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FULL RESEARCH PAPER
Nutrition/obesity (diet, alcohol)

Individual response to lifestyle interventions: a pooled analysis of three long-term weight loss trials

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Aims We explored the manifestations of individual weight loss (WL) response to long-term lifestyle interventions on cardiometabolic risk.

Methods and results We pooled data from three large long-term lifestyle WL-intervention trials: 24-month DIRECT (ClinicalTrials.gov: NCT00160108; $n = 322$; 87% adherence), 18-month CENTRAL (ClinicalTrials.gov: NCT01530724; $n = 278$; 86% adherence), and 18-month DIRECT PLUS (ClinicalTrials.gov: NCT03020186; $n = 294$; 89% adherence). We analyzed longitudinal changes in cardiometabolic risk markers, including anthropometrics, blood biomarkers, and magnetic-resonance-imaging-assessed fat depots, and measured DNA-methylation, proteomics, and metabolomics. Among trial completers ($n = 761$, mean age = 50.4 years; 89% men, baseline body-mass-index = 30.1 kg/m^2), mean WL was −3.3 kg (−3.5%). We classified participants as Successful-WL (36%) with relative-WL > 5%, WL-Resistant (28%) who did not lose or gained weight, and Moderate-WL (36%) with WL between 0% and 5%. Successful-WL achieved the greatest improvements in multiple health indicators. However, the WL-Resistant also showed some significant improvements, with increased high-density-lipoprotein-cholesterol (HDLc) and decreased leptin and visceral fat ($P < 0.05$ vs. baseline). Overall, each 1 kg sustained lifestyle-induced WL was associated with improvements in lipid markers and insulin resistance [HDLc (+1.44%), triglycerides (−1.37%), insulin (−2.46%), HOMA-IR (−2.71%), leptin (−2.79%)] and intrahepatic-fat regression (−0.49 absolute-units)] and modest but significant change in systolic and diastolic blood pressures (−0.26% and −0.36%). We identified 12 significant methylation sites that are associated with Successful-WL (FDR < 0.05; AUC = 0.73).

Conclusion While only ∼one-third of individuals achieved long-term WL, the Moderate-WL and WL-Resistant individuals could benefit improvements in visceral adiposity and cardiometabolic risk by shifting towards a healthy lifestyle pattern, beyond WL. Site-pecific DNA methylation may predict an individual's likelihood of successful WL.

Registration NCT00160108, NCT01530724, NCT03020186.

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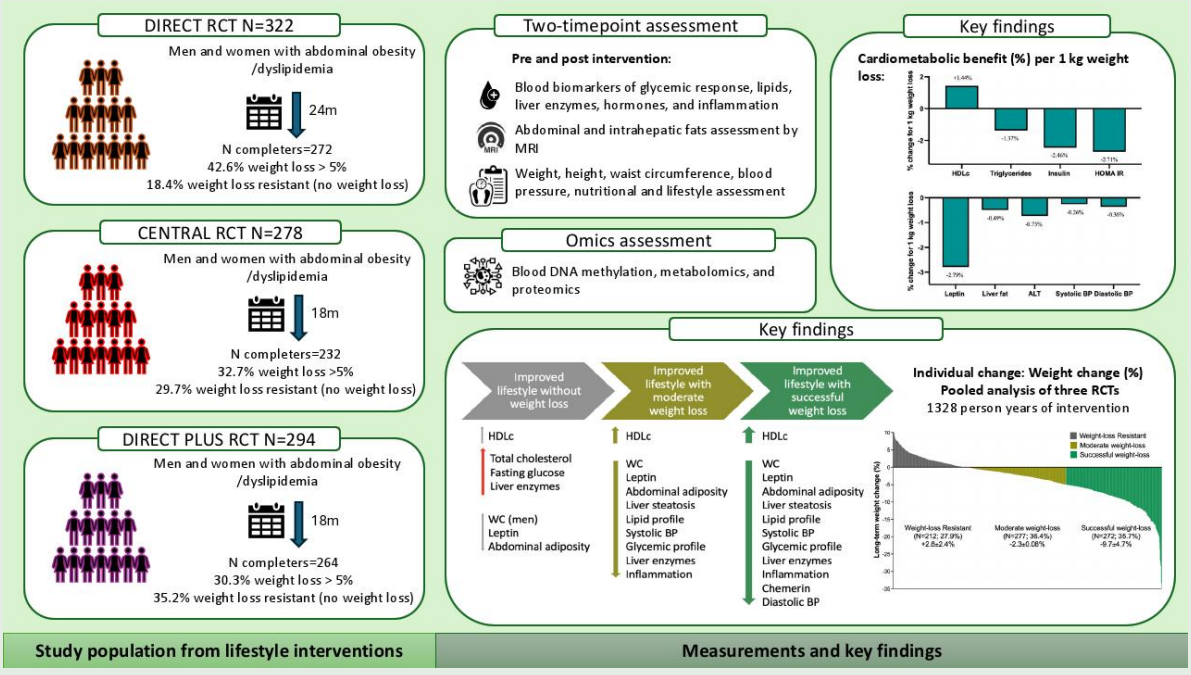
Lay summary

- In a pooled analysis of over 700 participants from three long-term lifestyle intervention trials, only one-third achieved significant WL (>5%). However, even individuals resistant to WL demonstrated meaningful health benefits.
- These benefits included improvements in cardiometabolic markers such as increased HDL cholesterol, reduced visceral fat, and lower leptin levels, suggesting that lifestyle changes can enhance metabolic health independent of weight reduction.
- Additionally, researchers identified specific DNA methylation patterns that may predict an individual's likelihood of achieving successful WL through lifestyle modification.

