference for liraglutide *vs* placebo (95% CI)	p value
Percentage changes				
Fasting blood glucose	0·83%	−5·62%	−6·45% (−2·15 to −10·75)	0·0048
Fasting insulin	7·73%	20·58%	12·85% (−9·48 to 35·18)	0·41
HOMA-IR	11·85%	15·35%	3·5% (−21·02 to 28·02)	0·88
Triglyceride: HDL-C ratio	−2·18%	−2·1%	0·08% (−10·25 to −10·41)	0·99
C-reactive protein	19·02%	−19·91%	−38·93% (−17·45 to −60·41)	0·038
NT-proBNP	20·47%	12·1%	−8·37% (−36·02 to 19·28)	0·38
Absolute changes				
Fasting blood glucose, mg/dL	−0·22	−6·49	−6·27 (−1·82 to −10·72)	0·0061
Fasting insulin mIU/L	−1·48	0·75	2·23 (−1·74 to 6·20)	0·47
HOMA-IR	−0·69	−0·15	0·54 (−1·02 to 2·10)	0·98
Triglyceride: HDL-C ratio	−0·16	−0·02	0·14 (−0·12 to 0·40)	0·58
C-reactive protein, mg/L	−0·64	−2·18	−1·54 (−3·35 to 0·28)	0·031
NT-proBNP, pg/mL	1·44	−8·10	9·54 (−25·13 to 6·05)	0·32

Values are estimated mean percentages or means. Estimated treatment differences are calculated using analysis of covariance without imputation. HOMA-IR=homoeostasis model assessment-insulin resistance. HDL-C=high-density lipoprotein cholesterol.

Table 3: **Biomarker outcomes of cardiovascular risk stratified by treatment assignment**

The reported adverse events were typical of side-effects historically reported in liraglutide trials (table 4). The most frequently reported adverse events were gastrointestinal-related (43 [47%] of 92 with liraglutide and 12 [13%] of 93 with placebo) and upper respiratory tract infections (10 [11%] of 92 with liraglutide and 14 [15%] of 93 with placebo). All adverse events were grade 1 or 2. There were no serious adverse events (grades 3 to 5) reported during the study. A greater proportion of participants in the placebo group withdrew from the study for adverse events (n=8) compared with participants in the liraglutide group (n=0). There were no significant differences in absolute pulse rate (+4·84 *vs* +2·67 beats per min, p=0·15), systolic blood pressure (–5·84 *vs* –0·02 mm Hg, p=0·076), or diastolic blood pressure (–2·01 *vs* –0·62 mm Hg, p=0·48) change between the liraglutide and placebo treated groups.

Median follow-up time on treatment was 36·2 (IQR 8·4) weeks with no significant difference observed in follow-up time on treatment between liraglutide and placebo treated groups (36·2 *vs* 36·1 weeks, p=0·71).

	Liraglutide (n=92)	Placebo (n=93)
Gastrointestinal related	43 (47%)	12 (13%)
Constipation	13 (14%)	5 (5%)
Nausea–vomiting	13 (14%)	3 (3%)
Gastrointestinal upset–dyspepsia	11 (12%)	3 (3%)
Diarrhoea–flatulence	6 (7%)	1 (1%)
Upper respiratory tract infection–pharyngitis	10 (11%)	14 (15%)
Injection site reaction	7 (8%)	8 (9%)
Headache	5 (5%)	5 (5%)
Joint pain	5 (5%)	3 (3%)
Insomnia	2 (2%)	0
Dizziness	3 (3%)	0
Fever	0	2 (2%)
Other	9 (10%)	12 (13%)
Hepatic cyst	3 (3%)	2 (2%)

Data presented as n participants (proportion) with reported adverse events among all randomly assigned participants (n=185). All adverse events were grade 1 or 2. There were no adverse events graded 3 to 5.

Table 4: **Summary of adverse events reported in the study**

In addition to guideline recommended diet and physical activity counselling during the trial period, liraglutide significantly reduced weight (–5·40%, 95% CI –3·74 to –7·01, p<0·0001), BMI (kg/m²; –5·45%, 95% CI –3·75 to –7·15, p<0·0001), and waist circumference (–2·74%, 95% CI –0·56 to –4·92, p=0·021) compared with placebo (table 2 and appendix pp 9–11). In post-hoc analyses, a higher proportion of participants in the liraglutide versus placebo group achieved weight loss of at least 5% (63·0% *vs* 21·8%) or 10% (19·2% *vs* 3·6%), p less than 0·0001 for both (table 2).

