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ORIGINAL RESEARCH ARTICLE

Lifestyle-Induced Visceral Fat Loss as a Key Target for Durable Cardiometabolic Health: MRI-Assessed 5- and 10-Year Follow-Up After 2 Clinical Trials

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BACKGROUND: During the 18-month CENTRAL (Effect of Weight-Loss Diet Strategies and Exercise on Dynamics of Body Fat Depots and Metabolic Rate) and DIRECT-PLUS (Dietary Intervention Randomized Controlled Trial Polyphenols Unprocessed) randomized controlled trials, participants achieved considerable reductions in abdominal and ectopic fat. We examined the long-term postintervention cardiometabolic profile associated with these changes.

METHODS: We invited participants from CENTRAL (2012–2014) and DIRECT-PLUS (2017–2018), which evaluated dietary patterns (low-fat, healthy dietary guidelines and Mediterranean diet variants, including standard, low-carbohydrate, and polyphenol-enriched "green" Mediterranean diets) combined with structured physical activity. Participants underwent additional magnetic resonance imaging of visceral adipose tissue, deep subcutaneous adipose tissue (SAT), superficial SAT, intrahepatic fat, and intrapancreatic fat, along with clinical follow-up measurements, 5 and 10 years after completion of the trials.

RESULTS: We reached 366 out of 381 eligible participants (96%) for follow-up. Despite complete weight regain, waist circumference and abdominal fat depots, including visceral adipose tissue, deep SAT, and superficial SAT, partially preserved their intervention-induced achievements at long-term follow-up (false discovery rate ≤0.01 for all). In contrast, postintervention reductions of intrahepatic fat and intrapancreatic fat were fully and excessively gained during follow-up, respectively (false discovery rate ≤0.01 for both). Each 10% intervention-induced loss of visceral adipose tissue, superficial SAT, and intrapancreatic fat were associated with long-term postintervention improvements in Metabolic Score for Insulin Resistance, composite risk score, and Metabolic Syndrome Severity Score (meta-analysis models adjusted to weight change, Mediterranean diet adherence and physical activity scores at follow-up, and further measures; all $P<0.05$). Only 10% visceral adipose tissue loss, however, was independently associated with a 28% lower risk of incident type 2 diabetes (hazard ratio, 0.72 [95% CI, 0.54–0.94]; multivariable model) during follow-up.

CONCLUSIONS: This 5- and 10-year follow-up of 18-month clinical trials suggests that diet and physical activity lifestyle interventions may yield long-term improvements in cardiometabolic measures despite weight regain. A 10% reduction in visceral fat due to lifestyle interventions may reduce future type 2 diabetes risk by nearly 30%. Visceral fat loss rather than weight loss emerges as a key target for durable cardiometabolic health.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifiers: NCT01530724 and NCT03020186.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: diabetes mellitus type 2 ■ intra-abdominal fat ■ magnetic resonance imaging ■ randomized controlled trial

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Clinical Perspective

What Is New?

- This is the first long-term follow-up (5 and 10 years) using magnetic resonance imaging to assess abdominal fat depots and ectopic fat deposits after lifestyle intervention in 2 randomized controlled trials with high retention (96%).
- A 10% visceral fat reduction during an 18-month dietary intervention predicts durable improvements in insulin sensitivity and cardiometabolic risk score and a 28% reduction in type 2 diabetes incidence.
- These effects are independent of weight regain, highlighting depot-specific contributions beyond total weight loss.

What Are the Clinical Implications?

- Lifestyle-induced loss of visceral adipose tissue may have long-lasting positive manifestations despite regain in body weight.
- Visceral fat loss may serve as a clinically meaningful marker of both physiologic benefit and sustained lifestyle change.
- Clinical focus should extend beyond weight alone, emphasizing visceral adipose tissue–targeted strategies for long-term cardiometabolic health management.

Nonstandard Abbreviations and Acronyms

CENTRAL	Effect of Weight-Loss Diet Strategies and Exercise on Dynamics of Body Fat Depots and Metabolic Rate
DIRECT-PLUS	Dietary Intervention Randomized Controlled Trial Polyphenols Unprocessed
^{1}H-MRS	proton magnetic resonance spectroscopy
HbA1c	glycated hemoglobin
HC3	heteroscedasticity-consistent
HDL-C	high-density lipoprotein cholesterol
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
HR	hazard ratio
IHF	intrahepatic fat
IPF	intrapancreatic fat
mDixon	modified Dixon
MET	metabolic equivalent of task
MetS	metabolic syndrome
METS-IR	Metabolic Score for Insulin Resistance
MRI	magnetic resonance imaging
PA	physical activity
RCT	randomized controlled trial
SAT	subcutaneous adipose tissue
VAT	visceral adipose tissue
WC	waist circumference

Lifestyle interventions can greatly reduce abdominal adipose depots, including visceral adipose tissue (VAT), deep subcutaneous adipose tissue (SAT), and superficial SAT,[1–4] as well as ectopic fat depositions, such as intrahepatic fat (IHF)[3,5,6] and intrapancreatic fat (IPF).[6–8] Reductions in these fat depots and deposits, excluding metabolic neutral or potentially cardioprotective superficial SAT,[9,10] are consistently associated with improvements in insulin resistance, dyslipidemia, and other cardiometabolic abnormalities.[6–9,11–15] In the 18-month CENTRAL (Effect of Weight-Loss Diet Strategies and Exercise on Dynamics of Body Fat Depots and Metabolic Rate)[3] and DIRECT-PLUS (Dietary Intervention Randomized Controlled Trial Polyphenols Unprocessed)[4,5] randomized controlled trials (RCTs), VAT, deep SAT, and IHF reductions were associated with significant improvements in cardiometabolic markers independent of overall weight loss. In contrast, superficial SAT reduction appeared to be metabolically neutral or favorable,[3,4] and IPF showed only a modest reduction in the CENTRAL trial.[3]

A Mediterranean-style dietary intervention incorporating polyphenol enrichment and carbohydrate reduction and physical activity (PA) resulted in greater reductions in these fats than a low-fat diet and basic health promotion guidelines, apart from superficial SAT, and was also associated with enhanced insulin sensitivity and improved lipid profiles.[3,4,11] These findings highlight the added value of targeting specific fat depots beyond weight loss alone.[5,16] However, the durability and long-term cardiometabolic impact are unclear,[12,17] particularly given the high prevalence of postintervention weight regain.[18–20]

We therefore followed CENTRAL and DIRECT-PLUS participants for 10 and 5 years, respectively, after RCT completion. We examined whether reductions in VAT, deep SAT, superficial SAT, IPF, and IHF achieved during the intervention were sustained over time and whether depot-specific changes remained associated with key cardiometabolic biomarkers. We also assessed whether these changes were associated with incident type 2 diabetes during follow-up.

METHODS

Data Availability

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Study Population

We followed participants from two 18-month RCTs. CENTRAL (URL: https://www.clinicaltrials.gov; Unique identifier:

NCT01530724), with 278 participants, was conducted from 2012 through 2014, with a 10-year follow-up. DIRECT-PLUS (URL: https://www.clinicaltrials.gov; Unique identifier: NCT03020186), with 294 participants, was conducted from 2017 through 2018, with a 5-year follow-up.

