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How effective is rejoining a long-term weight loss program? The 5- and 10-year MRI-assessed Follow Interventions Trial (FIT) project

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Abstract

Background It remains unclear whether reengaging in lifestyle weight loss interventions is effective for the long-term.

Methods We conducted the CENTRAL (trial 1, T1) lifestyle weight-loss trial in 2012–2014, and the DIRECT-PLUS (trial 2, T2) weight-loss trial in 2017–2018. All participants were invited for follow-up in 2022–2024 to assess weight, metabolic biomarkers, and fat depots via magnetic-resonance-imaging (MRI) five years after the second trial.

Results The analysis included 572 trial observations contributed by 480 participants; of these, 388 participated in one of the two trials and 92 participated in both (T1 + T2 rejoiners). At follow-up, 384/480 (80%) were re-evaluated, including 76/92 (83%) rejoiners. In T1, participants who participated once and those who later rejoined T2 exhibited similar responses to their first intervention, including comparable weight-loss (-3.3% vs. -3.4%; FDR = 0.93). However, T1 + T2 rejoiners began their second intervention with a similar baseline BMI to their first (31.8 kg/m^2 vs. 31.3 kg/m^2; FDR = 0.12). Nevertheless, they presented a more favourable abdominal fat and metabolic profiles at T2 baseline than at their initial T1 baseline (visceral adipose tissue (VAT): 135.5 cm^2 vs. 160.0 cm^2; homeostatic model assessment of insulin resistance (HOMA-IR): 3.8 vs. 4.5; high density lipoprotein cholesterol (HDL-C)/Triglycerides: 3.6 vs. 4.2; all FDR < 0.05). In response to T2, rejoiners exhibited attenuated improvements compared to those achieved during their previous T1 intervention (weight: -1.5% vs. -3.5%; VAT: -7.2% vs. -33.3%; deep subcutaneous adipose tissue (SAT): -4.0% vs. -31.9%; superficial SAT: -3.3% vs. -25.4%; all FDR < 0.05), and compared to first-time T2 participants (weight: -3.5%; FDR < 0.05, VAT: -11.6%; FDR = 0.20, deep SAT: -9.9%; FDR < 0.05, superficial SAT: -9.3%; FDR = 0.05). Yet, 5 years after completing T2, T1 + T2 rejoiners exhibited significantly less weight regain compared with first-time T2 participants (+ 0.2% vs. + 2.9%; FDR < 0.05), deep-SAT regain (+ 2.4% vs. + 13.3%; FDR < 0.05), and superficial-SAT regain (+ 12.8% vs. + 24.3%; FDR < 0.05), though similar VAT regain. Overall, although T1 + T2 rejoiners had higher baseline obesity parameters than first-time participants, they presented comparable values by the 5- and 10-year follow-up.

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Conclusions Despite an attenuated weight-loss response, repeated engagement in a structured lifestyle intervention yields meaningful long-term impacts with sustainable metabolic benefits.

Trial registration CENTRAL (Clinical-trials-identifier:NCT01530724); DIRECT-PLUS (Clinical-trials-identifier:NCT03020186).

Keywords Weight cycling, Weight-loss, Visceral adipose tissue, MRI, Randomized clinical trial, Lifestyle

Background

Repeated weight loss attempts are common and have been associated with mixed cardiometabolic outcomes [1]. While some studies reported adverse effects on body weight and increased cardiometabolic risk [2–5], others did not find detrimental associations between intentional repeated weight loss and long-term changes in body composition, morbidity, or mortality [2, 6–8].

Although total weight and weight loss are often emphasized, growing evidence indicates that the pattern of fat distribution is more critical for long-term health outcomes [9]. Specifically, the accumulation of visceral adipose tissue (VAT), a metabolically active fat depot surrounding internal organs, has emerged as a central driver of cardiometabolic dysfunction [10–14]. VAT is independently associated with insulin resistance, dyslipidemia, type 2 diabetes, and cardiovascular disease, potentially through its endocrine activity and secretion of pro-inflammatory mediators, regardless of overall body weight or body mass index (BMI) [15–19].

It remains unclear whether re-engagement in structured lifestyle interventions yields sustained or additive benefits, particularly in promoting VAT loss. Most existing studies are observational, rely on retrospective self-reported weight cycling history that is not well-defined, lack objective imaging, or controlled intervention designs [2–8, 20, 21]. To address this gap, we evaluated the physiological and metabolic responses of individuals who rejoined a second 18-month structured lifestyle trial after completing a similar prior intervention. We compared within-person changes across both trials and assessed follow-up outcomes relative to first-time participants. Given the conflicting evidence, our approach was exploratory, aiming to test whether outcomes may reflect not only the intervention itself but also the physiological and behavioral context of earlier experiences.

Methods

Study population

We followed participants from two 18-month randomized controlled trials (RCTs): the CENTRAL trial (trial 1, T1) [22] (ClinicalTrials.gov identifier: NCT01530724; n = 278, conducted 2012–2014, with 10-year follow-up) and the DIRECT-PLUS trial (trial 2, T2) [23, 24] (NCT03020186; n = 294, conducted 2017–2018, with 5-year follow-up). Of the 480 individuals enrolled across both trials, 92 participated in both T1 and T2.

Eligibility criteria for both trials included abdominal obesity, defined as waist circumference (WC) > 102 cm for male or > 88 cm for female, and/or dyslipidemia, defined as serum triglycerides > 150 mg/dL and high-density lipoprotein-cholesterol (HDL-C) ≤ 40 mg/dL for male or ≤ 50 mg/dL for female. DIRECT-PLUS additionally required participants to be over age 30. Exclusion criteria were consistent across both trials and are detailed in Additional file 1: Methods S1 [22–26]. Both RCTs and the Follow Interventions Trial (FIT) follow-up were approved by the Soroka University Medical Center Ethics Board and conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants. No monetary or material incentives were provided.

Both RCTs were conducted at the same workplace research site in southern Israel (Dimona). Retention rates at 18 months were 86.3% and 89.8% for CENTRAL and DIRECT-PLUS, respectively, as previously reported [22, 23].

Interventions

The CENTRAL trial [22] was designed to compare the effects of low-fat versus Mediterranean (MED)/low-carbohydrate diets, with or without added physical activity (PA), on specific body adipose depots as measured by MRI. Its primary aim was to test whether combinations of dietary and activity interventions could target VAT and ectopic fat deposits more effectively than conventional low-fat strategies. Participants were randomized to low-fat or MED/low-carbohydrate diets for 18 months, with a second randomization at 6 months to added PA or no PA. The low-fat diet focused on low total fat (< 30% of calories). The MED/low-carbohydrate diet restricted carbs to < 40–70 g/day, emphasized vegetables and legumes, and included 28 g/day of walnuts. The PA program included free gym membership, monthly group workshops, and supervised training three times per week combining aerobic and resistance exercises.

The DIRECT-PLUS trial [23] expanded on these findings by testing three interventions: healthy dietary guidelines (HDG), MED, and green-MED diets, all with structured PA. Its goal was to examine whether intensified dietary composition, including polyphenol-rich foods, further improved fat loss and metabolic markers. The MED groups followed calorie-restricted, low-carb, high-unsaturated-fat diets, including 28 g/day of walnuts. The green-MED group additionally consumed 3–4 cups/day of green tea and 100 g/day of Mankai, contributing ~ 800 mg/day of extra polyphenols. All participants received gym memberships, PA instruction, and combined nutrition and PA sessions (weekly in the first month, then monthly to bimonthly).

Both trials aimed to achieve moderate, sustainable weight loss through reduced intake of refined carbohydrates and trans fats, with increased consumption of vegetables and plant-based foods. In alignment with local dietary patterns, in which lunch is the principal meal of the day, the midday meal was prepared onsite at the workplace cafeteria and tailored to group-specific dietary assignments. MRI fat depot quantifications and all statistical analyses were conducted blinded to group allocation to minimize bias. Full intervention protocols are described elsewhere [22, 24].