In the per-protocol sensitivity analysis, median follow-up time on treatment did not significantly differ between liraglutide and placebo treated groups (39·0 *vs* 39·1 weeks, p=0·93) and baseline characteristics were generally similar (appendix p 6). In the per-protocol population, liraglutide significantly reduced the primary endpoint of percentage change in VAT compared with placebo (mean VAT change with placebo –0·71% (SD 12·7%); mean VAT change with liraglutide –13·88% (SD 9·1%), placebo-adjusted estimated treatment difference –13·17%, 95% CI –8·79 to –17·55, p<0·0001; appendix p 7). Liraglutide treatment also significantly reduced weight, BMI, waist circumference, total body fat, abdominal SAT, lower body SAT, liver fat, total body lean tissue, fasting blood glucose, and CRP compared with placebo (appendix p 7).

There were no significant differences in demographics, bodyweight, medical history, or baseline laboratory or imaging parameters between participants who finished the study compared with those who withdrew or were lost to follow-up (appendix p 8). However, those who finished the study tended to be numerically older with more prevalent hypertension (but with lower baseline blood pressure) and hyperlipidaemia compared with those who did not. Median follow-up time among those who did not finish the study was 19·2 (IQR 14·2) weeks with no difference in follow-up time on treatment between liraglutide and placebo treated groups (20·8 *vs* 18·5 weeks, p=0·67). The most common reason for study discontinuation was related to COVID-19. Participants allocated to liraglutide but who did not finish the study had greater weight loss compared with those participants allocated to placebo but who did not finish the study (placebo-adjusted estimated treatment difference –3·64%, 95% CI –1·61 to –5·67, p=0·0030); however, only two individuals in the placebo group and none in the liraglutide group withdrew because of self-reported lack of weight loss.

Discussion

Liraglutide at a once-daily dose of 3·0 mg, when used as an adjunct to a reduced-calorie diet and increased physical activity, resulted in significantly lower visceral and ectopic fat over a median 36 weeks on treatment compared with a placebo in a population of adults with overweight or obesity at high cardiovascular disease risk. The relative effects of liraglutide on fat reduction were two-times greater in the abdominal viscera and six times greater in the liver than seen on overall bodyweight. The treatment effect seemed consistent across race–ethnicity and baseline BMI categories, and among those with or without baseline prediabetes, similar to findings in a previous study[21] (albeit with the understanding that p values for subgroups should be interpreted with caution and are not definitive). Liraglutide also reduced fasting blood glucose and CRP in the trial population without diabetes, the majority of whom had normoglycaemia at baseline. Liraglutide was well tolerated with no withdrawals for medical concerns or adverse events. Although liraglutide primarily causes a glucose dependent stimulation of insulin secretion, reduction in plasma glucagon concentration, and decreased hepatic glucose production, there were no reported episodes of hypoglycaemia in the trial. The effects of liraglutide on biomarkers in our study are consistent with its known biological effects and support its efficacy and general safety, even among adults with overweight and obesity without diabetes. These data are consistent with previous studies[35] showing that liraglutide is safe and effective when used to reduce high-risk body fat in a population with overweight or obesity and normal glucose tolerance. Despite the effect of the COVID-19 pandemic on global research efforts, the overall withdrawal rate was similar to other weight loss studies done before the COVID-19 era.[21,23]

The liraglutide 3·0 mg dose used in this study was selected on the basis of dose-dependent effects on VAT and abdominal SAT in a previous liraglutide body composition substudy.[26] Several previous studies have