The original inclusion criteria for both RCTs required participants to have abdominal obesity (waist circumference [WC] >102 cm for men, >88 cm for women) or dyslipidemia (serum triglycerides >150 mg/dL and high-density lipoprotein cholesterol [HDL-C] <40 mg/dL for men, <50 mg/dL for women). DIRECT-PLUS was further limited to participants >30 years of age. Both RCTs had nearly identical exclusion criteria, as fully described in Methods S1. Both RCTs and their follow-up were approved and monitored by the Medical Ethics Board and Helsinki Committee of the Soroka University Medical Center. All participants gave written consent. Participants received no financial compensation or gifts.

Both RCTs were conducted in the same research center workplace in Dimona, Israel. The retention rates at 18 months were 86.3% and 89.8%, as previously described in detail.[3,5] Pooled RCT data included 572 observations. However, 92 participants participated in both trials,[21] so we considered data from their initial trial only. Of the 480 eligible participants, 381 (79%) had available MRI data from the trials; 366 of those (96%) were followed for the current analysis.

Interventions

All diets aimed for moderate, long-term weight loss with restricted consumption of trans fats and refined carbohydrates, along with increased intake of vegetables. Lunch, commonly the primary meal in this region, was tailored to meet the specific dietary requirements of each group and was prepared by the workplace cafeteria. Investigators responsible for measuring study outcomes were blind to group assignment.

For the CENTRAL trial, participants were randomized to low-fat, Mediterranean, or low-carbohydrate diets. These groups were further divided after 6 months to those with or without added PA for the last 12 months of intervention. For the DIRECT-PLUS trial, participants were randomized to one of 3 groups—healthy dietary guidelines only, Mediterranean diet, or green Mediterranean diet—all combined with PA. The characteristics of each group are fully described elsewhere.[3,5]

Data Collection: Outcome Measures

Abdominal Adipose Depots

We quantified abdominal fat using the same protocols as in the original trials, with imaging performed on a 3T magnetic resonance imaging (MRI) scanner (Ingenia 3.0T; Philips Healthcare) using MATLAB-based semiautomatic software.[3,4] Abdominal fat was measured using a 3-dimensional modified Dixon (mDixon) imaging technique, with breath-hold to minimize motion artifacts. A continuous line was manually traced along the fascia superficialis to distinguish between deep SAT and superficial SAT.[3,4] Fat depot areas were calculated as the average of 2 axial MRI slices obtained at the L4-L5 and L5-S1 vertebral levels. Interclass and intraclass reliability, assessed in a subset of 30 scans, were both high ($r>0.96$; $P<0.001$).[3,4]

Hepatic Fat Content

IHF fraction was assessed using mDixon, single-voxel proton magnetic resonance spectroscopy (^{1}H-MRS), or mDixon quant, depending on trial protocol. In mDixon-based scans, hepatic fat fraction was computed from multiple regions of interest distributed across axial liver slices using software from Philips Medical Systems.[3] For ^{1}H-MRS, a voxel was placed in the right hepatic lobe, and spectra were analyzed to calculate fat fraction as the lipid to total signal ratio.[3,5] For participants scanned during long-term follow-up, the mDixon quant fat fraction quantification technique was applied based on the mDixon method. Across imaging modalities, hepatic fat fraction was expressed as a continuous percentage. Measurement agreement across techniques was validated in several subsets ($r\geq0.90$; $P<0.001$).

Pancreatic Fat

IPF content was assessed using mDixon fat- and water-phase images. Three regions of interest were manually placed in the pancreatic head, body, and tail to avoid vessels, ducts, and adjacent VAT. Segmental fat fractions were calculated using a standard formula and averaged to obtain whole-pancreas IPF. In CENTRAL, historical MATLAB-based quantification was recalibrated using a second-order polynomial model to align with current region of interest–based measurements ($r=0.86$; intraclass correlation coefficient=0.93). Analyses were performed using a standardized protocol validated by radiology and imaging physics experts.

All analyses were conducted by trained observers blinded to group assignment and to timepoint (ie, baseline versus end of intervention). The entire protocol is described in detail in Methods S2.

Anthropometric indices, fasting blood biomarkers, and structured dietary and lifestyle questionnaires, including smoking status and PA levels, were collected at baseline, 18 months, and long-term follow-up (5 or 10 years), as detailed in Methods S3.

Cardiometabolic indices were derived as follows:

1. HOMA-IR (Homeostatic Model Assessment of Insulin Resistance)[22]=(fasting insulin×fasting glucose)/405
2. METS-IR (Metabolic Score for Insulin Resistance)[23]=(ln[2×fasting glucose+fasting triglycerides]×body mass index)/ln(HDL-C)
3. Triglyceride–glucose index[24]=ln(fasting triglycerides×fasting glucose/2)

Metabolic syndrome (MetS) was defined using the harmonized clinical criteria,[25] incorporating medication use for glucose, lipid, or blood pressure management where applicable. MetS was analyzed both as a binary outcome (presence of ≥3 components) and as a continuous severity score (range, 0–5).

A composite cardiometabolic risk score was computed at baseline, 18 months, and 5- and 10-year follow-ups by standardizing continuous measures of metabolic syndrome–related traits. The score included 6 variables: WC, average blood pressure ([systolic+diastolic]/2), fasting glucose, insulin, triglycerides, and inverted HDL-C (so that higher values consistently indicate greater risk). Glucose, insulin, and triglycerides were log-transformed due to skewed distributions. Each variable was then standardized (z score) using the baseline sample mean and SD. Sex-specific standardization was applied to WC and HDL-C. The final composite score was calculated as the mean of the 6 standardized components, with higher values reflecting worse overall cardiometabolic status, as previously described.[26–30] For all follow-up timepoints, standardization was anchored to baseline distributions to preserve interpretability of changes over time.

Glycemic status was classified as type 2 diabetes (fasting plasma glucose ≥126 mg/dL or glycated hemoglobin [HbA1c] ≥6.5%), prediabetes (fasting glucose 100–125 mg/dL or HbA1c 5.7%–6.4%), or no diabetes. At follow-up, type 2 diabetes classification was supplemented by reported insulin use or self-reported physician diagnosis by questionnaire.

At follow-up, dietary patterns were further assessed using the validated 14-item Mediterranean Diet Adherence Screener.[31] PA was quantified as metabolic equivalent of task (MET)–hours per week (MET score), reflecting the energy cost of activities relative to rest.[32] Missing Mediterranean diet score (n=19 [5%]) or MET score (n=22 [5.8%]) follow-up data were imputed using K-Nearest Neighbors imputation,[33] incorporating age, sex, intervention group, and follow-up duration as predictors.

Incidence of Type 2 Diabetes

Incidence of type 2 diabetes was ascertained from the Ministry of Health national type 2 diabetes registry and health care provider service records (International Classification of Diseases–9 code 250).