Clinical assessments and imaging protocols

Quantification of abdominal fat compartments followed identical protocols in the original trials and in the 5- and 10-year follow-up. Imaging was conducted using a 3-Tesla MRI scanner (Ingenia 3.0 T, Philips Healthcare) using MATLAB-based semiautomated software [22, 23]. Abdominal fat was measured using a 3D modified DIXON (mDIXON) technique with breath-hold acquisition to minimize motion artifacts. All image analysts were blinded to group assignment and to time point (baseline vs. end of intervention). Inter- and intra-observer reliability for fat quantification was high ($n = 30$, $r > 0.96$, $p < 0.001$) [22, 23]. Deep and superficial subcutaneous adipose tissue (SAT) were delineated by manually tracing the fascia superficialis. Two axial slices were analyzed per participant, corresponding to L4–L5 and L5–S1 vertebral spaces. Intrahepatic fat (IHF) measurements were obtained using mDIXON, mDIXON Quant, and proton magnetic resonance spectroscopy (^{1}H-MRS) techniques, following previously validated and cross-referenced protocols [24, 26]. Full imaging protocols are provided in Additional file 1: Methods S2. Missing baseline MRI measurements were due to technical reasons. Anthropometric measurements, fasting blood biomarkers, and comprehensive lifestyle questionnaires, including smoking status, PA levels, and the validated food frequency questionnaire (FFQ) [27], were collected at baseline, after 18 months, and again at long-term follow-up (5 and 10 years), as detailed in Additional file 1: Methods S3. The MED Diet Adherence Screener [28] was also assessed at follow-up. PA was quantified in metabolic equivalent of task (MET)-hours per week, representing the ratio of energy expended during activity to the resting metabolic rate [29]. Missing MED and PA scores follow-up data ($n = 29$, 7.6% and $n = 31$, 8.1%, respectively) were imputed using the k-nearest neighbours (KNN) method [30], based on age, sex, intervention group, and follow-up duration as predictive variables. Cardiometabolic indices were computed using established formulas: Homeostatic model assessment of insulin resistance (HOMA-IR) = (fasting insulin × fasting glucose)/405 [31]; metabolic score for insulin resistance (METS-IR) = (ln(2 × fasting glucose + fasting triglycerides) × BMI)/ln(HDL-C) [32]; and triglyceride-glucose (TyG) index = ln(fasting triglycerides × fasting glucose/2) [33].

Statistical analyses

The primary outcomes were changes in three MRI-derived abdominal adipose tissue compartments: VAT, deep SAT, and superficial SAT, assessed at three time points for single-time participants (baseline, 18 months, and 5- and 10-year follow-up), and at five time points in rejoiners (baseline and 18 months for each intervention, plus 5-year follow-up). Secondary outcomes included anthropometric parameters, MRI-derived IHF, and cardiometabolic biomarkers.

The analytic framework was structured to reflect both between-group and within-person comparisons across interventions and over time. First, we assessed whether participants who later rejoined (T1 + T2) differed from T1-only participants in their baseline characteristics and response to the T1 intervention. Next, we compared baseline measures and intervention responses during T2 between T1 + T2 rejoiners and T2-only participants. We then evaluated within-person changes among T1 + T2 rejoiners across both interventions. This included comparing T1 and T2 baseline values to assess whether rejoining participants entered the second trial with different anthropometric or metabolic profiles. Post-intervention follow-up outcomes (5 and 10 years after trial completions) were subsequently compared between rejoiners and single-time participants from either T1 or T2. These comparisons focused on long-term regain from the end-of-intervention to follow-up in weight, abdominal fat compartments, and cardiometabolic markers. In addition, we examined within-person longitudinal trajectories across all available time points to characterize patterns in anthropometry, body composition, and cardiometabolic indices over time. Finally, we compared follow-up measurements between T1 + T2 rejoiners and single-time participants. All comparisons were restricted to participants with available data at the relevant time points, with analytic sample sizes varying accordingly across outcomes and analyses. Continuous variables are presented as mean ± standard deviation (SD), and categorical variables as frequencies (percentages). Distributional assumptions were assessed using Shapiro–Wilk tests and visual inspection of histograms. Percent change between time points was calculated as ((Later – Earlier)/Earlier) × 100. IHF and high-sensitivity C-reactive protein (hsCRP) changes were reported as an absolute difference due to near-zero baseline values. Baseline and follow-up characteristics were compared between single-time and rejoining participants using Wilcoxon rank-sum tests (continuous variables) and χ^2 tests (categorical variables). Changes during the intervention between single and rejoining participants were analyzed using analysis of covariance (ANCOVA), with adjustment for baseline BMI specific to the relevant trial. Changes during follow-up between single and rejoining participants were analyzed using ANCOVA with adjustment for MED diet adherence score at follow-up. Within-person changes over time were assessed using repeated-measures ANCOVA, adjusting for trial-specific baseline BMI and age. Non-parametric paired Wilcoxon signed-rank tests were additionally used to compare time points. Significance was set a priori at $p < 0.05$. False discovery rate (FDR) correction was applied to all comparisons [34].

All analyses were conducted in R version 4.4.1, using the following packages: dplyr [35], tidyr [36], gtsummary [37], ggplot2 [38], DiagrammeR [39], and VIM [40].

Results

Study population and follow-up

T1 and T2 included 278 and 294 participants, respectively, among 480 individuals, of whom 92 took part in both trials (T1 + T2, = 'rejoiners'). Of these, 384 (80%) completed MRI and clinical assessments during the 2022–2024 post-intervention follow-up. Among these 384 participants, 147 took part only in T1, 161 participated only in T2, and n = 76 were T1 + T2 rejoiners (Fig. 1). At follow-up, the mean age was 57.1 years, and 89% were male (Additional file 1: Table S1).

Baseline characteristics by participation status

At the onset of T1, T1 + T2 future rejoiners had higher BMI (31.3 kg/m^2 vs. 30.0 kg/m^2), WC (109.3 cm vs. 105.4 cm), and deep SAT (291.6 cm^2 vs. 253.0 cm^2), compared with T1-only participants (all FDR < 0.05). Other baseline demographic, anthropometric, and cardiometabolic markers, including sex, age, VAT, glycemic indices, and lipid profiles, were similar across groups (Table 1). At T2 baseline, similar characteristics remained higher among T1 + T2 rejoiners compared with T2-only participants (BMI: 31.8 kg/m^2 vs. 30.7 kg/m^2, WC: 111.1 cm vs. 108.2 cm, and deep SAT: 232.7 cm^2 vs. 202.9 cm^2) (all FDR < 0.05, Table 1). Baseline daily energy intake and PA levels did not differ significantly between single-time and rejoining participants in either trial (Table 1).

At T1 and T2 baselines, rejoiners had comparable BMI values after adjusting for trial-specific baseline age (31.3 kg/m^2 vs. 31.8 kg/m^2; FDR = 0.12). However, at T1 baseline, rejoiners had lower WC (109.3 cm vs. 111.1 cm), diastolic BP (79.0 mmHg vs. 82.3 mmHg), and systolic BP (122.0 mmHg vs. 131.6 mmHg) (all FDRs < 0.05), compared to their own T2 baseline values (Fig. 2 and Additional file 1: Table S2). In contrast, rejoiners showed improved abdominal adipose tissue distribution and metabolic profiles at the T2 baseline compared to the T1 baseline timepoint, including 15.7% lower VAT (135.5 cm^2 vs. 160.0 cm^2), 20.2% lower deep SAT (232.7 cm^2 vs. 289.3 cm^2), and 28.8% lower superficial SAT (114.0 cm^2 vs. 157.0 cm^2), as well as significantly improved HOMA-IR (3.8 vs. 4.5) and triglycerides/HDL-C (3.6 vs. 4.2), all adjusted for trial-specific baseline BMI and age (all FDR < 0.05) (Fig. 2).

Intervention responses among single and rejoining participants

During T2, T1 + T2 rejoiners had significantly smaller benefits across most outcomes, compared to their own response to T1 (Fig. 3 and Additional file 1: Table S3). Weight decreased by −1.5% during T2 compared to −3.5% in T1, VAT decreased by −7.2% vs. −33.3%, deep SAT decreased by −4.0% vs. −31.9%, superficial SAT decreased by −3.3% vs. −25.4%, and IHF decreased by −1.7% vs. −5.4% (all FDRs < 0.05). WC change, however, remained similar between interventions (−3.6% vs. −4.1%; FDR = 0.85).