investigated the effects of liraglutide at doses between 1·8 mg and 3·0 mg daily on body fat distribution in participants with type 2 diabetes or prediabetes. Most showed a significant difference between VAT and liver fat reduction with liraglutide compared with placebo,[19,36,37] although two smaller studies (n=50 and n=47) of the liraglutide 1·8 mg dose did not.[17,18] In contrast, our study included almost exclusively participants with normal fasting glucose (96%) but with elevated cardiovascular disease risk due to other components of the metabolic syndrome such as abdominal obesity, elevated blood pressure, high triglycerides, and low HDL-C. To our knowledge, this is the first prospectively designed study in a population at high risk for CVD, but without type 2 diabetes or prediabetes, to definitively show that liraglutide reduces visceral and ectopic fat measured by MRI in adults with overweight or obesity. Given the emerging recognition of visceral and ectopic fat as important cardiovascular risk factors, future pharmacological studies for weight loss should incorporate dedicated, gold-standard imaging of VAT and liver fat as high-value, modifiable targets for obesity treatment. Newer agents in development, such as once-weekly semaglutide 2·4 mg have provided some insight with preliminary, substudy data by means of less precise methods such as dual x-ray absorptiometry,[38] but further research is needed.

Liraglutide probably modifies body fat distribution through a combination of mechanisms related to reduction in plasma glucagon, delayed gastric emptying, and appetite suppression via neuronal pathways.[20] Although individual body fat depot reductions were highly correlated with overall bodyweight loss, VAT, and to a greater degree liver fat, were less well correlated with weight loss. This could suggest a partially weight-independent effect of GLP-1 receptor agonism on body fat distribution. We also observed correlations between loss of body fat with reductions in plasma glucose and CRP. Notably, VAT loss was the fat depot most highly correlated with reduction in inflammation. This finding is consistent with data showing an innate relationship between genetic determinants of excess VAT and higher concentrations of CRP.[39] As trial data have suggested,[40,41] reduction in inflammation might be a novel mechanism to reduce cardiovascular disease risk. We also saw that reduction in liver fat was the only adiposity parameter to be correlated with decrease in the triglyceride:HDL-C ratio. Liraglutide was seen to reduce postprandial atherogenic lipid remnants in a previous study as well.[42] Excess liver fat is known to be associated with overproduction of hepatic VLDL, a hepatic-secreted lipoprotein that primarily carries excess triglycerides to systemic tissues.[43] Given the evolving recognition of triglyceride-rich lipoproteins as a risk factor for atherosclerotic cardiovascular disease,[44] inhibition of this pathway might be an important future strategy to mitigate cardiovascular disease risk. Taken together, although our study was not designed to directly examine the associations between liraglutide-mediated VAT loss, changes in biomarkers, and risk for CVD events, our findings suggest that reductions in visceral fat and hepatic fat could be mechanisms underpinning the cardiovascular disease risk benefit that has been seen with liraglutide in patients with type 2 diabetes.[24]

Previous studies have proposed mechanisms for the modulation of visceral adiposity and its effect on cardiovascular risk. Early hypotheses associated excess VAT with cardiovascular risk by means of impaired liver metabolism, which in turn contributes to impaired glucose tolerance and hypertriglyceridaemia.[45] However, more recent studies suggest that an overactive hypothalamic–pituitary–adrenal axis might be the primary driver of an unfavourable cardiometabolic profile resulting in increased VAT and cardiovascular disease risk.[46] Accumulation of VAT is also believed to result in increased circulating blood volume and systemic proatherogenic inflammatory factors and adipokines, which together translate to an increased risk of developing cardiovascular disease.[9] In our study, although participants randomly assigned to placebo had, on average, modest reductions in weight and VAT, there was an increase in CRP and glucose concentrations during the study. In contrast, participants randomly assigned to liraglutide had a significant reduction in CRP and glucose concentrations. Liraglutide might therefore affect all of these aforementioned pathways mediated through its modulation of VAT given its diverse effects on glucose homeostasis, atherogenic lipids,[42] neuromediated appetite suppression, and inflammation.[47]

The strengths of our study include its prospective, randomised, placebo-controlled design, racially and ethnically diverse study population, suitable sample size, and use of gold-standard dedicated imaging for body fat assessment. Several limitations also merit comment. First, liver fat change was highly dynamic over the course of the study, with a much larger magnitude of variance compared with other fat depots. Although this is not specific to our study, liver fat measurement can be highly sensitive to the analytical approach when MRI-based assessment is used and there is currently no standardised imaging analysis procedure for the most accurate estimate of liver fat. One study showed that liver fat content can vary widely across the liver span, with some slices averaging 54% lower and others 75% higher fat content than the mean of all slices (total volume).[48] Therefore, the liver fat results observed in our study might not be directly comparable to studies in which other methodologies are used. Second, among randomly assigned participants, there was a 31% rate of attrition (ie, participants who left the trial early and did not obtain follow-up imaging assessment). However, we powered the study a priori accounting for this degree of withdrawal, as seen in previous studies of liraglutide.[26] There was also differential dropout from the trial with more attrition among the placebo group. This is a frequent issue in