Statistical Analyses

The primary outcome variables of this study were 5 MRI-assessed abdominal adipose tissue depots and ectopic fat deposits—VAT, deep SAT, superficial SAT, IHF, and IPF—measured at baseline, 18 months, and 5 and 10 years postintervention. Secondary outcome variables were anthropometric measures, cardiometabolic biomarkers, and incidence of type 2 diabetes.

Continuous variables are presented as mean±SD and categorical variables as frequency (%). The normality of continuous variables was evaluated using histograms and the Shapiro-Wilk test. Non-normally distributed variables were log-transformed before modeling. Changes in anthropometric measures, MRI-assessed outcomes, and biochemical variables were calculated as a relative percent change from baseline to 18 months and from 18 months to follow-up, as follows: $([\text{Time}_{\text{later}}-\text{Time}_{\text{earlier}}]/\text{Time}_{\text{earlier}})\times 100$. For variables with low or near-zero baseline values, including IHF, high-sensitivity C-reactive protein, MetS score, and the composite cardiometabolic risk score, absolute differences ($\text{Time}_{\text{later}}-\text{Time}_{\text{earlier}}$) were used instead, to avoid inflation or instability in percentage-based estimates.

Changes over time were assessed using ANCOVA models with the later timepoint as the outcome and the earlier timepoint entered as a mean-centered covariate (additionally adjusted for mean-centered age and sex). Adjusted mean changes were calculated by subtracting the sample mean of the earlier timepoint from the model-estimated adjusted mean at the later timepoint, and 95% CIs were derived from model-based variance estimates (linear contrasts). Within-person differences in PA levels across the timepoints were assessed using the Friedman nonparametric repeated-measures test. Differences between VAT maintainers (follow-up VAT ≤ baseline VAT) and VAT regainers were evaluated using Wilcoxon rank-sum tests for continuous measures, and χ^2 tests for categorical variables. Significance was set a priori at $P<0.05$, and false discovery rate correction was applied for multiple comparisons.[34]

For each fat depot/deposit, meta-analysis models were computed, using a 2-stage approach, combining trial-specific estimates from the CENTRAL and DIRECT-PLUS trials, to determine whether fat depot loss during the intervention was sustained at follow-up. Linear regression models were fitted separately within each trial, adjusting for age, sex, baseline depot/deposit, weight change during the intervention, weight regain at follow-up, intervention diet group, Mediterranean diet and PA scores at follow-up, glucagon-like peptide-1 analogue use at follow-up, and dual participation in both trials. Trial-specific regression estimates and standard errors were then pooled using fixed-effect meta-analysis. Additional linear models evaluated associations between WC and depot-specific loss and follow-up metabolic biomarkers (including fasting glucose, fasting insulin, HbA1c, triglycerides, HDL-C, high-sensitivity C-reactive protein, triglycerides/HDL-C, HOMA-IR, METS-IR, triglyceride–glucose index, MetS score, and composite risk score). These models included further adjustments for relevant biomarker changes during the intervention and medication use (eg, glucose- or lipid-lowering therapies). Trial-specific effect estimates and standard errors were then combined using fixed-effect meta-analysis to estimate the overall association across studies. Model diagnostics included assessment of collinearity (variance inflation factors), heteroscedasticity (Breusch-Pagan test), and linearity of continuous predictors (nested-model F tests comparing linear terms with natural spline specifications). Where indicated, sensitivity analyses used HC3 (heteroscedasticity-consistent) standard errors and spline-based functional-form specifications. For spline sensitivity analyses, effects were summarized as Δ(P90–P10): the adjusted difference in predicted outcome comparing the 90th versus 10th percentile of the predictor distribution.

Survival analyses were conducted using the Cox proportional hazards model to estimate hazard ratios (HRs) for incident type 2 diabetes. For these models only, participants were excluded if they had type 2 diabetes by the end of the intervention, defined as reported use of glycemic control medications, fasting glucose ≥126 mg/dL, HbA1c ≥6.5%, or a self-reported or coded diagnosis of type 2 diabetes. Time to event was defined as the interval between the end of the intervention and the first documented diagnosis of type 2 diabetes or censoring (December 2021 for national registry data and December 2023 for health care provider records). Changes in abdominal adipose tissue and IPF were modeled per 10% relative reduction (change/−10), whereas WC and IHF changes were modeled per 1% relative and 1% absolute reduction (change/−1), respectively, reflecting clinically relevant magnitudes. Models were adjusted for baseline HbA1c and WC or fat depot/deposit, weight loss, absolute reduction in HbA1c during the intervention, trial type, diet group, age, sex, dual participation in both trials, and weight and fat loss interaction. The proportional hazards assumption was tested using Schoenfeld residuals and was not violated. As a sensitivity analysis, VAT change was also modeled using a natural cubic spline ($df=3$) in the fully adjusted Cox model, with HRs plotted relative to 0% VAT change (HR=1).

Given that this is a predominantly male cohort, secondary analyses were also conducted for men only. All statistical analyses were conducted using R version 4.4.1. Key packages included metafor[35] and survival.[36]

RESULTS

Participant Retention and Follow-Up Ascertainment

As seen in Figure 1A, of the 381 eligible MRI trial completers from the CENTRAL and DIRECT-PLUS studies,