During T1, future T1 + T2 rejoiners experienced similar improvements in their anthropometric measurements, abdominal adipose depots, and cardiometabolic biomarkers compared to T1-only participants, controlling for T1 baseline BMI (weight: −3.4% vs. −3.3%, WC: −3.7% vs. −3.9%, VAT: −32.7% vs. −34.5%, deep SAT: −30.8% vs. −32.1%, superficial SAT: −23.8% vs. −24.6%, HOMA-IR: −6.0% vs. −14.6%, Triglycerides/HDL-C: −2.2% vs. −14.5%; all FDRs > 0.57) (Additional file 1: Table S4).

In contrast, during T2, T1 + T2 rejoiners had a decreased response relative to T2-only participants, adjusting for T2 baseline BMI (Table 2). Rejoiners had smaller reductions in weight (−1.3% vs. −3.5%), WC (−3.5% vs. −5.9%), deep SAT (−3.4% vs. −9.9%), and superficial SAT (−3.7% vs. −9.3%) compared with single participants (all FDRs ≤ 0.05). Change in VAT showed the

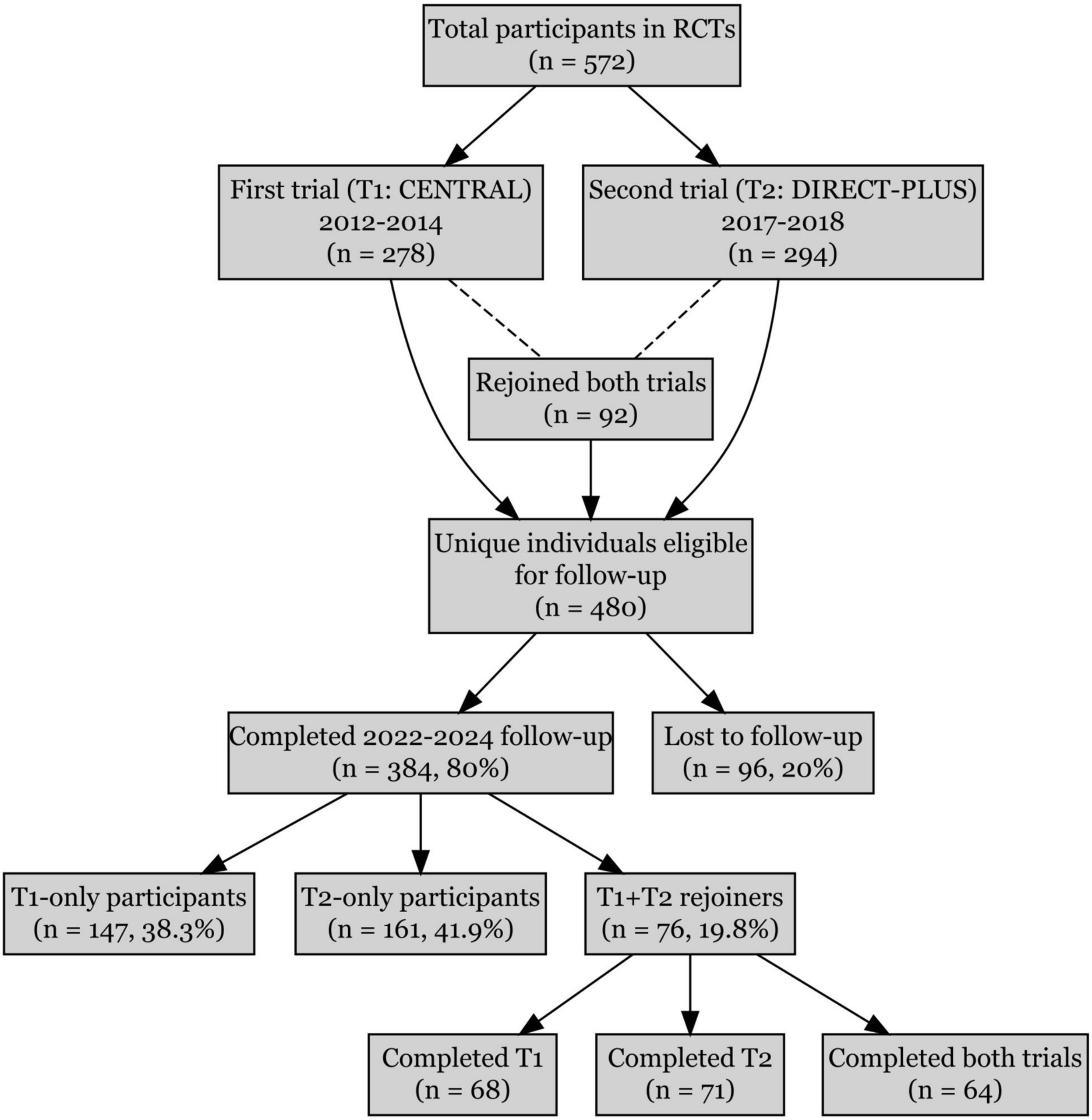

Fig. 1 Participant inclusion flowchart from the CENTRAL and DIRECT-PLUS 18-month trials to the 5- and 10-year Follow-Up Interventions Trial (FIT) study (n = 384). The diagram illustrates the inclusion of single-time and rejoining participants who completed MRI and clinical assessments during the 2022–2024 post-intervention follow-up

same trend but was not statistically significant (−5.9% vs. −11.6%; FDR = 0.20).

Reductions in daily energy intake and increases in PA in response to the lifestyle intervention did not differ significantly between single-time and rejoining participants in either trial (Table 2 and Additional file 1: Table S4).

Table 1 Baseline characteristics of the CENTRAL and DIRECT-PLUS 18-month Trials Participants, Stratified by Participation Status (Single and Rejoiners, n = 384)

Characteristic[1]	T1-only baseline (N = 147)[2]	T1 + T2, T1 baseline (N = 76)[2,3]	T1 baseline Comparison (FDR-adjusted)[4]	T2-only baseline (N = 161)[2,3]	T1 + T2, T2 baseline (N = 76)[2]	T2 baseline Comparison (FDR-adjusted)[4]
Age, years	48.20 ± 9.13	46.64 ± 9.27	0.386	51.49 ± 11.20	51.85 ± 9.25	0.671
Sex (% Male)	131 (89%)	72 (95%)	0.382	139 (86%)	72 (95%)	0.160
BMI, Kg/m^2	29.98 ± 3.80	31.28 ± 3.67	0.026	30.68 ± 3.85	31.79 ± 3.47	0.034
Weight, Kg	89.56 ± 13.45	94.89 ± 12.71	0.021	91.10 ± 13.78	95.98 ± 12.69	0.012
Waist circumference, cm	105.35 ± 9.38	109.31 ± 9.46	0.021	108.21 ± 9.10	111.12 ± 8.06	0.013
VAT area, cm^2	153.52 ± 61.44	160.63 ± 56.21	0.442	129.95 ± 46.58	135.45 ± 49.20	0.671
Deep SAT area, cm^2	253.02 ± 81.92	291.64 ± 92.92	0.021	202.86 ± 63.03	232.70 ± 65.65	0.012
Superficial SAT area, cm^2	149.46 ± 66.97	160.11 ± 66.81	0.382	109.95 ± 44.95	114.01 ± 41.36	0.505
Intrahepatic fat, %	8.89 ± 9.11	12.26 ± 12.07	0.249	10.06 ± 8.88	10.69 ± 8.60	0.671
Diastolic, mmHg	79.86 ± 10.89	79.18 ± 9.96	0.780	80.71 ± 10.32	82.34 ± 10.31	0.663
Systolic, mmHg	124.38 ± 15.13	122.34 ± 14.39	0.691	130.09 ± 13.94	131.57 ± 13.69	0.671
Fasting Glucose, mg/dL	106.61 ± 17.26	108.32 ± 22.99	0.748	103.29 ± 23.37	103.08 ± 21.33	0.894
Fasting Insulin, µU/mL	17.05 ± 9.67	16.57 ± 9.47	0.842	14.59 ± 7.87	14.64 ± 7.68	0.814
HOMA-IR	4.54 ± 2.74	4.48 ± 3.00	0.768	3.77 ± 2.42	3.80 ± 2.21	0.671
HbA1c, %	5.54 ± 0.44	5.62 ± 0.57	0.442	5.45 ± 0.63	5.58 ± 0.64	0.160
Triglycerides/HDL-C	4.51 ± 3.52	4.24 ± 3.69	0.442	3.60 ± 2.16	3.64 ± 3.39	0.671
TyG Index	8.97 ± 0.52	8.88 ± 0.51	0.442	8.83 ± 0.49	8.79 ± 0.51	0.671
METS-IR	47.80 ± 7.87	49.85 ± 8.71	0.249	47.51 ± 7.54	48.96 ± 7.15	0.310
hsCRP, mg/L	3.29 ± 3.82	3.37 ± 2.83	0.382	4.48 ± 6.55	3.74 ± 6.03	0.671
Energy intake, Kcal/day	3,025.53 ± 1,344.77	2,790.60 ± 1,103.77	0.442	2,215.15 ± 1,016.18	1,989.97 ± 1,045.39	0.160
Physical activity, MET-hour/week	37.64 ± 32.34	34.90 ± 25.78	0.784	35.01 ± 36.13	32.11 ± 23.95	0.671