weight loss trials among participants who do not lose weight.[49] However, we observed that only two participants in the placebo group reported the reason for withdrawal as lack of weight loss. Moreover, we expect this potential bias to be conservative in nature as those who dropped out from the trial owing to a lack of weight loss would not have been expected to have a meaningful decrease in VAT. Additionally, other reasons for dropout such as did not respond to calls, could not make appointments, and medical concerns (which were greater in the placebo group) don't exclude the possibility that some of these dropouts were because of less weight loss than hoped for by the participants who withdrew, particularly in the COVID-19 environment. Third, the majority of participants were female (consistent with female-predominance in other weight loss trials[21,38]), so our results might not be directly generalisable to males with regard to the magnitude of VAT reduction; nevertheless, we did not observe any significant heterogeneity of effect by sex. Fourth, although ectopic fat is seen in several other organs aside from the liver (eg, in the epicardium, myocardium, and pancreas), the imaging protocol for our study was not designed to measure these other compartments, so we are unable to comment on their changes in relation to liraglutide treatment. Fifth, our study was not designed to directly compare the statistical differences between the liraglutide effects on the various fat compartments within a single treatment group, so we are unable to definitively answer whether liraglutide preferentially reduces VAT and liver fat compared with other fat compartments. Future studies including larger sample sizes or meta-analyses of several modestly sized trials will be required to investigate this further. Sixth, although we designed the trial to include individuals with elevated cardiovascular risk through specific risk factors (eg, obesity and metabolic syndrome), our study was not designed to ascertain prospective cardiovascular events and, thus, cannot quantify exact cardiovascular risk, nor are we able to evaluate the effects of liraglutide on cardiovascular risk through its effects on visceral adipose tissue. Finally, it is possible that the participants who were enrolled might represent a subgroup with greater commitment to weight loss efforts than the general population, thereby magnifying the degree of VAT reduction by a modest degree than would otherwise be observed in a non-clinical trial setting.

In conclusion, our trial showed that liraglutide at a once-daily dose of 3·0 mg, when used as an adjunct to a reduced-calorie diet and increased physical activity, significantly lowered visceral fat and ectopic fat over a median 36 weeks on treatment compared with a placebo in a population of adults with overweight and obesity at high cardiovascular disease risk.

Contributors

IJN, SPM, CRA, and PHJ conceived and designed the study and analysed and interpreted the data. IJN, SPM, CRA, BL, RO, WF, SR, AP, and PHJ drafted, revised, and approved the final version of the report. Both IJN and PHJ accessed and verified the data. All authors had full access to all the data in the study. IJN (guarantor) takes full responsibility for the work as a whole, including study design, access to data, and the decision to submit for publication.

Declaration of interests

IJN has previously received consulting income from Merck, honoraria, consulting, speaking fees, and travel support from Boehringer-Ingelheim–Lilly Alliance, a research grant from Novo Nordisk, and has been a member of the scientific advisory board of AMRA Medical. PHJ has received consulting income from Regeneron and Bayer, reports equity in G3 Therapeutics, and grant support from AHA, NASA, Novo Nordisk, Amgen, GlaxoSmithKline, Sanofi, AstraZeneca, and Novartis. SPM has received consulting income from Novo Nordisk, Boston Scientific, Asahi Intec, and Abbott Vascular. All other authors have no potential competing interests to report. AP has served on the advisory board of Roche Diagnostics, has received non-financial support from Pfizer and Merck, has received research support from the Texas Health Resources Clinical Scholarship, the Gilead Sciences Research Scholar Program, the National Institute of Aging GEMSSTAR Grant (1R03AG067960-01), and Applied Therapeutics.

Data sharing

The protocol and datasets generated during or analyzed during the current study have been verified by IJN and are available from the corresponding author on reasonable request. No applicable resources were generated or analysed during the current study.

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