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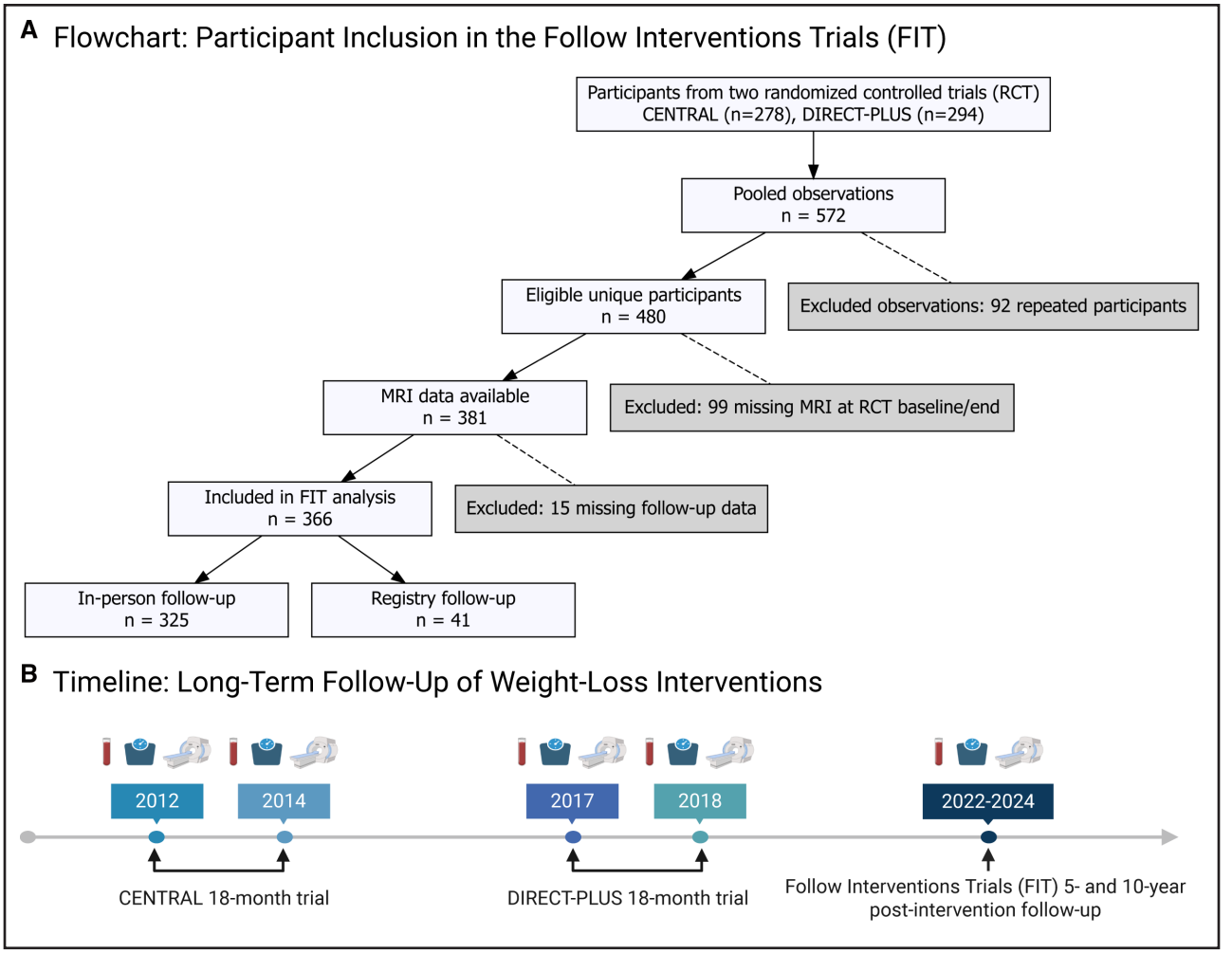

Figure 1. Participant inclusion flowchart and timeline from CENTRAL and DIRECT-PLUS 18-month trials to the 5- and 10-year follow-up.

A, Participant inclusion flowchart. **B**, Timeline from CENTRAL and DIRECT-PLUS 18-month trials to the 5- and 10-year follow-up (n=381). CENTRAL indicates Effect of Weight-Loss Diet Strategies and Exercise on Dynamics of Body Fat Depots and Metabolic Rate; DIRECT-PLUS, Dietary Intervention Randomized Controlled Trial Polyphenols Unprocessed; and MRI, magnetic resonance imaging. Partially created in BioRender. Klein, H. (2026) https://biorender.com/nzivoy8

366 participants (96%) were successfully followed. This included 325 (88.8%) who returned for in-person follow-up assessments and 41 who were followed via registry data. The registry sources, which covered the whole cohort, provided comprehensive and validated ascertainment of long-term diabetes outcomes.

Baseline Characteristics at the Beginning of the Interventions: CENTRAL and DIRECT-PLUS

As reported in the Table, 381 participants underwent 2 MRI scans (at the start and end of the 18-month intervention period). At intervention baseline, participants had a mean age of 49.5 years, body mass index of 30.5 kg/m^2, WC of 107.6 cm, VAT area of 148.6 cm^2, deep SAT area of 242.1 cm^2, and superficial SAT area of 132.2 cm^2. The cohort was 91.3% male; at baseline, 64.1% met MetS criteria (score=2.9), and 10.2% had type 2 diabetes.

Follow-Up Characteristics at 5 and 10 Years

At follow-up, participants who attended in-person assessments (n=325) underwent repeat anthropometric and imaging evaluations (Table). Their average age was 57.3 years, and they had an average body mass index of 30.6 kg/m^2, WC of 103.5 cm, VAT area of 124.8 cm^2, deep SAT area of 211.5 cm^2, and superficial SAT area of 117.6 cm^2. At follow-up, 59.9% met the criteria for MetS (score=2.9), and 21.8% had diabetes.

Trajectories of Anthropometric Measurements, Abdominal Adipose Depots, and Ectopic Fat During the CENTRAL and DIRECT-PLUS 18-Month Trials and 5- and 10-Year Follow-Up

As shown in the Table and Figure 2, ANCOVA models adjusted for age and sex demonstrated reductions in

Table. Baseline, End of Intervention (18 Months), and Follow-Up (5 and 10 Years) Characteristics of the CENTRAL and DIRECT-PLUS 18-Month Trials Participants (n=381)