Graphical Abstract



Keywords Intervention trials • Nutrition • Weight-loss • Lifestyle • Epigenetics • Metabolomics • Proteomics

Introduction

Weight loss (WL) can promote metabolic and cardiovascular health in a variety of ways, as reducing the risk of type 2 diabetes,[1] heart disease,[2] and hypertension[3] and reducing the risk of all-cause mortality for intentional WL.[4] WL therapy may be approached in a more personally tailored manner, adapted to the individual's genetic[5,6] and non-genetic characteristics.[7–10] A WL of at least 5% was associated with improved cardiometabolic risk factors, including total body fat, truncal fat, waist circumference (WC), systolic and diastolic blood pressure (BP), and high-density lipoprotein cholesterol (HDLc).[11–14]

Weight regain after WL is a common challenge; a meta-analysis of 29 directed WL studies showed a 25%, 50%, and 75% weight regain after 1, 2, and 5 years, respectively.[15] There is wide variation in how individuals respond to WL interventions of diet and exercise habits changes. Some individuals may see significant WL with these interventions, while others may experience minimal or no changes.[16] This variability may be due to various factors, including genetic,[17] metabolic,[18] and behavioural adaptations.[19] Initial WL during the first months of a diet, the 'rapid WL phase', is often the most substantial and is followed by weight regain or maintenance ('plateau').[20] Factors contributing to weight regain include a slowing of metabolism,[21] changes in hormone levels[22] that stimulate appetite, and a return to previous dietary and lifestyle habits.

We aimed to estimate the extent of improvement in cardiometabolic outcomes per modest WL, further explored individual responses across categories of responders to lifestyle interventions for WL, and explored potential baseline indicators of successful WL. We pooled data from three landmark large long-term lifestyle WL-intervention trials: The DIRECT ($n = 322$; 24 months, 87% adherence-rate)[23] CENTRAL ($n = 278$; 18 months, 86% adherence-rate),[24] and DIRECT PLUS ($n = 294$; 18 months, 89% adherence-rate).[25]

Methods

Study population

Individuals from three long-term, large-scale randomized controlled trials who completed the intervention were included in this analysis: DIRECT (NCT00160108; *n* completers = 272), CENTRAL (NCT01530724; *n* completers = 232), DIRECT PLUS (NCT03020186; *n* completers = 264). We

also performed a sub-analysis of abdominal and liver imaging data for the CENTRAL and DIRECT PLUS. Inclusion and exclusion criteria for each trial are detailed in Supplementary material online, Methods *S1*. Assessment of adherence to the intervention is detailed in Supplementary material online, Methods *S2*. Study protocols were published elsewhere.[23–25]

The DIRECT trial included three diet-only hypocaloric intervention arms: a low-fat diet, a low-carbohydrate diet, and a Mediterranean diet. The CENTRAL trial employed a two-factorial lifestyle intervention consisting of hypocaloric diets (similar in composition and caloric restriction to those in the DIRECT trial) followed by a lifestyle accommodation phase after 6 months. The diets in CENTRAL included a low-fat diet and a combined low-carbohydrate/Mediterranean diet. The DIRECT PLUS trial included a combined diet and lifestyle intervention from the outset, comprising three regimens: a guideline-recommended healthy lifestyle without caloric restriction, a low-carbohydrate Mediterranean diet (similar to CENTRAL), and a green-Mediterranean diet—an adaptation of the low-carbohydrate Mediterranean diet with further red meat restriction and the addition of green tea and a Mankai shake as a dinner substitute. Despite some differences in intervention design, all three studies demonstrated similar patterns and magnitudes of WL: a peak after six months followed by a plateau or partial weight regain. Across all trials, WL emerged as the primary driver of cardiometabolic improvements, with modest but meaningful contributions from the specific lifestyle approaches.

WL response patterns

We used long-term WL to define retrospectively three categories of weight response by the end of intervention: Successful-WL: individuals who lost more than 5% of their initial body weight; Moderate-WL: individuals who lost 0–5%; WL-Resistant: individuals who completed the intervention but did not lose any weight or gained weight.

Measurement of outcome indicators

We evaluated weight, height, WC, systolic and diastolic BP, and blood biomarkers three times during the interventions, as detailed before.[23–25] Briefly, the participants were weighed without shoes to the nearest 0.1 kg. A wall-mounted stadiometer was used to measure height to the nearest millimetre. WC was measured halfway between the last rib and the iliac crest. BP was measured using an automated system (Datascop Acutor 4). Blood samples were obtained by venipuncture at 8 a.m. after a 12-h fast at baseline, 6, and the trial end and were stored at –80°C until an assay for lipids, inflammatory biomarkers, and insulin could be performed at Leipzig University, Germany. For the CENTRAL and DIRECT PLUS trials, we assessed visceral adipose tissue (VAT) and intrahepatic fat percentage (IHF%) pre- and post-intervention (two timepoints) using magnetic resonance imaging (MRI), as detailed before.[24,25]

Omics sub-study to predict WL categories

We used DNA methylation (Illumina EPIC array), proteomics (Olink CVD II), and plasma metabolomics (liquid chromatography-tandem mass spectrometry) data measured at baseline in the DIRECT PLUS and CENTRAL trials. Preprocessing information is available in Supplementary Methods *S3*. We employed two methods for the discovery of omics predictors for WL: (i) a wide association study: we used the DIRECT PLUS as a discovery set to predict WL in kg and the CENTRAL as a validation set to predict WL in kg, WL above/below 5%, and WL-resistant vs. Successful-WL. Models are detailed in Supplementary material online, Methods *S4*. (ii) An elastic net regression with Leave One Out cross-validation (LOOCV) to predict WL in kg by each omics in the DIRECT PLUS. The CENTRAL study was used to validate the prediction models. Models are detailed in Supplementary material online, Methods *S4*.