[1] *BMI* body mass index, *HbA1c* glycated hemoglobin, *HDL-C* 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, *SAT* subcutaneous adipose tissue, *T1* trial 1, *T2* trial 2, *TyG Index* triglyceride-glucose index, *VAT* visceral adipose tissue

[2] Mean ± standard deviation (SD) for continuous variables; Number (%) for categorical variables

[3] The "T1 + T2, T1 baseline" and "T1 + T2, T2 baseline" columns represent the same 76 individuals who participated in both trials

[4] Continuous variables were analysed using the Wilcoxon rank sum test, while categorical variables were evaluated using Pearson's Chi-squared test. False discovery rate correction for multiple testing was applied

Changes during post-intervention, long-term follow-up among single and rejoining participants

Ten years after the first trial, T1-only participants and future T1 + T2 rejoiners exhibited similar regain from end-of-intervention to follow-up (Additional file 1: Table S5). However, five years after the second trial, T1 + T2 rejoiners exhibited significantly less weight regain (+ 0.2% vs. + 2.9%), deep SAT regain (+ 2.4% vs. + 13.3%), superficial SAT regain (+ 12.8% vs. + 24.3%), and IHF regain (0% vs. + 2.8%) compared to T2-only participants (all FDRs < 0.05; Fig. 4 and Additional file 1: Table S6).

Sustained long-term effects at 5 and 10 years

During the intervention period, both single-time and rejoining participants demonstrated significant improvements in anthropometric measures, abdominal adipose tissue depots, and glycemic and lipid profiles (Fig. 5). However, by the 10-year follow-up, many of these metabolic benefits had diminished among T1-only participants, with significant increases observed in BMI, WC, VAT, deep SAT, superficial SAT, HOMA-IR, and triglycerides/HDL-C (all FDR < 0.05). In contrast, T1 + T2 rejoiners maintained stability in WC, superficial SAT, HOMA-IR, triglycerides/HDL-C, and METS-IR levels over the same period. Five years after completing the second intervention, T2-only participants exhibited

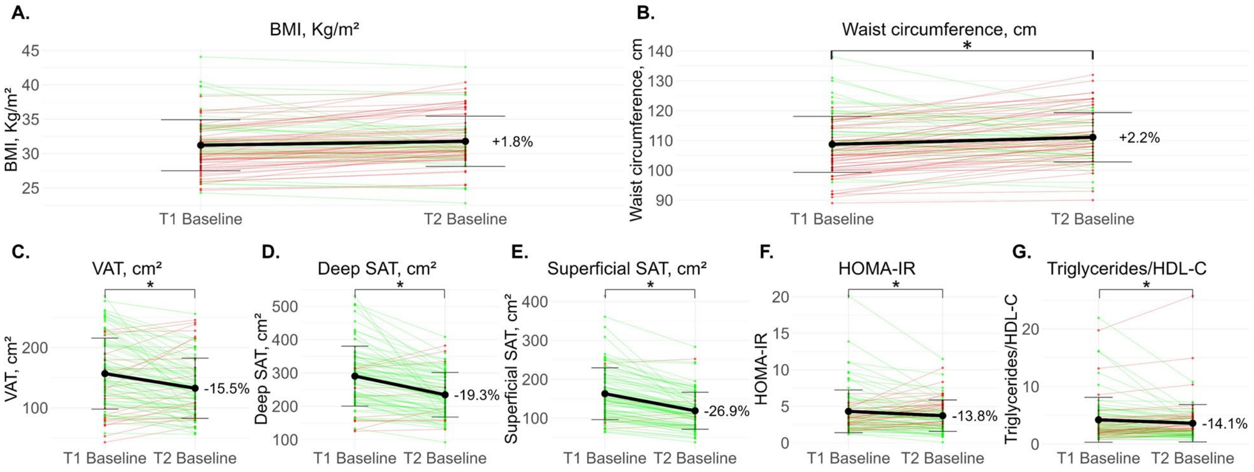

Fig. 2 Baseline Characteristics of T1 + T2 Rejoining Participants: Comparison Between the Start of Their First vs. Second Lifestyle Interventions (n = 76). Individual trajectories and group-level mean ± SD are shown at baseline of the first (T1) and second (T2) lifestyle intervention trials for weight, waist circumference, visceral adipose tissue (VAT), deep subcutaneous adipose tissue (SAT), superficial SAT, homeostatic model assessment of insulin resistance (HOMA-IR), and triglycerides-to-HDL cholesterol ratio. Red lines and dots represent individual participants' exhibiting increases (T2 value – T1 value > 0) from T1 to T2; green indicates decreases. The percentage change from T1 to T2 is shown adjacent to the mean value at T2. Asterisks (*) indicate statistically significant differences between T1 and T2 (FDR < 0.05). BMI was compared using repeated-measures ANCOVA adjusted for trial-specific baseline age. All other variables were analyzed using repeated-measures ANCOVA adjusted for trial-specific baseline BMI and age. Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; SAT, subcutaneous adipose tissue; T1, trial 1; T2, trial 2; VAT, visceral adipose tissue; WC, waist circumference

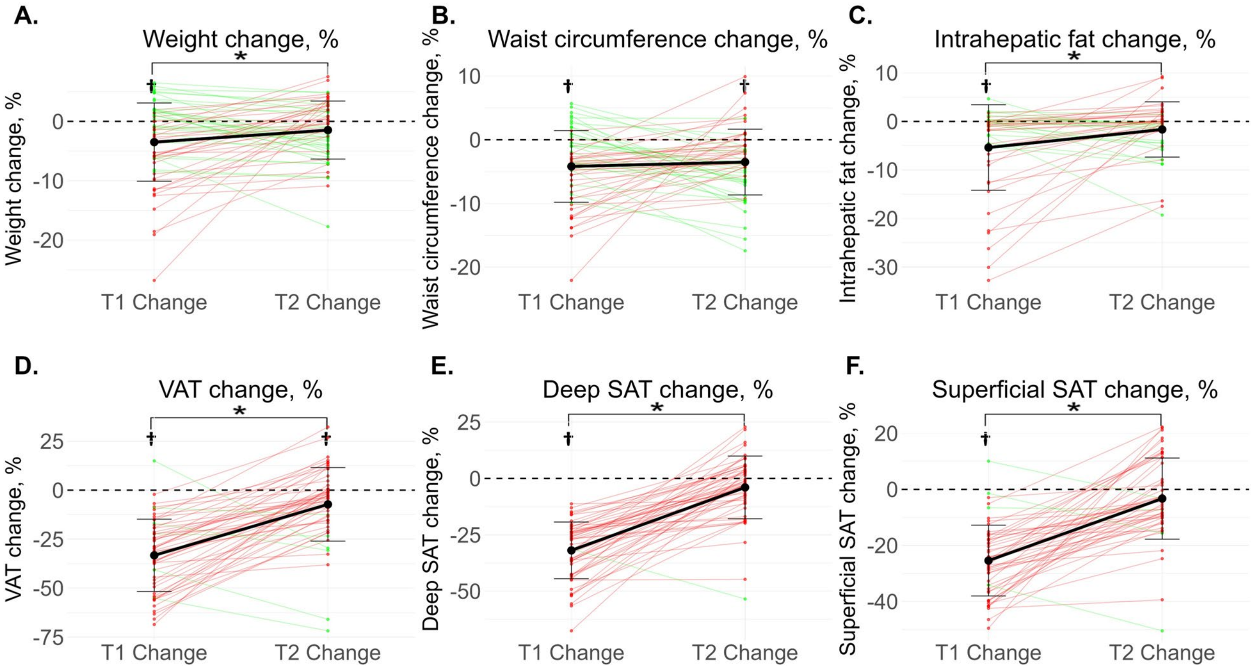

Fig. 3 Intervention Changes Among T1 + T2 Rejoiners During the First and Second Interventions (n = 64). Percent changes from baseline to end of intervention are shown for weight, waist circumference, intrahepatic fat, visceral adipose tissue (VAT), deep subcutaneous adipose tissue (SAT), and superficial SAT. Intrahepatic fat change is reported as absolute difference due to near-zero baseline values. Each line represents an individual participant, colored by the direction of change between T1 and T2 (red: increase, green: decrease). Black circles and error bars denote mean ± SD; bold lines connect means across time points. Asterisks (*) indicate a significant between-intervention difference (T1 vs. T2) tested by repeated-measures ANCOVA, adjusted for trial-specific baseline BMI and age. Daggers (†) denote a significant within-intervention change (vs. baseline), tested using paired Wilcoxon tests. Abbreviations: BMI, body mass index; SAT, subcutaneous adipose tissue; T1, trial 1; T2, trial 2; VAT, visceral adipose tissue