Characteristics	Baseline (n=381)*	End of RCT (18 mo; n=381)*	Follow-up (5 and 10 y after RCT completion; n=325)*	Adjusted change during RCT†	FDR-adjusted *P* value during RCT‡	Adjusted change during follow-up†	FDR-adjusted *P* value during follow-up‡	Adjusted change from baseline to follow-up†	FDR-adjusted *P* value for total change‡
Age, y	49.5±10.4	51.0±10.4	57.3±10.4	–	–	–	–	–	–
Male sex, %	91.3	91.3	92.0	–	–	–	–	–	–
VAT area, cm^2	148.6±60.9	109.0±49.0	124.8±55.7	−39.53 (−43.05 to −36.01)	<0.001	17.88 (13.10 to 22.66)	<0.001	−22.05 (−27.17 to −16.92)	<0.001
Available observations, n	379	379	304	377		303		302	
Deep SAT area, cm^2	242.1±84.2	185.1±70.4	211.5±86.1	−60.65 (−65.10 to −56.21)	<0.001	28.47 (23.22 to 33.73)	0.001	−32.44 (−38.44 to −26.44)	<0.001
Available observations, n	378	381	302	378		302		299	
Superficial SAT area, cm^2	132.2±57.0	106.1±45.2	117.6±46.9	−28.78 (−31.08 to −26.48)	<0.001	12.07 (9.20 to 14.94)	0.001	−15.81 (−19.00 to −12.61)	<0.001
Available observations, n	374	378	301	373		299		296	
VAT proportion, %	28.9±9.0	27.5±8.8	27.8±9.3	−1.33 (−1.70 to −0.96)	<0.001	0.50 (−0.04 to 1.04)	0.080	−0.97 (−1.55 to −0.39)	0.002
Deep SAT proportion, %	46.1±6.1	45.9±6.1	46.1±6.9	−0.13 (−0.45 to 0.19)	0.449	−0.06 (−0.54 to 0.42)	0.810	−0.15 (−0.64 to 0.34)	0.617
Superficial SAT proportion, %	25.1±6.7	26.6±6.8	26.1±6.4	1.44 (1.11 to 1.77)	<0.001	−0.65 (−1.08 to −0.22)	0.004	1.08 (0.69 to 1.47)	<0.001
Intrahepatic fat, %	10.2±9.7	6.4±7.3	9.6±7.4	−3.99 (−4.56 to −3.41)	<0.001	3.35 (2.58 to 4.11)	<0.001	−0.71 (−1.47 to 0.06)	0.100
Available observations, n	369	372	304	360		296		296	
Pancreatic fat, %	14.6±6.7	14.1±7.0	15.6±8.1	−0.42 (−0.87 to 0.02)	0.071	1.76 (1.19 to 2.34)	<0.001	1.14 (0.46 to 1.82)	0.002
Available observations, n	380	376	301	376		296		300	
Weight, Kg	91.7±13.6	88.5±13.8	91.4±14.1	−3.41 (−4.01 to −2.80)	<0.001	3.40 (2.62 to 4.18)	<0.001	−0.27 (−1.07 to 0.54)	0.609
BMI, Kg/m^2	30.5±3.7	29.5±4.0	30.6±4.1	−1.14 (−1.34 to −0.94)	<0.001	1.16 (0.89 to 1.42)	<0.001	−0.03 (−0.31 to 0.25)	0.848
Waist circumference, cm	107.6±9.4	102.4±10.0	103.5±10.9	−5.23 (−5.87 to −4.59)	<0.001	1.27 (0.40 to 2.14)	0.005	−4.13 (−5.04 to −3.22)	<0.001
Systolic BP, mm Hg	127.0±15.0	127.0±15.8	131.4±16.1	−0.02 (−1.24 to 1.21)	0.980	4.64 (2.94 to 6.34)	<0.001	4.66 (2.96 to 6.36)	<0.001
Diastolic BP, mm Hg	80.3±10.5	79.7±9.2	80.0±11.2	−0.47 (−1.28 to 0.35)	0.282	0.66 (−0.48 to 1.80)	0.280	0.10 (−1.06 to 1.26)	0.866
Fasting glucose, mg/dL	106.5±22.5	105.3±19.7	100.1±20.9	−0.99 (−2.57 to 0.59)	0.246	−4.65 (−6.81 to −2.48)	<0.001	−5.83 (−7.77 to −3.90)	<0.001
Fasting insulin, µU/mL	16.3±9.7	13.3±7.5	16.8±9.6	−3.06 (−3.63 to −2.49)	<0.001	3.59 (2.71 to 4.48)	<0.001	0.41 (−0.54 to 1.35)	0.490
HOMA-IR	4.3±3.0	3.5±2.3	4.2±2.7	−0.84 (−1.02 to −0.66)	<0.001	0.73 (0.46 to 1.01)	<0.001	−0.14 (−0.42 to 0.14)	0.416
HbA1c, %	5.5±0.6	5.5±0.6	5.7±0.7	−0.04 (−0.08 to −0.01)	0.032	0.21 (0.13 to 0.28)	<0.001	0.15 (0.09 to 0.21)	<0.001
Triglycerides, mg/dL	159.1±81.6	142.7±82.7	151.2±80.7	−15.94 (−23.02 to −8.85)	<0.001	11.09 (3.55 to 18.62)	0.005	−8.15 (−15.66 to −0.64)	0.055
HDL-C, mg/dL	44.2±11.5	47.6±12.8	45.0±11.5	3.62 (2.79 to 4.45)	<0.001	−2.96 (−3.78 to −2.15)	<0.001	0.88 (0.07 to 1.69)	0.055

(*Continued*)

Table. Continued

Characteristics	Baseline (n=381)*	End of RCT (18 mo; n=381)*	Follow-up (5 and 10 y after RCT completion; n=325)*	Adjusted change during RCT†	FDR-adjusted *P* value during RCT‡	Adjusted change during follow-up†	FDR-adjusted *P* value during follow-up‡	Adjusted change from baseline to follow-up†	FDR-adjusted *P* value for total change‡
Triglycerides/HDL-C	4.1±3.1	3.5±3.0	3.8±3.0	−0.62 (−0.86 to −0.38)	<0.001	0.47 (0.18 to 0.75)	0.002	−0.26 (−0.53 to 0.00)	0.078
Triglyceride–glucose index	8.9±0.5	8.8±0.5	8.8±0.5	−0.12 (−0.16 to −0.08)	<0.001	0.02 (−0.03 to 0.06)	0.463	−0.12 (−0.16 to −0.07)	<0.001
METS-IR	48.2±7.8	45.4±8.5	47.6±8.2	−3.06 (−3.60 to −2.52)	<0.001	2.32 (1.70 to 2.94)	<0.001	−0.84 (−1.49 to −0.19)	0.022
hsCRP, mg/L	3.6±4.8	2.9±2.4	3.4±4.1	−0.74 (−0.99 to −0.50)	<0.001	0.50 (0.05 to 0.94)	0.033	−0.29 (−0.74 to 0.16)	0.278
Composite risk score, *Z*	0.0±0.5	−0.3±0.6	−0.1±0.6	−0.28 (−0.33 to −0.24)	<0.001	0.15 (0.10 to 0.20)	<0.001	−0.15 (−0.20 to −0.09)	<0.001
MetS score	2.9±1.2	2.5±1.2	2.9±1.3	−0.39 (−0.51 to −0.28)	<0.001	0.37 (0.24 to 0.50)	<0.001	−0.02 (−0.15 to 0.10)	0.762
MetS, %	64.1	50.1	59.9	–	–	–	–	–	–
Prediabetes, %	48.3	51.4	34.2	–	–	–	–	–	–
Diabetes, %	10.2	7.9	21.8	–	–	–	–	–	–
Lipid-lowering drugs, %	11.3	11	26.5	–	–	–	–	–	–
Glycemic control drugs, %	5.2	6	23.1	–	–	–	–	–	–
GLP-1 agonists, n (%)	1 (0.003)	0	35 (10.8)	–	–	–	–	–	–
Physical activity, MET-h/wk	34.9±31.4	47.3±41.8	28.8±33.1	13.21 (8.92 to 17.51)	<0.001	−18.25 (−22.31 to −14.19)	<0.001	−5.54 (−9.65 to −1.43)	0.017

BMI indicates body mass index; BP, blood pressure; CENTRAL, Effect of Weight-Loss Diet Strategies and Exercise on Dynamics of Body Fat Depots and Metabolic Rate; DIRECT-PLUS, Dietary Intervention Randomized Controlled Trial Polyphenols Unprocessed; FDR, false discovery rate; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; hsCRP, high-sensitivity C-reactive protein; MET, metabolic equivalent of task; MetS, metabolic syndrome; METS-IR, Metabolic Score for Insulin Resistance; RCT, randomized controlled trial; SAT, subcutaneous adipose tissue; and VAT, visceral adipose tissue.

*Values are mean±SD for continuous variables or % for categorical variables.

†Reported changes are age- and sex-adjusted model-based mean differences (95% CIs) derived from ANCOVA models.

‡*P* values were derived from age- and sex-adjusted ANCOVA models (with the later timepoint modeled as the outcome and the earlier timepoint as a covariate); false discovery rate (FDR) was used to adjust for multiple comparisons.

anthropometric measures and MRI-assessed outcomes during the 18-month interventions. Over the 5- and 10-year follow-up, WC and all abdominal adipose tissue compartments were partially regained, yet remained significantly reduced compared with baseline. Body weight and IHF returned to baseline, and IPF increased beyond baseline. Participants who maintained VAT loss and those who regained it had similar baseline profiles; however, at follow-up, VAT maintainers had lower weight, WC, and VAT, and more favorable cardiometabolic markers (Table S1). Participants' PA levels differed over time in most intervention groups (Table S2).