Statistical analysis

We primarily aimed to examine the association of 1 kg WL with multiple health outcomes. The initial sample size for this analysis was determined by the number of people with baseline and long-term follow-up weight measurements ($n = 768$). For eligible observations, we removed outliers three standard deviations (SD) from the mean weight for baseline and end of the intervention (18 or 24 months) separately and then re-calculated the number of people with weight measurements at both time points (see Supplementary material online, *Figure S1*). Relative weight change was determined as (weight at the end of the intervention—weight at the beginning of the intervention)/weight at the beginning of the intervention × 100. Next, as needed, we removed values 3SD from the mean for the following markers for the 761 people mentioned above (see Supplementary material online, Methods *S5*). We calculated the difference between the end of the intervention (18 or 24 months; 'long-term WL') to the beginning using the clean data. We also calculated relative change (difference/baseline) × 100. We followed the same steps for our MRI sub-study, only within the trials with available data (CENTRAL, DIRECT PLUS). The *P*-value threshold for the primary outcome was corrected by dividing 0.05 by the number of tests. Continuous variables are presented as mean ± SD. Nominal variables are expressed as numbers or percentages. Summary statistics were examined using the chi-square or ANOVA test. Benjamini Hochberg False Discovery Rate (FDR) was used to correct for multiple comparisons in the omics sub-study. Differences between time points (baseline and end of the intervention) were tested using the Paired sample *t*-test. A meta-analysis was conducted using the 'meta' R package. Interactions were tested using linear models, and *P* of interactions was reported for the interaction term. Multinomial multivariable regression was used to test differences between WL categories. To quantify the effect of WL on the percentage change in outcome indicators, we tested the assumption of whether linear models were correctly specified using the Ramsey Regression Equation Specification Error Test (RESET), 'lmtest' R package. When RESET test results were insignificant, we used Linear regression. Otherwise, we used cubic spline regression ('splines' R package). We performed a sensitivity analysis using Quintile regression using the 'quantreg' R package. All statistical analyses were performed using R (version 4.2; R Foundation for Statistical Computing).

Results

Characterization of WL categories by baseline characteristics

Baseline characteristics across three patterns of long-term WL categories are presented in *Table 1*. In a univariate test, the following markers significantly differ between the WL-Resistant and the other WL categories: younger age, higher percentage of females, lower WC (compared with Successful-WL), lower liver enzymes, and least IHF (least %). A meta-analysis for the potential differentiating factors observed in the univariate test (type of diet, sex, age, WC, leptin, fetuin-A, ALT, AST, VAT%, and IHF) between the extreme WL phenotypes WL-Resistant and Successful-WL yielded similar results (see Supplementary material online, *Figure S2*). After adjustment for age, sex, trial, and BMI, most of the characteristics were not significantly different between groups. Supplementary material online, *Table S1* presents a sensitivity multivariable analysis for markers that significantly differed between WL categories of below/above 5% at baseline. A sensitivity analysis of each trial separately showed similar results (see Supplementary material online, *Table S2*).

Baseline omics as predictors of long-term WL and WL categories

We performed an exploratory analysis in a subset of individuals with DNA methylation, proteomics, and blood metabolomics to find predictors for WL, using Elastic net models with each pre-intervention omics as predictors for WL (in kg) and wide association study with each

Table 1 Baseline characteristics across three categories of long-term WL

	WL-Resistant (no WL; $n = 212$)	Moderate-WL (0–5% WL; $n = 277$)	Successful-WL (>5% WL; $n = 272$)
Background characteristics			
Age, years	48.8 (9.03)	51.0 (8.48)	51.1 (9.35)
Sex, % of men	84.4%	89.2%	91.9%
Smokers, %	14.62%	16.77%	13.65%
Oral glycemic control, %	5.66%	4.33%	6.25%
Lipid-lowering, %	14.62%	15.88%	18.01%
Antihypertensive, %	12.74%	19.86%	20.59%
Anthropometric and BP			
BMI, kg/m^2	30.9 (3.59)	30.3 (3.09)	30.8 (3.25)
WC, cm	107 (9.66)	106 (8.52)	108 (8.43)
Systolic BP, mmHg	127 (14.5)	129 (14.1)	129 (14.6)
Diastolic BP, mmHg	79.4 (9.39)	80.5 (9.28)	79.7 (9.85)
Blood markers			
HDLc, mg/dL	43.0 (10.7)	41.9 (10.4)	41.8 (9.89)
LDLc, mg/dL	125 (27.2)	123 (32.1)	120 (31.6)
Total cholesterol, mg/dL	197 (32.0)	196 (34.6)	193 (34.6)
Triglycerides, mg/dL	152 (70.4)	157 (68.6)	155 (63.7)
Fasting plasma glucose, mg/dL	98.1 (16.9)	97.7 (19.2)	97.2 (18.8)
HOMA IR	3.64 (1.96)	3.52 (2.05)	3.42 (1.98)
Insulin, µU/mL	14.6 (7.05)	13.9 (6.47)	14.2 (7.11)
CRP, mg/L	3.10 (2.11)	2.99 (2.17)	3.11 (2.04)
Leptin, ng/mL	13.0 (8.40)	11.2 (7.87) [a]	11.9 (7.73)
Chemerin, ng/mL	199 (35.6)	198 (33.7)	197 (31.6)
Fetuin-A, µg/mL	329 (94.1)	341 (83.3)	349 (85.6) [b]
ALKP, U/L	70.8 (16.9)	72.8 (17.8)	72.1 (17.5)
ALT, U/L	28.5 (13.4)	31.5 (13.6) [b]	31.9 (13.5) [b]
AST, U/L	24.7 (7.55)	26.4 (8.13) [a]	26.7 (7.82)
MRI-assessed major fat deposits			
VAT, cm^2	145 (61.0)	152 (53.5)	157 (56.3)
VAT %	29.7 (10.0)	32.2 (8.93)	31.8 (9.71)
Intrahepatic fat, %	8.44 (8.44)	10.9 (9.59) [b]	10.2 (9.10) [a]
Retrospective intervention assignment			
MED and/or LC (vs. control), %	55.19%	58.48%	68.38% [a,b]

[a]*P*-value < 0.1 in a multinomial regression with age, sex, trial, and baseline BMI as covariates; Moderate-WL as reference (highlighted in gray: *P*-value < 0.05). WL, weight loss.
[b]*P*-value < 0.1 in a multinomial regression with age, sex, trial, and baseline BMI as covariates; WL-Resistant as reference (highlighted in gray: *P*-value < 0.05).
ALKP, Alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; HDLc, high-density lipoprotein cholesterol; HOMA IR, Homeostatic model assessment for insulin resistance; LC, low carbohydrates; LDL, low-density lipoprotein cholesterol; MED, Mediterranean; WL, weight loss.