Table 2 Intervention Responses of the Second Trial Participants Among Single and Rejoiner Participants

Characteristic[1]	N	T2-only participants (n = 153)[2]	T1 + T2 rejoiners (n = 71)[2]	*P*-value[3]	FDR-adjusted *P*-value[4]
Weight change during intervention, %	224	−3.45 ± 6.10	−1.31 ± 4.71	0.007	0.041
Waist circumference change during intervention, %	223	−5.94 ± 5.41	−3.52 ± 4.92	0.003	0.027
VAT area change during intervention, %	197	−11.62 ± 24.03	−5.86 ± 18.56	0.108	0.195
Deep SAT area change during intervention, %	196	−9.91 ± 14.70	−3.36 ± 13.37	0.002	0.027
Superficial SAT area change during intervention, %	188	−9.32 ± 14.70	−3.67 ± 14.04	0.014	0.050
Intrahepatic fat change during intervention, %[5]	184	−3.22 ± 6.78	−1.54 ± 5.51	0.086	0.177
Diastolic BP change during intervention, %	219	−0.80 ± 12.16	−2.52 ± 11.46	0.365	0.438
Systolic BP change during intervention, %	219	−0.47 ± 10.48	−1.21 ± 8.24	0.562	0.595
Fasting Glucose change during intervention, %	220	−1.98 ± 10.28	2.27 ± 15.18	0.012	0.050
Fasting insulin change during intervention, %	224	−10.64 ± 39.10	−4.15 ± 35.22	0.150	0.245
HOMA-IR change during intervention, %	218	−10.02 ± 41.05	−1.23 ± 41.37	0.088	0.177
HbA1c change during intervention, %	222	0.23 ± 7.80	0.84 ± 4.27	0.543	0.595
Triglycerides/HDL-C change during intervention, %	223	−4.83 ± 48.57	−3.55 ± 41.88	0.908	0.908
TyG Index change during intervention, %	219	−1.55 ± 4.46	−0.73 ± 4.50	0.241	0.334
METS-IR change during intervention, %	219	−5.25 ± 9.96	−2.62 ± 7.92	0.058	0.150
hsCRP change during intervention, mg/L[5]	215	−1.54 ± 6.46	0.15 ± 1.93	0.040	0.120
Energy intake change during intervention, Kcal/day	200	−563.01 ± 973.88	−399.59 ± 612.30	0.191	0.287
Physical activity change during intervention, MET-hour/week	195	11.71 ± 45.20	4.86 ± 40.29	0.338	0.435

[1] *BMI* body mass index, *HbA1c* glycated hemoglobin, *HDL-C* 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, *SAT* subcutaneous adipose tissue, *T1* trial 1, *T2* trial 2, *TyG Index* triglyceride-glucose index, *VAT* visceral adipose tissue

[2] Mean ± standard deviation (SD)

[3] ANCOVA test, controlled for T2 baseline BMI

[4] False discovery rate correction for multiple testing

[5] IHF and hsCRP changes are reported as absolute differences due to near-zero baseline values

significant regain in most measures compared to end-of-intervention values (FDR < 0.05), with the exception of WC, which remained stable. In contrast, T1 + T2 rejoiners sustained the reductions in both WC, VAT, and METS-IR throughout the 5-year follow-up period (FDR < 0.05). Notably, by the FIT 5- and 10-year follow-up, all anthropometric and cardiometabolic markers were similar across groups (Additional file 1 Table S1).

Discussion

This study examined the long-term physiological impact of rejoining a structured lifestyle intervention program, highlighting key differences between single and rejoining participants. Despite similar baseline weights across the two trials, rejoiners began the second intervention with a more favourable metabolic and abdominal fat profile than at their initial baseline, indicating lasting benefit from the first intervention. In addition, while rejoiners showed a significantly attenuated weight loss, abdominal fat reduction, and cardiometabolic improvement in the second intervention compared with both their own first intervention-induced response and with single-time participants, they experienced significantly less weight and abdominal fat regain over the subsequent 5-year post-intervention period. These findings suggest more sustainable, beneficial long-term effects of rejoining a second weight-loss intervention program.

Several strengths and limitations should be acknowledged. First, the number of rejoiners was modest. However, the ability to follow this subgroup across two interventions and five time points, including repeated MRI and clinical assessments, may enable some meaningful insights into the physiology of repeated lifestyle intervention. In addition, the generalizability of our findings may be limited, as rejoiners were self-selected and the cohort was predominantly male, reflecting the workplace's demographic composition. Strengths include the detailed tracking of changes in abdominal adiposity and metabolic biomarkers across a prolonged period. Most participants underwent standardized MRI assessments at all key time points, with high adherence rates and consistent imaging protocols.

A key finding is that although rejoiners began the second intervention at a similar weight as their initial baseline, their abdominal fat depots and blood biomarkers had improved, indicating a residual metabolic benefit,