Loss of Abdominal and Ectopic Fat During the Intervention and Their Values at 5- and 10-Year Postintervention Follow-Up

Meta-analysis results showed that each 10% reduction in VAT, deep SAT, superficial SAT, and IPF during the intervention predicted lower values of their respective depots/deposit at 5- and 10-year follow-up (Table S3; all *P*<0.001). In contrast, 1% IHF reduction did not predict altered IHF values at follow-up. In the DIRECT-PLUS trial-specific subanalysis, 1% IHF reduction predicted lower IHF at follow-up (−0.02 [−0.04 to −0.002]; *P*=0.04). Associations persisted after adjusting for baseline fat depot/deposit, weight changes during and after the intervention, sex, age, intervention diet group, Mediterranean diet and PA scores at follow-up, glucagon-like peptide-1 analogue use, and dual trial participation.

Among lifestyle covariates, a higher Mediterranean diet score was independently associated with lower IHF at the 5- and 10-year follow-up (−0.03 [−0.06 to −0.001]; *P*=0.04). In addition, higher PA at follow-up, measured as MET-h/wk, was independently associated with lower VAT at follow-up (−0.001 [−0.002 to −0.0002]; *P*=0.01). In a subanalysis of the CENTRAL trial, assignment to the PA intervention groups was independently predictive of lower superficial SAT (−0.06 [−0.12 to −0.0004]), deep SAT (−0.07 [−0.13 to −0.002]) and VAT (−0.12 [−0.22

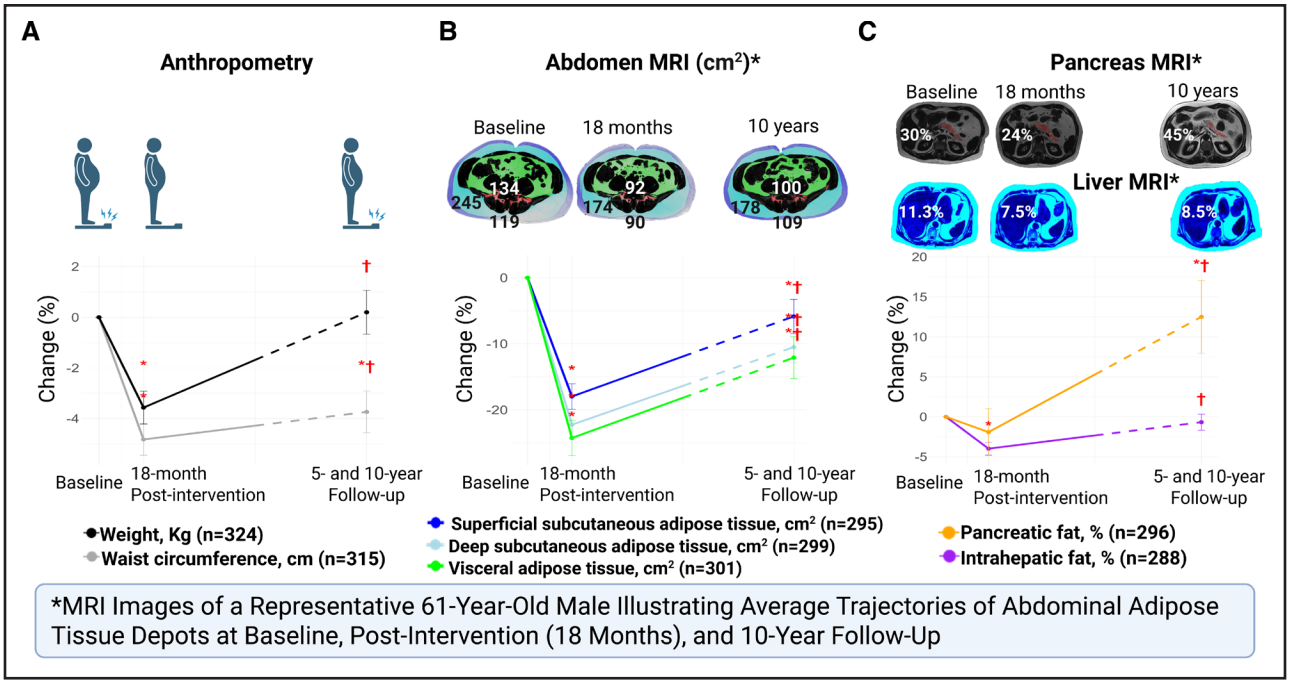

Figure 2. Trajectories of anthropometric measurements, abdominal adipose depots, and ectopic fat during the CENTRAL and DIRECT-PLUS 18-month trials and 5- and 10-year follow-up (n=325).

Magnetic resonance imaging (MRI) results illustrate fat depots/deposits at 3 timepoints—baseline, 18 months postintervention, and at 10-year follow-up—from a representative 61-year-old male participant. **A**, Weight (black) and waist circumference (gray). **B**, Visceral adipose tissue (green), deep subcutaneous adipose tissue (light blue), and superficial subcutaneous adipose tissue (dark blue). **C**, Intrahepatic fat (purple) and pancreatic fat (orange). Mean trajectories are shown at baseline, postintervention (18 months), and at 5- and 10-year follow-up. Values represent group means with 95% CIs. Red asterisks indicate statistically significant changes from baseline to postintervention or follow-up. Red daggers indicate statistically significant changes from postintervention to follow-up, based on age- and sex-adjusted ANCOVA timepoint comparisons (false discovery rate–adjusted for multiple comparisons). CENTRAL indicates Effect of Weight-Loss Diet Strategies and Exercise on Dynamics of Body Fat Depots and Metabolic Rate; and DIRECT-PLUS, Dietary Intervention Randomized Controlled Trial Polyphenols Unprocessed. Partially created in BioRender. Klein, H. (2026) https://biorender.com/5hhg71a

to −0.03]) at follow-up (all $P<0.05$). In the DIRECT-PLUS trial, both higher follow-up Mediterranean diet score and the use of glucagon-like peptide-1 receptor agonists were independently associated with lower superficial SAT at follow-up (−0.01 [−0.02 to −0.001] and −0.11 [−0.21 to −0.01], respectively; both $P<0.05$). Secondary analyses limited to men yielded consistent results (Table S4).