pre-intervention omics associated with WL in kg. Elastic net models using DNA methylation, metabolomics, or proteomics as predictors did not perform well in predicting WL (see Supplementary material online, *Table S3*). In an epigenome-wide association study (by likelihood ratio test), we found 12 CpGs significantly associated with WL (FDR < 0.05) in our discovery set (DIRECT PLUS; *Figure 1A*; Supplementary material online, *Figure S4 and Table S4*). Using these CpGs in a validation set (CENTRAL) to predict WL below/above 5% in a logistic regression model yielded an AUC of 0.733 [95% CI (0.641, 0.825); *Figure 1D*]. Employing the 12 CpGs detected in the DIRECT PLUS epigenome-wide association study for WL in a cross-validated linear regression in the CENTRAL to predict WL (in kg) resulted in poor prediction ($R^2 = 0.001$, RMSE = 5.86), similar to the results of the elastic net with forced covariates ($R^2 = 0.003$, RMSE = 5.63; Supplementary material online, *Table S3*). We further examined the associations of proteomics and metabolomics with WL in our discovery set using multivariable linear models in the DIRECT PLUS (*Figure 1B and C*); No FDR < 0.05 markers were observed. Nevertheless, due to the exploratory nature of this analysis, we further used proteins and metabolites with $P < 0.1$ to predict WL above/below 5% in our validation set (CENTRAL). This yielded AUC of 0.611 [95% CI (0.534, 0.687)] and 0.609 [95% CI (0.530, 0.688)] proteomics and metabolomics, respectively (*Figure 1E and F*). Of note, serine, a metabolite found as a significant predictor in the training set, was not available in the CENTRAL data.

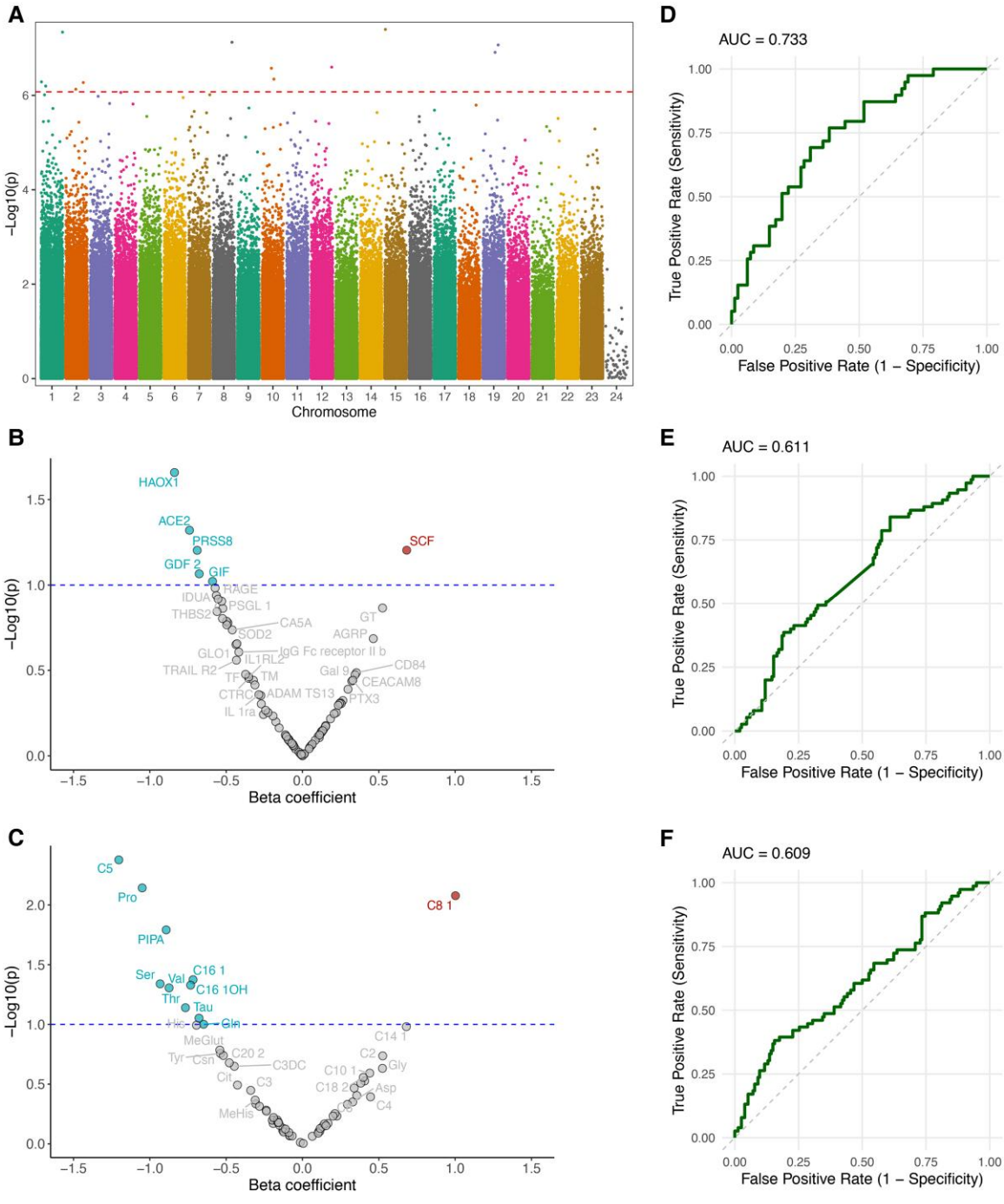


Figure 1 Wide association studies for WL. An exploratory analysis. (*A*) Discovery, DNA methylation; (*B*) Discovery, proteomics; (*C*) Discovery, metabolomics; (*D*) Prediction of WL above/below 5% by selected CpGs; (*E*) Prediction of WL above/below 5% by selected proteins; Prediction of WL above/below 5% by selected metabolites. Red dashed line indicates FDR of 0.05. Blue dashed line indicaes *P*-value of 0.1. Volcano plots: light blue dots indicates negative expression, and red dots indicate positive expression.

Using the proteins from DIRECT PLUS discovery set on the CENTRAL in a linear model without cross-validation resulted in $R^2 = 0.019$ and RMSE = 5.56, similar to the LOOCV elastic net with forced covariate (see Supplementary material online, *Table S3*), compared with a cross-validated linear model with $R^2 = 0.001$ and RMSE = 5.61. Replacing the proteins with metabolites discovered in the DIRECT PLUS, linear models using the CENTRAL data in a cross-validated vs. no validation resulted in $R^2 = 0.002$ vs. $R^2 = 0.06$.