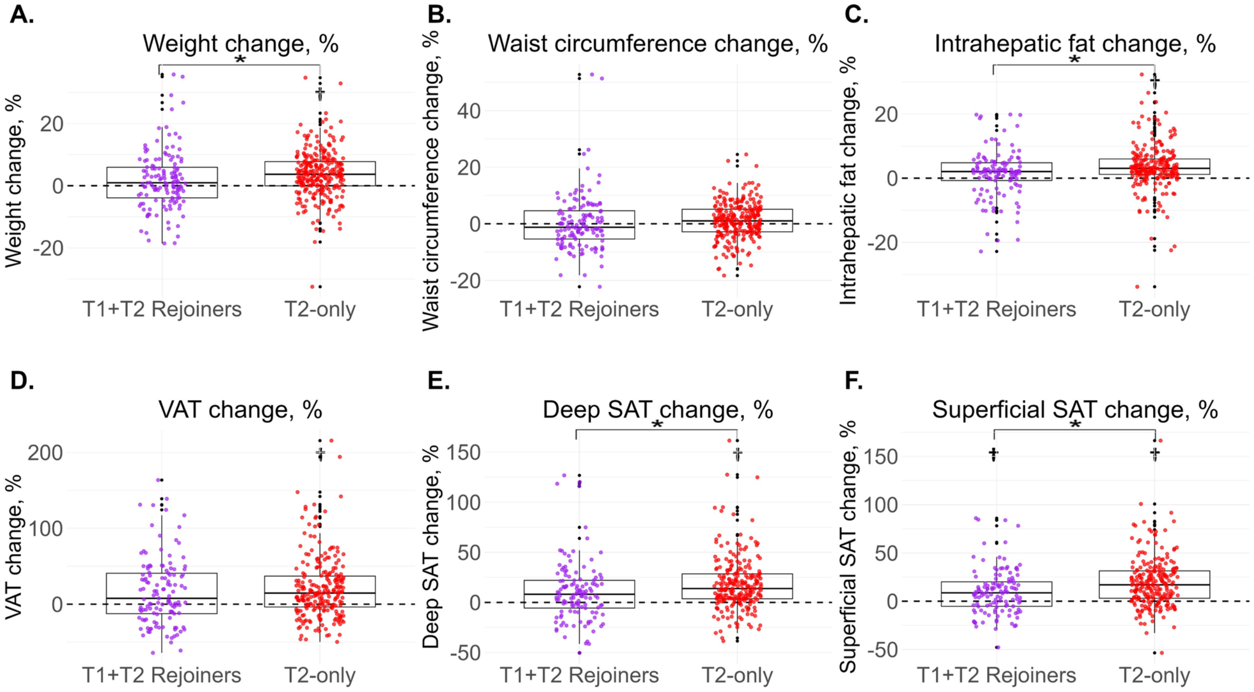

Fig. 4 Changes During the 5-Year post-intervention Follow-up After T2, Stratified by Participation Status (Single and Rejoining Participants, n = 224). Boxplots show the percent change in weight, waist circumference, intrahepatic fat, visceral adipose tissue (VAT), deep subcutaneous adipose tissue (SAT), and superficial SAT between the end of the DIRECT-PLUS trial and 5-year follow-up among participants who either completed only the second trial (T2-only) or rejoined from a prior trial (T1 + T2 Rejoiners). Intrahepatic fat change is reported as absolute difference due to near-zero baseline values. Individual values are overlaid as colored jittered points (red: T2-only, purple: T1 + T2 Rejoiners). The dashed horizontal line at y = 0 represents no change. * indicates FDR < 0.05 between groups (ANCOVA adjusted for Mediterranean diet adherence at follow-up), † indicates a significant within-group change from the end of trial to follow-up (FDR < 0.05, Wilcoxon signed-rank test). Abbreviations: SAT, subcutaneous adipose tissue; T1, trial 1; T2, trial 2; VAT, visceral adipose tissue

beyond BMI. This is consistent with prior observations that not all metabolic parameters strictly mirror weight dynamics over time [9, 41].

While some metabolic markers maintained between interventions, rejoining participants experienced attenuated improvements in adiposity and metabolic outcomes during the second intervention compared to the first. Weight, VAT, deep SAT, superficial SAT, and IHF were all reduced to a lesser extent in the second intervention, after adjustment for baseline age and BMI. Importantly, the observed differences in adiposity and metabolic outcomes during the interventions were not explained by differences in lifestyle adherence. Reductions in daily energy intake and increases in PA were comparable between single-time and rejoining participants. This suggests that the attenuated response observed among rejoiners was not driven by reduced engagement, but may instead reflect physiological adaptations to prior weight loss, such as lowered resting energy expenditure

(See figure on next page.)

Fig. 5 Trajectories of Adiposity and Metabolic Markers Across Two Trials and a Long-term Follow-up. Longitudinal means (±95% confidence intervals) are shown for BMI, waist circumference, visceral adipose tissue (VAT), deep subcutaneous adipose tissue (SAT), superficial SAT, Homeostatic model assessment of insulin resistance (HOMA-IR), triglycerides/HDL-C, and METS-IR. Data are stratified into three groups: single-time participants from the CENTRAL trial (T1) only (blue), DIRECT-PLUS trial (T2) only (red), and those who participated in both trials (purple, "T1 + T2 rejoiners"). Asterisks (*) indicate statistically significant changes between baseline and the end of interventions (2012 to 2014 and 2017 to 2018); plus signs (+) indicate changes between first trial end of intervention and 10-year follow-up (2014 to 2023); carets (^) mark significant changes between second trial end of intervention and 5-year follow-up (2018 to 2023) (Wilcoxon paired tests FDR < 0.05). Sample sizes (n) shown per group and time point reflect only participants with complete data for all respective time points used in paired analyses. Abbreviations: BMI, Body mass index; HDL-C, High-density lipoprotein cholesterol; HOMA-IR, Homeostatic model assessment of insulin resistance; METS-IR, metabolic score for insulin resistance; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue

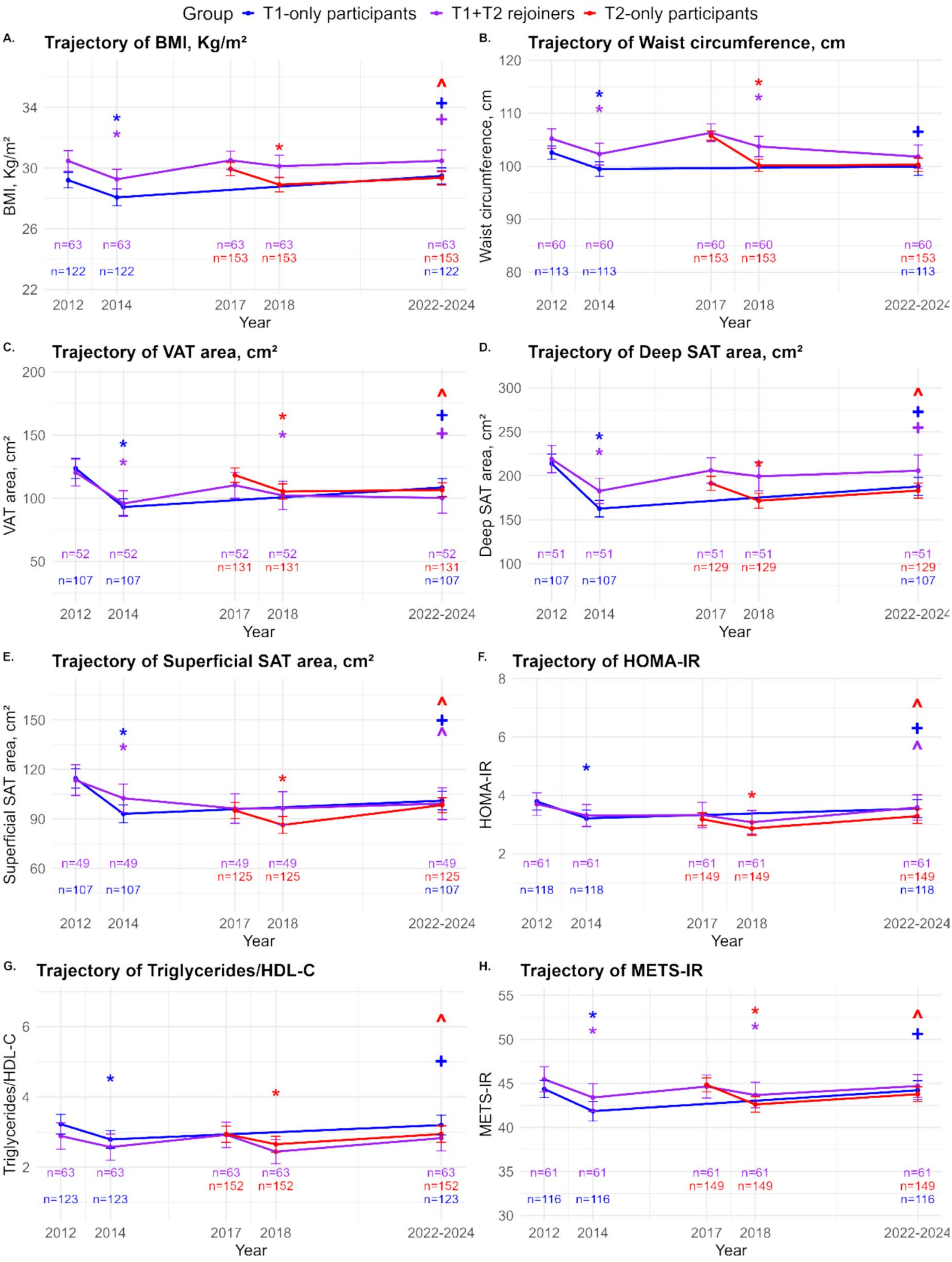

Fig. 5 (See legend on previous page.)

[42, 43], or a narrower physiological margin for improvement due to residual benefits from the first intervention.

Notably, rejoiners also exhibited significantly less reduction in weight, deep SAT, and superficial SAT compared to T2-only participants during the second intervention, whereas VAT reduction was not statistically different between the groups. This may reflect VAT's higher sensitivity to lifestyle interventions [22, 23, 44–46], which could lead to more consistent reductions even upon repeated exposure.

At the same time, rejoiners experienced significantly less weight and abdominal fat regain over the 5-year post-intervention period compared to single-time participants. This finding may reflect the benefits of renewed engagement, behavioral reinforcement, and structured support, which are known to enhance adherence and facilitate long-term weight stability [47, 48]. This pattern is reminiscent of findings from other areas of health behaviour change, such as smoking cessation, where multiple quit attempts are often necessary to achieve long-term success [49]. Similarly, repeated engagement in lifestyle interventions may promote habit formation and durable behaviour change, contributing to sustained health benefits over time.