Loss of Abdominal and Ectopic Fat During the Intervention and Cardiometabolic Risk Markers at 5- and 10-Year Follow-Up

We quantified the association between MRI-assessed fat change during the intervention and cardiometabolic biomarker values measured at 5- and 10-year follow-up using fixed-effect meta-analysis of trial-specific models (Figure 3). Each 10% VAT reduction during the intervention was associated with sustained improvements in several cardiometabolic indices at long-term follow-up, including METS-IR, MetS score, and composite risk score (all $P<0.05$; Figure 3A). A 10% reduction in superficial SAT and IPF predicted similar long-term improvements; 1% WC loss was associated with lower METS-IR and composite risk score (both $P<0.05$); losses of deep SAT and IHF were associated with lower METS-IR score ($P<0.05$; Figure 3, B–E). In trial-specific subanalyses, 10% VAT loss in the CENTRAL trial was additionally predictive of increased HDL-C and decreased triglycerides ($P<0.05$ for both). These associations remained robust after multivariable adjustment, which included the same covariates used in the abdominal and ectopic fat predictive models, as well as biomarker change during the intervention and lipid- and glucose-lowering medication use at follow-up. Among covariates, higher follow-up MET-h/wk was independently associated with lower insulin levels, HOMA-IR, and composite risk score (all $P<0.05$). Secondary analyses limited to men resulted in consistent findings (Figure S1). Model diagnostics and sensitivity analyses addressing heteroscedasticity (HC3 standard errors) and functional-form assumptions (spline-based linearity checks) are provided in Tables S5 and S6, respectively; these sensitivity analyses yielded directionally consistent results.

Abdominal Fat Loss and Incident Diabetes During 5- and 10-Year Follow-Up

VAT loss during the intervention was associated with lower diabetes incidence over 5- and 10-year follow-up

ORIGINAL RESEARCH ARTICLE

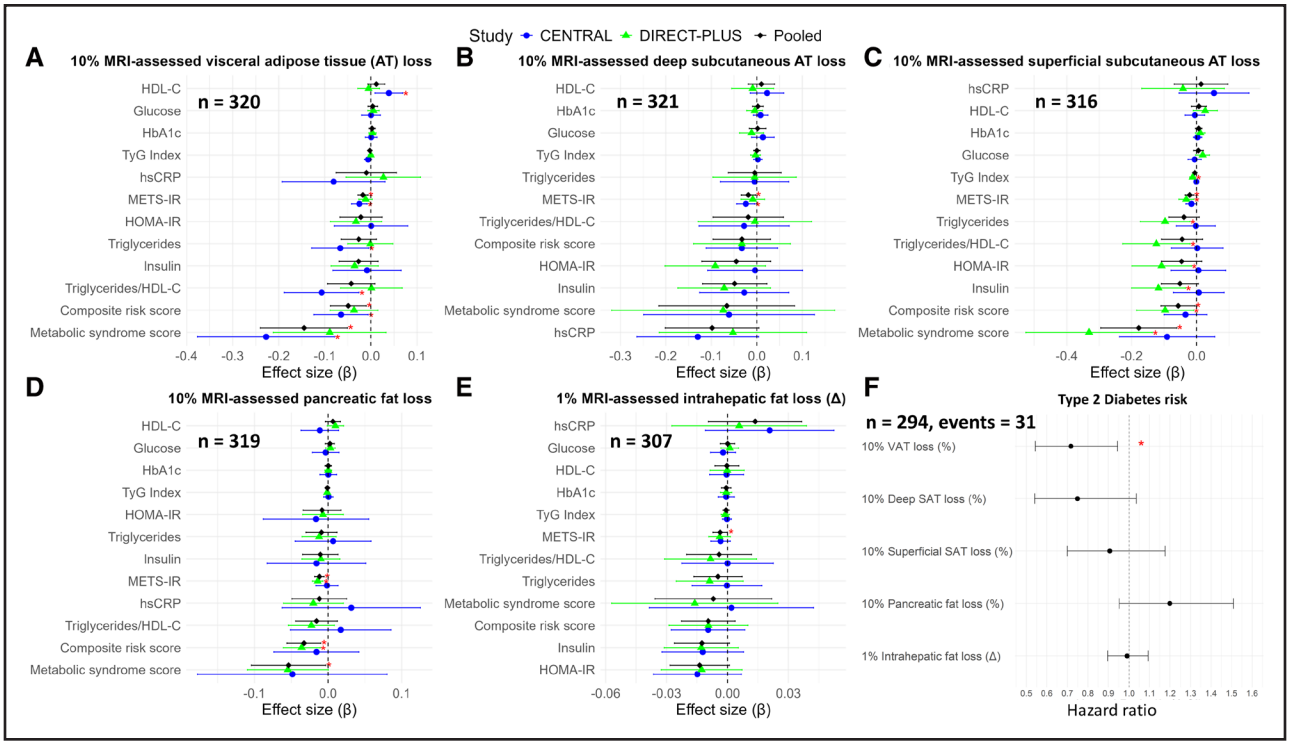

Figure 3. Abdominal and ectopic fat loss during the 18-month CENTRAL and DIRECT-PLUS interventions and cardiometabolic state and diabetes risk at 5- and 10-year follow-up.

Forest plots display associations between a 10% reduction in (**A**) visceral adipose tissue (VAT), (**B**) deep subcutaneous adipose tissue (SAT), (**C**) superficial SAT, and (**D**) pancreatic fat and a 1% absolute reduction in (**E**) intrahepatic fat during the 18-month intervention and multiple cardiometabolic markers measured at 5- and 10-year follow-up (n=324). Fixed-effect meta-analyses combined trial-specific linear regression estimates for the associations between fat depots/deposits reductions and cardiometabolic markers at 5- and 10-year follow-up. The forest plots display standardized β coefficients and 95% CIs for each predicted biomarker at follow-up, with a dashed vertical line at β=0 indicating the null hypothesis. Red asterisks denote statistically significant associations (P<0.05). Models were adjusted for baseline fat, change during intervention in weight and the respective biomarker, weight regain during follow-up, intervention diet group, Mediterranean diet and physical activity scores at follow-up, age, sex, glucose- and lipid-lowering medication use at follow-up, and dual trial participation. **F**, Forest plot summarizing Cox proportional hazards models for incident type 2 diabetes during follow-up (n=294; 31 events), showing hazard ratios (HRs) and 95% CIs per 10% reduction in each adipose tissue depot (VAT, deep SAT, superficial SAT, pancreatic fat) or per 1% absolute intrahepatic fat reduction achieved during intervention. Models adjusted for baseline fat depot and glycated hemoglobin (HbA1c), weight and HbA1c reductions during the intervention, trial type (CENTRAL [Effect of Weight-Loss Diet Strategies and Exercise on Dynamics of Body Fat Depots and Metabolic Rate] or DIRECT-PLUS [Dietary Intervention Randomized Controlled Trial Polyphenols Unprocessed]), diet group, age, sex, dual trial participation, and weight and fat loss interaction. Dashed vertical line indicates the null (HR=1). Red asterisks denote statistically significant associations (P<0.05). HDL-C indicates high-density lipoprotein cholesterol; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; hsCRP, high-sensitivity C-reactive protein; METS-IR, Metabolic Score for Insulin Resistance; and TyG, triglyceride–glucose index.