We repeated the validation analysis using logistic regression comparing extreme categories of WL for prediction of Successful-WL vs.

Table 2 Long-term within-group changes across three weight response categories

Parameter: Baseline vs. end	WL-resistant $n = 212$		Moderate WL $n = 277$		Successful-WL $n = 272$	
	Mean	*P*-value[a,b]	Mean	*P*-value[a,b]	Mean	*P*-value[a,b]
Anthropometric and BP						
WC, cm	−0.32	0.34	−3.61	**<0.001**	−8.82	**<0.001**
WC (men only), cm	−0.62	*0.08*	−3.56	**<0.001**	−8.77	**<0.001**
WC (women only), cm	+1.37	0.21	−4.08	**0.001**	−9.38	**<0.001**
Systolic BP, mmHg	+1.19	0.14	−2.13	**0.006**	−3.89	**<0.001**
Diastolic BP, mmHg	+0.53	0.36	−0.99	*0.0504*	−2.97	**<0.001**
Blood markers						
HDLc, mg/dL	+1.16	**0.008**	+3.57	**<0.001**	7.64	**<0.001**
LDLc, mg/dL	+1.10	0.51	0.01	0.99	−0.72	0.68
Total cholesterol, mg/dL	+4.71	**0.02**	0.99	0.59	−0.96	0.61
Triglycerides, mg/dL	+6.42	*0.08*	−14.9	**<0.001**	−34.8	**<0.001**
Fasting plasma glucose, mg/dL	+2.34	**0.003**	+1.12	0.13	−1.05	0.16
HOMA IR	−0.02	0.86	−0.36	**<0.001**	−1.02	**<0.001**
Insulin, µU/mL	−0.30	0.40	−1.53	**<0.001**	−4.09	**<0.001**
CRP, mg/L	+0.23	*0.08*	−0.24	**0.04**	−0.82	**<0.001**
Leptin, ng/mL	−0.81	**0.02**	−1.82	**<0.001**	−5.15	**<0.001**
Chemerin, ng/mL	+6.28	**0.02**	−0.45	0.84	−6.54	**0.002**
Fetuin-A, µg/mL	−43.5	**<0.001**	−49.6	**<0.001**	−56.6	**<0.001**
ALKP, U/L	+0.46	0.49	−1.57	**0.018**	−2.27	**<0.001**
ALT, U/L	+2.65	**0.002**	−3.67	**<0.001**	−7.26	**<0.001**
AST, U/L	+0.46	0.42	−1.89	**0.001**	−2.79	**<0.001**
MRI-assessed major fat deposits						
VAT, cm^2[c]	−7.15	**<0.001**	−22.9	**<0.001**	−56.9	**<0.001**
Intrahepatic fat, %[c]	−0.005	0.99	−3.11	**<0.001**	−7.11	**<0.001**

[a]Paired *T*-test.
[b]Bold values denote statistical significance at the *P*-value < 0.05 level; Italic values denote statistical significance at the *P*-value < 0.1 level.
[c]CENTRAL and DIRECT PLUS only.
ALKP, Alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CRP, C-reactive protein; HDLc, high-density lipoprotein cholesterol; HOMA IR, Homeostatic model assessment for insulin resistance; LDL, low-density lipoprotein cholesterol; VAT, visceral adipose tissue; WC, waist circumference; WL, weight loss.

WL-resistant (see Supplementary material online, *Figure S4*). This slightly, but not significantly, improved the prediction by DNA methylation to an AUC of 0.791 [95% CI (0.684, 0.898)] and prediction by metabolomics AUC of 0.619 [95% CI (0.528, 0.701)]. The prediction by proteomics was not improved with an AUC of 0.604 [95% CI (0.509, 0.698)].

Long-term changes within WL categories

We examined the long-term (*Table 2*) differences pre- and post-intervention across the WL categories, as shown in *Figure 2A and B*. WL-resistant participants experienced HDLc elevation and MRI-assessed decrease of visceral and intra-hepatic fat ($P < 0.05$ for all, compared with baseline). However, there were increases in total cholesterol, chemerin, FPG, ALT, and a statistically marginal increase in triglycerides and CRP. Participants who reduced up to 5% of their initial body weight (Moderate-WL) improved the following health indicators: WC, systolic BP, HDLc, triglycerides, insulin, HOMA IR, CRP, leptin, fetuin-A, liver enzymes, abdominal fat depots areas, and liver fat. As expected, participants who lost more than 5% of their body weight (WL-Successors) showed the most improvement in health indicators, with all health indicators, excluding LDLc, total cholesterol, and FGP ($P < 0.05$ for all, baseline vs. T18). Key differences in health improvement between WL categories are summarized in Supplementary material online, *Figure S5*.

The effect of moderate WL on long-term health indicators

For individuals who lost at least 1 kg ($n = 482$, 9.54% women) sustained for the long-term, we quantified the beneficial effect of every 1 kg WL on different health biomarkers. We tested the linearity between weight change (in kg) and each outcome as the relative change in the marker (**3a** presents selected pairs). For the pairs with RESET test *P*-value > 0.05, suggesting that a linear model is sufficient to explain the relationship between the dependent and independent variable, we present beta from the linear model, representing the magnitude of change for marker per 1-unit weight change (1 kg WL, *Figure 3B*, Supplementary material online, *Table S5*). After accounting for multiple linear testing, we observed the following change per −1 kg WL: HDLc (+1.44%), triglycerides (−1.37%), insulin (−2.46%), HOMA IR (−2.71%), leptin (−2.79%), and IHF (−0.49%). A modest but significant change was observed for chemerin (−0.47%), ALT (−0.73%), systolic and diastolic BPs (−0.26% and −0.36%). We repeated this analysis by adjusting for trial and examining WL×trial interactions (see Supplementary material online, *Table S6*). The interaction was only observed for ALKP (*P* of