The combination of modest but significant improvements during the second intervention and reduced regain contributed to sustained reductions across a 10-year follow-up in anthropometric measures as well as glycemic and lipid profiles initially achieved during the first trial. Importantly, these long-term benefits were not observed among single-time participants of the first trial, who showed reversal of earlier improvements by the 10-year follow-up. Furthermore, when compared to single-time participants of the second trial, both groups (single-time and rejoiners) maintained lower WC levels achieved during the intervention. However, only rejoiners sustained reduced VAT and METS-IR levels at the 5-year, post-T2, follow-up. Overall, by the 5- and 10-year FIT follow-up, anthropometric measurements were comparable between rejoiners and single-time participants, despite rejoiners having entered both the first and second interventions with higher levels of adiposity.

While some studies report metabolic harm or diminishing benefits [2–5], others suggest that multiple interventions can yield continued advantages [6, 8]. Our findings support the notion that repeated, intentional programs can still confer additive or stabilizing effects on abdominal fat distribution and cardiometabolic health, even in the context of weight regain. This has important clinical and public health implications, challenging the assumption that weight loss is a futile endeavor [21, 50]. Repeated structured interventions may be a viable strategy for maintaining improvements in metabolic health over time, even when weight loss is modest.

Conclusions

Although a repeated, second intervention resulted in smaller improvements than the initial program, rejoiners experienced attenuated weight and fat regain with meaningful and sustained benefits in body composition and cardiometabolic health. These findings underscore abdominal fat depots, particularly VAT, which is preferentially responsive to lifestyle modification [22, 23, 44–46], as both modifiable and sustainable targets of intervention, beyond BMI. The observation of residual metabolic benefit despite weight regain highlights the lasting physiological impact of previous interventions. Collectively, these results support the value of repeated participation in structured lifestyle programs, even in the absence of substantial weight loss, as a strategy for achieving long-term metabolic stability and reducing regain.

Abbreviations

ANCOVA	Analysis of Covariance
BMI	Body Mass Index
BP	Blood Pressure
FDR	False Discovery Rate
^{1}H-MRS	Proton magnetic resonance spectroscopy
HDG	Healthy Dietary Guidelines
HDL-C	High-Density Lipoprotein Cholesterol
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
hsCRP	High Sensitivity C Reactive Protein
IHF	Intrahepatic Fat
KNN	K-Nearest Neighbours
MED	Mediterranean
MET	Metabolic Equivalent for Task
METS-IR	Metabolic Score for Insulin Resistance
mDIXON	Modified DIXON
MRI	Magnetic Resonance Imaging
PA	Physical Activity
RCT	Randomized Controlled Trial
SAT	Subcutaneous Adipose Tissue
SD	Standard Deviation
TyG	Triglyceride-glucose
T1	Trial 1
T2	Trial 2
VAT	Visceral Adipose Tissue
WC	Waist Circumference

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-026-04663-9.

Additional file 1: Methods S1. Exclusion Criteria for CENTRAL and DIRECT-PLUS Trials. Methods S2. Magnetic Resonance Imaging and Fat Quantification. Methods S3. Anthropometric and Clinical Measurements. Table S1. Follow-up Characteristics of the CENTRAL and DIRECT-PLUS 18-month Trials Participants, 5- and 10-Years Post-Intervention, Stratified by Participation Status (Single and Rejoiners, n=384). Table S2. Baseline Characteristics of T1+T2 Rejoining Participants: Comparison Between the Start of Their First vs. Second Lifestyle Interventions (n=76). Table S3. Intervention Changes Among Rejoiners During the First and Second Interventions (n=64). Table S4. Intervention Responses of the First Trial Participants

Among Single and Future Rejoining Participants. Table S4. Intervention Responses of the First Trial Participants Among Single and Future Rejoining Participants. Table S5. Changes During the 10-Year Follow-up After the First Trial, Stratified by Participation Status (Single and Future Rejoining Participants, n=194). Table S6. Changes During the 5-Year Follow-up After the Second Trial, Stratified by Participation Status (Single and Rejoining Participants, n=224).

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Authors' contributions
HK had full access to all the data in the study and takes responsibility for the integrity and accuracy of the data and the analysis. Concept and design: IS2; Conduct of the FIT: HK, DP, DTGT, OK, LA, NEK, IS2; Statistical analysis: HK; Collection, management, analysis, and interpretation of the data: HK, DP, DTGT, OK, LA, NEK, YC, IS1, AR, UY, GBA, HZ, AYM, GT, CB, MB, MS, UC, BI, MJS, LQ, FBH, IS2; Review and approval of the manuscript: HK, DP, DTGT, OK, LA, NEK, YC, IS1, AR, UY, GBA, HZ, AYM, GT, CB, MB, MS, UC, BI, MJS, LQ, FBH, IS2; Supervision: IS2. All authors read and approved the final manuscript.

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Data availability
The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate
The Soroka University Medical Centre Medical Ethics Board and the Institutional Review Board approved the study protocols for the CENTRAL (0239-11-SOR) and DIRECT-PLUS (0280-16-SOR) trials, and the FIT follow-up (0373-21-SOR). All participants provided written informed consent and received no financial compensation.

Consent for publication
Not applicable.

Competing interests
M.B. received honoraria as a consultant and speaker from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Lilly, Novo Nordisk, Novartis, and Sanofi. All other authors declare that they have no competing interests.

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References

1. Quinn DM, Puhl RM, Reinka MA. Trying again (and again): Weight cycling and depressive symptoms in U.S. adults. PLoS ONE. 2020;15(9):e0239004.
2. Mackie GM, Samocha-Bonet D, Tam CS. Does weight cycling promote obesity and metabolic risk factors? Obes Res Clin Pract. 2017;11(2):131–9.
3. Jacquet P, Schutz Y, Montani J-P, Dulloo A. How dieting might make some fatter: modeling weight cycling toward obesity from a perspective of body composition autoregulation. Int J Obes. 2020;44(6):1243–53.
4. Halali F, Lapveteläinen A, Aittola K, Männikkö R, Tilles-Tirkkonen T, Järvelä-Reijonen E, et al. Associations between weight loss history and factors related to type 2 diabetes risk in the Stop Diabetes study. Int J Obes. 2022;46(5):935–42.
5. Zou H, Yin P, Liu L, Duan W, Li P, Yang Y, et al. Association between weight cycling and risk of developing diabetes in adults: A systematic review and meta-analysis. J Diabetes Inves. 2021;12(4):625–32.
6. Sanaya N, Janusaite M, Dalamaga M, Magkos F. The physiological effects of weight-cycling: a review of current evidence. Curr Obes Rep. 2024;13(1):35–50.
7. Mehta T, Smith DL, Muhammad J, Casazza K. Impact of weight cycling on risk of morbidity and mortality. Obes Rev. 2014;15(11):870–81.
8. Willis EA, Huang WY, Saint-Maurice PF, Leitzmann MF, Salerno EA, Matthews CE, Berndt SI. Increased frequency of intentional weight loss associated with reduced mortality: a prospective cohort analysis. BMC Med. 2020;18(1):248. https://doi.org/10.1186/s12916-020-01716-5. PMID: 32938465; PMCID: PMC7495833.
9. Yaskolka Meir A, Tsaban G, Rinott E, Zelicha H, Schwarzfuchs D, Gepner Y, et al. Individual response to lifestyle interventions: a pooled analysis of three long-term weight loss trials. Eur J Prev Cardiol. 2025;32(16):1660–70. https://doi.org/10.1093/eurjpc/zwaf308. PMID: 40472282.
10. Neeland IJ, Ross R, Despres JP, Matsuzawa Y, Yamashita S, Shai I, et al. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. Lancet Diabetes Endocrinol. 2019;7(9):715–25.
11. Ross R, Neeland IJ, Yamashita S, Shai I, Seidell J, Magni P, et al. Waist circumference as a vital sign in clinical practice: a consensus statement from the IAS and ICCR working group on visceral obesity. Nat Rev Endocrinol. 2020;16(3):177–89.
12. Rana MN, Neeland IJ. Adipose tissue inflammation and cardiovascular disease: an update. Curr Diabetes Rep. 2022;22(1):27–37.
13. Tchernof A, Despres JP. Pathophysiology of human visceral obesity: an update. Physiol Rev. 2013;93(1):359–404.
14. Rubino F, Cummings DE, Eckel RH, Cohen R, Wilding JPH, Brown WA, et al. Definition and diagnostic criteria of clinical obesity. Lancet Diabetes Endocrinol. 2025;13(3):221–62.
15. Arsenault BJ, Carpentier AC, Poirier P, Després JP. Adiposity, type 2 diabetes and atherosclerotic cardiovascular disease risk: Use and abuse of the body mass index. Atherosclerosis. 2024;394:394:117546. https://doi.org/10.1016/j.atherosclerosis.2024.117546. Epub 2024 Apr 14. PMID: 38692978.
16. Tejani S, McCoy C, Ayers CR, Powell-Wiley TM, Despres JP, Linge J, et al. Cardiometabolic Health Outcomes Associated With Discordant Visceral and Liver Fat Phenotypes: Insights From the Dallas Heart Study and UK Biobank. Mayo Clin Proc. 2022;97(2):225–37.
17. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu C-Y, et al. Abdominal visceral and subcutaneous adipose tissue

compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation. 2007;116(1):39–48.
18. Klein H, Zelicha H, Yaskolka Meir A, Rinott E, Tsaban G, Kaplan A, et al. Visceral adipose tissue area and proportion provide distinct reflections of cardiometabolic outcomes in weight loss; pooled analysis of MRI-assessed CENTRAL and DIRECT PLUS dietary randomized controlled trials. Erratum in: BMC Med. 2025;23(1):92. https://doi.org/10.1186/s12916-025-03939-w. PMID: 39901232; PMCID: PMC11792534.
19. Shah RV, Murthy VL, Abbasi SA, Blankstein R, Kwong RY, Goldfine AB, et al. Visceral adiposity and the risk of metabolic syndrome across body mass index: the MESA study. JACC Cardiovasc Imaging. 2014;7(12):1221–35.
20. Madigan CD, Pavey T, Daley AJ, Jolly K, Brown WJ. Is weight cycling associated with adverse health outcomes? A cohort study. Prev Med. 2018;108:47–52.
21. Nordmo M, Danielsen YS, Nordmo M. The challenge of keeping it off, a descriptive systematic review of high-quality, follow-up studies of obesity treatments. Obes Rev. 2020;21(1):e12949. https://doi.org/10.1111/obr.12949. Epub 2019 Nov 1. PMID: 31675146.
22. Gepner Y, Shelef I, Schwarzfuchs D, Zelicha H, Tene L, Yaskolka Meir A, et al. Effect of distinct lifestyle interventions on mobilization of fat storage pools: CENTRAL magnetic resonance imaging randomized controlled trial. Circulation. 2018;137(11):1143–57.
23. Zelicha H, Kloting N, Kaplan A, Yaskolka Meir A, Rinott E, Tsaban G, et al. The effect of high-polyphenol Mediterranean diet on visceral adiposity: the DIRECT PLUS randomized controlled trial. BMC Med. 2022;20(1):327.
24. Yaskolka Meir A, Rinott E, Tsaban G, Zelicha H, Kaplan A, Rosen P, et al. Effect of green-Mediterranean diet on intrahepatic fat: the DIRECT PLUS randomised controlled trial. Gut. 2021;70(11):2085–95.
25. Thomas EL, Fitzpatrick JA, Malik SJ, Taylor-Robinson SD, Bell JD. Whole body fat: content and distribution. Prog Nucl Magn Reson Spectrosc. 2013;73:56–80.
26. Gepner Y, Shelef I, Komy O, Cohen N, Schwarzfuchs D, Bril N, et al. The beneficial effects of Mediterranean diet over low-fat diet may be mediated by decreasing hepatic fat content. J Hepatol. 2019;71(2):379–88.
27. Shai I, Shahar DR, Vardi H, Fraser D. Selection of food items for inclusion in a newly developed food-frequency questionnaire. Public Health Nutr. 2004;7(6):745–9.
28. Martínez-González MA, García-Arellano A, Toledo E, Salas-Salvadó J, Buil-Cosiales P, Corella D, et al. A 14-item Mediterranean diet assessment tool and obesity indexes among high-risk subjects: the PREDIMED trial. PLoS ONE. 2012;7(8):e43134.
29. Ainsworth BE, Haskell WL, Leon AS, Jacobs DR, Montoye HJ, Sallis JF, et al. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc. 1993;25(1):71–80.
30. Parr CL, Hjartåker A, Scheel I, Lund E, Laake P, Veierod MB. Comparing methods for handling missing values in food-frequency questionnaires and proposing k nearest neighbours imputation: effects on dietary intake in the Norwegian Women and Cancer study (NOWAC). Public Health Nutr. 2008;11(4):361–70.
31. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412–9.
32. Bello-Chavolla OY, Almeda-Valdes P, Gomez-Velasco D, Viveros-Ruiz T, Cruz-Bautista I, Romo-Romo A, et al. METS-IR, a novel score to evaluate insulin sensitivity, is predictive of visceral adiposity and incident type 2 diabetes. Eur J Endocrinol. 2018;178(5):533–44.
33. Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. Metab Syndr Relat Disord. 2008;6(4):299–304.
34. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B Stat Methodol. 1995;57(1):289–300.
35. Wickham H, François R, Henry L, Müller K. dplyr: A grammar of data manipulation. R package version 0.4. 2015;3:p156.
36. Wickham H, Henry L. Tidyr: Tidy messy data. R package version. 2020;1(2):397.
37. Daniel dS, Whiting K, Curry M, Lavery JA, Larmarange J. Reproducible summary tables with the gtsummary package. The R Journal. 2021;13(1):570–80.
38. Ginestet C. ggplot2: elegant graphics for data analysis. JOURNAL-ROYAL STATISTICAL SOCIETY SERIES A. 2011;174:245-.
39. Iannone R, Roy O. Package 'DiagrammeR'. R Package Version 1.1. 2016.
40. Prantner B. Visualization of imputed values using the R-package VIM. Visualization of Imputed Values Using the R-package VIM. 2011.
41. Bluher M, Rudich A, Kloting N, Golan R, Henkin Y, Rubin E, et al. Two patterns of adipokine and other biomarker dynamics in a long-term weight loss intervention. Diabetes Care. 2012;35(2):342–9.
42. Hafida S, Apovian C. Physiology of the weight-reduced state and its impact on weight regain. Endocrinol Metab Clin North Am. 2022;51(4):795–815.
43. Monnier L, Schlienger JL, Colette C, Bonnet F. The obesity treatment dilemma: Why dieting is both the answer and the problem? A mechanistic overview. Diabetes Metab. 2021;47(3):101192. https://doi.org/10.1016/j.diabet.2020.09.002. Epub 2020 Sep 28. PMID: 33002604.
44. Chaston TB, Dixon JB. Factors associated with percent change in visceral versus subcutaneous abdominal fat during weight loss: findings from a systematic review. Int J Obes. 2008;32(4):619–28.
45. Ross R, Bradshaw AJ. The future of obesity reduction: beyond weight loss. Nat Rev Endocrinol. 2009;5(6):319–25.
46. Fischer K, Pick JA, Moewes D, Nöthlings U. Qualitative aspects of diet affecting visceral and subcutaneous abdominal adipose tissue: a systematic review of observational and controlled intervention studies. Nutr Rev. 2015;73(4):191–215.
47. Hall KD, Kahan S. Maintenance of lost weight and long-term management of obesity. Med Clin North Am. 2018;102(1):183–97.
48. Hartmann-Boyce J, Theodoulou A, Oke JL, Butler AR, Scarborough P, Bastounis A, et al. Association between characteristics of behavioural weight loss programmes and weight change after programme end: systematic review and meta-analysis. BMJ. 2021;374:n1840. https://doi.org/10.1136/bmj.n1840. PMID: 34404631; PMCID: PMC8369384.
49. Chaiton M, Diemert L, Cohen JE, Bondy SJ, Selby P, Philipneri A, et al. Estimating the number of quit attempts it takes to quit smoking successfully in a longitudinal cohort of smokers. BMJ Open. 2016;6(6):e011045.
50. Mann T, Tomiyama AJ, Westling E, Lew A-M, Samuels B, Chatman J. Medicare's search for effective obesity treatments: diets are not the answer. Am Psychol. 2007;62(3):220–33.

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