(Figure 3F). In a fully adjusted Cox proportional hazards model (n=294; 31 events), each 10% VAT reduction corresponded to a 28% decrease in diabetes risk (HR, 0.72 [CI, 0.54 to 0.94]; P=0.02), adjusting for baseline VAT and HbA1c, weight and HbA1c reductions during intervention, age, sex, trial type, diet adherence group, dual trial participation, and weight and VAT loss interaction. Among covariates, HbA1c reduction during the intervention was also independently associated with decreased diabetes risk (HR, 0.15 [0.03 to 0.73]; P=0.02 for 1% absolute reduction); weight loss showed a nonsignificant association (HR, 1.06 [0.93 to 1.21]; P=0.41). WC, deep SAT, superficial SAT, IPF, and IHF reductions appeared unrelated to diabetes risk. In spline sensitivity analyses, VAT loss was inversely associated with incident type 2 diabetes across the range most densely represented in the data (0%–20% loss), with HRs of 0.83 (0.72 to 0.96) at 5% loss, 0.70 (0.53 to 0.94) at 10% loss, 0.60 (0.38 to 0.94) at 15% loss, and 0.52 (0.27 to 0.99) at 20% loss (Figure S2). Results were directionally consistent in subanalyses conducted restricted to men, where 10% reduction in deep SAT was also associated with lower diabetes incidence (HR, 0.72 [0.51 to 0.99]; P=0.05; Figure S1).

DISCUSSION

This long-term postintervention follow-up study demonstrated that visceral fat loss achieved during lifestyle intervention is associated with durable metabolic benefits up to a decade later. Despite complete weight regain, WC and abdominal fat depots, including VAT, deep SAT,

and superficial SAT, partially preserved their intervention-induced achievements at long-term follow-up. In contrast, intervention-induced reductions of IHF and IPF were fully and excessively gained during follow-up, respectively. Each 10% VAT loss was associated with improvements in cardiometabolic risk indices, and corresponded to a 28% lower risk of developing type 2 diabetes during the follow-up period. These findings highlight VAT loss during intervention as a clinically meaningful target for long-term cardiometabolic health and diabetes risk reduction. To our knowledge, this is the first large-scale long-term reassessment of reductions in MRI-derived abdominal fat compartments and ectopic fat depositions after a structured, extended lifestyle intervention.

This study has several strengths and limitations. First, because the cohort was predominantly male (>90%), our findings primarily reflect outcomes in men, limiting their generalizability to women. To support internal validity, all main analyses were also replicated in a male-only subsample, yielding consistent results. Second, perivascular adipose tissue and epicardial adipose tissue, which are highly relevant to cardiovascular pathophysiology, were not assessed in the imaging protocol and therefore could not be examined in the current analyses. Third, participants were followed at 2 different posttrial timepoints (5 or 10 years) based on their original trial. To address this, we conducted meta-analyses or incorporated time-to-event data, depending on the analysis. The combination of 18-month randomized interventions with 5- and 10-years of posttrial follow-up offers a rare opportunity to examine the durability and long-term physiologic effects of abdominal fat loss. Use of standardized imaging protocols, high follow-up retention, and comprehensive cardiometabolic phenotyping further strengthens the robustness and clinical relevance of the findings.

This extended follow-up revealed that abdominal fat reductions achieved during the intervention are not transient. Despite weight regain, participants who reduced VAT, deep SAT, or superficial SAT during the intervention maintained significantly lower areas of those depots 5 and 10 years later. These associations persisted after multivariable adjustment, independent of baseline adiposity, weight change, intervention group, and lifestyle factors assessed at follow-up, including diet, PA levels, and medication use. Both assignment to PA intervention groups and higher PA levels at follow-up were independently associated with lower VAT. These findings are consistent with the well-established, independent effects of PA on visceral fat reduction.[37] The durability of these reductions is notable, particularly given the expected age-related accumulation of VAT.[38,39]

Although body weight returned to preintervention levels by the 5- and 10-year follow-up, the partial regain of WC reflected the sustained reduction in abdominal fat depots. These results reinforce existing evidence that WC is a more informative marker than body weight for monitoring long-term changes in fat distribution, particularly in clinical settings where imaging is unavailable.[40] Reductions in ectopic fat depots (IHF and IPF) achieved during the 18-month intervention, similar to body weight, were largely regained during follow-up. Still, a greater reduction in IPF during the intervention predicted lower IPF levels at follow-up. For IHF, a similar association was observed only at the 5-year follow-up in DIRECT-PLUS, but not at the 10-year follow-up in CENTRAL, suggesting that IHF loss may be less durable over longer periods.

Among the specific depots examined, sustained reductions in VAT after the intervention emerged as a robust and independent predictor of long-term metabolic health. Each 10% reduction in VAT was associated with favorable long-term cardiometabolic risk indices, even after accounting for weight loss and regain, Mediterranean diet adherence, and PA level assessed at the follow-up, underscoring the unique contribution of depot-specific fat loss beyond change in total body weight and lifestyle. Our findings support previous evidence positioning VAT as a key mediator of insulin resistance and cardiometabolic risk.[12–15]

Similar to intervention-induced VAT loss, IPF and superficial SAT reductions also predicted improved cardiometabolic indices over time. These results align with evidence showing that IPF is associated with MetS, impaired glucose metabolism, and type 2 diabetes.[7,8] However, whereas previous analyses from the CENTRAL and DIRECT-PLUS trials showed no consistent adverse associations between superficial SAT and metabolic outcomes during the 18-month interventions,[3,4,11] the current findings suggest that a change in superficial SAT is linked to long-term cardiometabolic state. Deep SAT and IHF losses during the RCTs were associated with lower METS-IR scores. The current findings align with earlier evidence from these trials, showing that deep SAT and IHF losses were linked to improved insulin resistance during the intervention period.[3–5,11]

In addition to improvements in biomarker profiles, VAT reduction was independently associated with a lower long-term risk of developing type 2 diabetes. Each 10% VAT reduction during the intervention was associated with a 28% lower risk of incident diabetes over the follow-up period. This association was independent of baseline HbA1c and its change during the intervention. Previous studies have established that overall weight loss reduces diabetes risk[41–44]; our results highlight the added value of targeting visceral fat specifically, offering protection independent of total body weight loss. Whereas WC and SAT depots showed similar partial regain patterns, and were associated with improved cardiometabolic indices at follow-up, only VAT reduction significantly predicted lower diabetes risk.

These findings suggest that lifestyle-induced moderate weight loss may yield long-lasting metabolic benefits, particularly through sustained visceral fat reduction. Evidence from previous trials has shown that even a 5%

reduction in body weight can lead to significant improvements in insulin sensitivity, glycemic control, and cardiometabolic risk factors.[45–48] Our results extend this concept by showing that a targeted 10% reduction in VAT confers substantial and durable protection against type 2 diabetes, underscoring the value of fat distribution, rather than weight alone, in predicting long-term health outcomes.

This extended follow-up of the CENTRAL and DIRECT-PLUS trials demonstrates that visceral fat reduction during lifestyle intervention is associated with sustained improvements in metabolic health, even in the context of long-term weight regain. These findings emphasize the importance of shifting clinical focus from general weight loss to targeted fat reduction, highlighting VAT loss as a key therapeutic target for both metabolic disease prevention and management.

ARTICLE INFORMATION

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Disclosures

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Supplemental Material

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Tables S1–S6
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