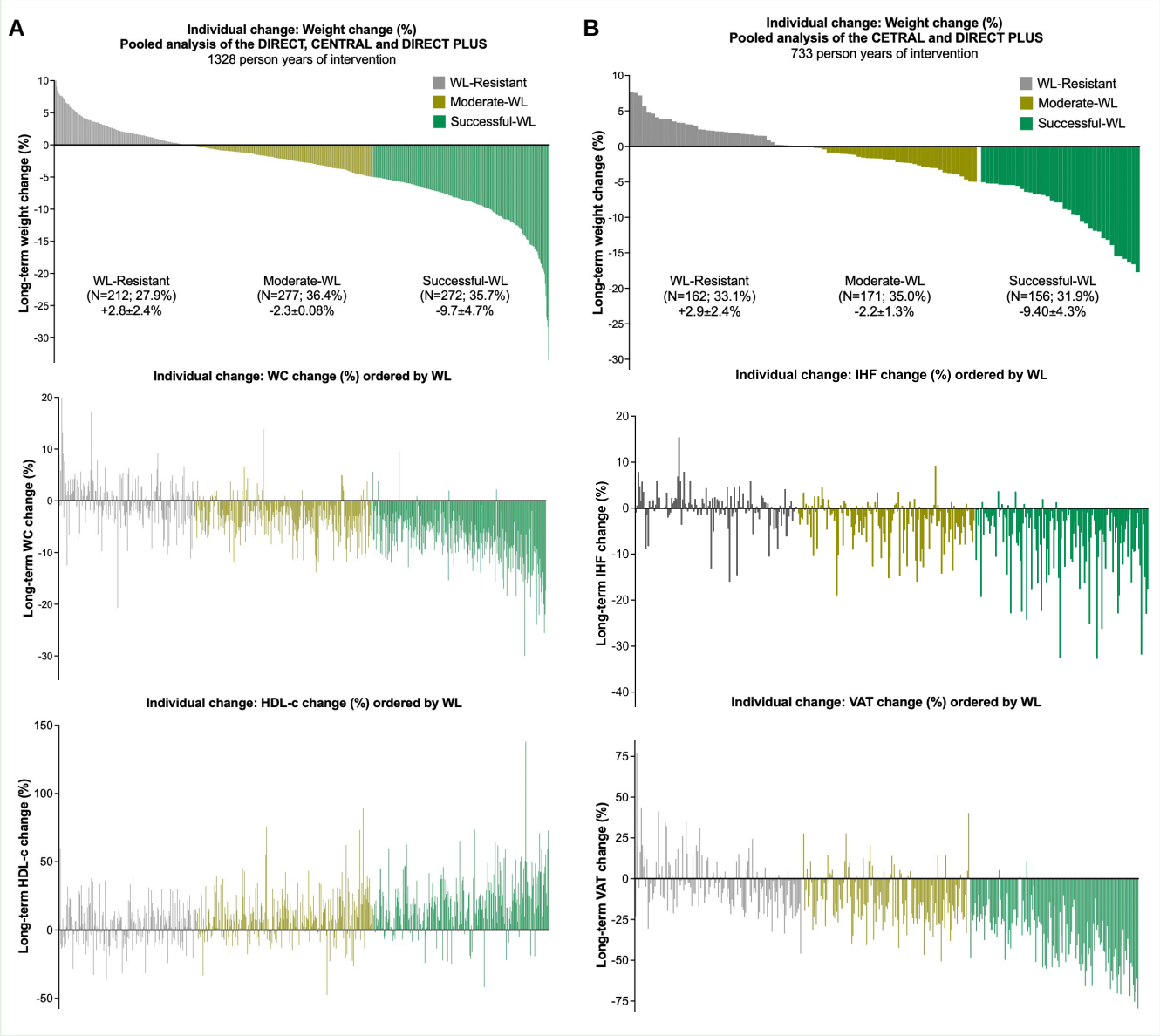


Figure 2 Individual long-term changes. (*A*) WL (in %) in all three trials ordered from top WL-Resistant to top Successful-WL, with below WC and HDLc order by the WL extent, from top WL-Resistant to top Successful-WL. (*B*) WL (in %) in CENTRAL and DIRECT PLUS ordered from top WL-Resistant to top Successful-WL, with below VAT and IHF by WL extent, from top WL-Resistant to top Successful-WL.

interaction = 0.035). When adjusted for age, sex, and trial, the following outcomes improved by WL: all glycemic markers, some blood lipids, serum chemerin, leptin, diastolic and systolic BP, and IHF (all % change; Supplementary material online, *Table S7*). We did not observe any WL×sex interactions (see Supplementary material online, *Table S8*).

For CRP and VAT, we fitted cubic spline with the following cut points (see Supplementary material online, *Figure S6*): −1 kg, −2 kg, −3 kg, −4 kg, −5 kg, −10 kg, and −15 kg. Although there were significant knots, CRP did not show any obvious pattern. For VAT, significant knots were observed with increased WL.

As a sensitivity analysis, we performed quantile regression with 10th-90th percentiles for the markers showing significant associations after accounting for multiple testing (see Supplementary material online, *Table S9*; Scatter plots of these markers are available in Supplementary material online, *Figure S7*). This analysis yielded results similar to those of linear regression.

Discussion

This study pooled patient-level data from three long-term WL-intervention trials, suggesting that while only one-third achieve long-term Successful-WL, WL-Resistant individuals may benefit from lifestyle interventions even without WL. Each 1-kg sustained intentional lifestyle-induced WL was associated with significant improvement in cardiometabolic risk and atherosclerosis and insulin resistance promoting ectopic fats. Specific omics signatures, such as DNA-methylation, were related to WL individual response. Our findings represent an

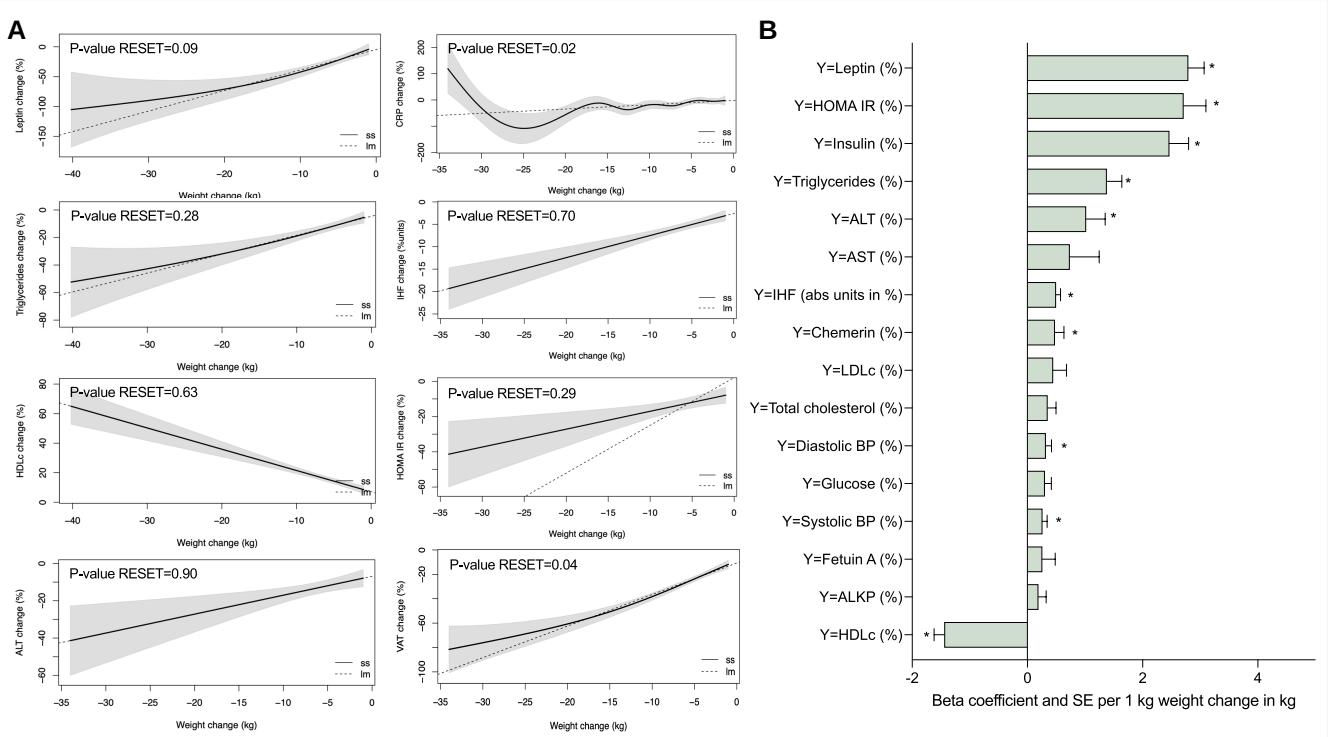


Figure 3 Linearity and the association between weight change (kg) and markers change (%). (*A*) Plots of a fitted model, smoothing spline for weight change (kg) and each marker change (%)—selected markers. *P*-value for RESET test presented for detection of mis-specified linear models. ss = smoothing spline line. lm = linear model line. (*B*) Beta coefficients for linear models. * Denotes significance of predictor while adjusting for multiple testing ($N = 16$ linear tests) at the level of *P*-value < 0.003. The analysis included individuals who lost at least 1 kg ($N = 482$).

'average predicted response' across all participants, irrespective of the specific lifestyle intervention. This aligns with our study's main goal: characterize the generalisable association between WL and cardiometabolic improvements during structured lifestyle interventions.

Our analysis has some limitations. The WL-intervention trials included in this study had different follow-up times of 18 months (CENTRAL and DIRECT PLUS) and 24 months (DIRECT), although the inclusion and exclusion criteria for all studies were similar, and the population participating in all studies was from the same workplace and geographical location. Second, we did not stratify our analyses per individual adherence or specific intervention. Nevertheless, based on our previous reports, most of the participants highly adhered to their assigned intervention for the entire intervention period, as reported by self-reports (DIRECT, CENTAL, DIRECT PLUS)[23–25] or estimated by objective measurements (DIRECT PLUS).[25] Moreover, all the intervention arms were active at the same intensity, healthy, and with no passive control groups. Third, the small number of women participating in these cohorts did not allow us to quantify the effect of 1 kg WL using subgroup analysis in women. The high proportion of men participants reflects the workplace profile, as acknowledged before.[25] This limits our ability to extrapolate our results to women. Due to a small sample size, we were underpowered to detect associations in some of the omics studies. Additionally, our elastic net models performed poorly when predicting WL using either omics. Elastic net models' lack of predictive performance may reflect potential overfitting during model training. Although some CpGs were significantly associated with the outcome in the wide association study, their effect sizes were small and insufficiently robust to generalize across cross-validation folds. Given the relatively small sample size and the high-dimensional nature of the omics data, the models may have fit to noise or spurious patterns in the training set that did not hold in the validation folds. This is a well-known risk in high-dimensional settings, even when using regularized models such as elastic net, particularly when the true signal is weak or diffuse. However, the omics sub-study is exploratory and should be used as preliminary data for future larger-scaled omics studies. A key strength of our study is using three intensive trials with high adherence. Another strength of our study lies in the rigorous and multifaceted approach used to evaluate the robustness of our findings. We conducted a series of sensitivity analyses to assess the stability of results under varying model specifications and assumptions, thereby reducing the likelihood that analytical choices drove findings. Stratified analyses by trial further allowed us to explore potential effect modification by key demographic or clinical variables, offering insights into population-specific associations and enhancing interpretability. Additionally, we performed a meta-analysis across trials, explicitly modelling between-study heterogeneity. This validated the pooled findings and ensured that any single trial did not disproportionately influence the observed differences between WL categories. We conducted sensitivity analyses using alternative modelling strategies, including replacing linear models with quantile regression and multiple multivariable models, to assess whether associations held across the outcome distribution rather than relying solely on mean effects. Additionally, we examined results across different subgroups (three WL categories and below/above 5% WL) to evaluate the consistency and potential effect modification

by key characteristics. Finally, we explored interactions between WL and both sex and cohort, allowing us to assess potential effect modification and uncover population-specific differences.

Our primary aim was to quantify sustainable WL's effect in cardiometabolic blood indicators of lipids, glycemic, liver enzymes, inflammation, and adipokines. Previous studies have assessed the beneficial effect of each 1 kg of WL on different health outcomes. A meta-analysis of 30 randomized controlled trials of diet and/or exercise intervention with follow-up of at least six months quantified the beneficial effect of WL on blood lipids in 2434 adults.[26] After 12 months, for every 1 kg of WL, triglycerides were reduced by −4.0 mg/dL, total cholesterol by −1.66 mg/dL, LDLc by −1.28 mg/dL, and HDLc increased by 0.46 mg/dL. Another meta-analysis of 43 studies with a median follow-up time of 6 months found that every 1 kg WL led to 0.83 U/L of ALT, 0.56 U/L of AST, and a 0.77% point reduction in hepatosteatosis.[27] Our current analysis confirms the effect of 1 kg WL for 18− or 24-month well-controlled lifestyle intervention on blood lipids and liver enzymes. It further suggests information on improving other blood biomarkers, including glycemic indicators and abdominal and intrahepatic fats.

Our secondary aim was to profile different categories of WL: successful, moderate, and no WL groups. A previous study of unsuccessful responders to a low-energy diet[16] reported that unsuccessful responders had higher resting heart rates, self-reported perceived stress, higher dietary restraint levels, and lower disinhibition levels than successful responders. In our current study, WL-Resistant had a lower percentage of individuals assigned to Mediterranean and/or Low carbohydrate diets (vs. control), were more likely to be women, younger, with lower baseline weight and WC, liver enzymes, and less IHF. This group also tended to have lower VAT% and fetuin-A and higher leptin. As shown in previous studies, higher weight reductions led to more remarkable improvement in cardiometabolic health indicators,[11–14] including ectopic fat depots. Yet, in our study, individuals who did not lose weight by the end of 18 and 24 months of the intervention improved their health profile, with significant reductions in leptin, abdominal adiposity, WC (in men), and an increase in HDLc, though their adverse changes in total cholesterol, FPG, and ALT levels.

In a previous epigenetic analysis of the CENTRAL trial, we observed that WL responders (top 10% of WL in the cohort) had differential DNA methylation at specific genomic regions, compared with non-responders (bottom 10% of WL in the cohort).[28] Our current results highlighting selected CpGs as predictors for WL (kg) are exploratory and should be interpreted with caution. The previous and current findings raise the possibility that successful or unsuccessful WL may be pre-identified based on various markers, including biological molecules.

The long-term sustainability of lifestyle-induced changes in cardiometabolic health beyond the trial period was demonstrated in several studies that performed follow-up on individuals who enrolled in intervention studies. The 4-year follow-up of the 2-year DIRECT trial showed favourable post-intervention effects on blood lipids, particularly among participants receiving the Mediterranean and low-carbohydrate diets, despite a partial regain of weight.[29] A five-year follow-up of a randomized WL trial on a digital health behaviour change support system (HBCSS) showed no differences in maintaining reduced weight between the intervention groups (a web-based HBCSS utilising persuasive systems design and cognitive behavioural therapy methods).[30] However, individuals in the HBCSS group had a decrease in the need for antihypertensives at the 5-year checkpoint compared with the other groups. In the Look AHEAD lifestyle intervention trial among overweight/obese individuals with type 2 diabetes, larger WL during the intervention period produced greater improvements in glycemic markers, blood lipids, and systolic BP at years 1 and 4.[31] Despite maintaining WL, HbA1c levels worsened between years 1 and 4 and remained below baseline only in those with large WL. Importantly, individuals who had large initial WL but full regain of weight had greater improvements in HbA1c levels at year 4 than those with smaller or no initial WL. These findings suggest that the magnitude of initial WL may have lasting metabolic benefits, even without sustained weight reduction.

Lifestyle interventions are the backbone of cardiovascular prevention. Obesity is a chronic disease, largely driven by long-term lifestyle choices, and is now increasingly recognized as a modifiable risk factor for cardiovascular disease.[32] Given that lifestyle-induced WL is often modest yet frequently accompanied by meaningful cardiometabolic benefits, the current study sought to quantify and characterize the expected improvements in cardiometabolic health parameters per unit of WL, independent of the intervention method. We believe our findings hold significant clinical relevance. In routine practice, healthcare providers are often asked to advise patients on the expected benefits of lifestyle interventions. While such projections are well established for certain pharmacologic therapies, the anticipated cardiometabolic effects of lifestyle-induced WL remain less clearly defined, particularly those not tied to a specific dietary regimen, remain less clearly defined.[33] Our study addresses this important gap by providing objective, evidence-based estimates that can support clinical decision-making and enhance patient counselling. As the management of obesity gains increasing prominence in cardiovascular prevention, these findings underscore the critical value of adopting a healthy lifestyle and the measurable benefits it can yield.

Future perspective and conclusions

Cumulative exposure to unfavourable cardiometabolic status is linked to higher risks of type 2 diabetes, atherosclerosis progression, heart failure, and mortality[34–36]. Cardiometabolic prevention is now at the forefront of preventive cardiology efforts, with strong evidence emphasising the importance of diagnosing and treating obesity.[37–39] However, with the growing reliance on pharmaceutical and surgical interventions, the critical role of lifestyle management in cardiometabolic health is often overlooked. Additionally, dedicated studies focused on women are necessary to better characterize the relationship between lifestyle-induced WL and cardiometabolic health in this understudied population. Our study offers new insights into the cardiometabolic response to WL in individuals with obesity, highlighting the crucial, WL-independent benefits of maintaining a healthy lifestyle for reducing cardiovascular risk. Our results suggest the benefits of switching to healthier lifestyles, even for those who experience no long-term WL.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Author contributions

IShai was the principal investigator of the clinical trials. I.Shai, M.J.S., D.D.W., P.K., M.B., N.K., M.S., U.C., and B.I. obtained funding. A.Y.M., G.T., H.Z., E.R., Y.G., and D.S. coordinated the clinical trials and collected the raw data. A.Y.M., G.T., H.Z., YG, A.R., M.B., U.C., M.K., P.K., D.D.W., L.Q., L.L., F.B.H., M.J.S., and I.Shai contributed to the design of the current study. A.Y.M., G.T., H.Z., E.R., and Y.G. set up the database and entered the data. A.Y.M., G.T., H.Z., E.R., Y.G., D.S., I.Shelef, and I.Shai screened and enrolled the participants, obtained informed consent, and provided patient care and documentation of study data. I.Shelef supervised the radiology scans. M.K. and P.K. isolated DNA samples and performed the DNA methylation analysis. U.C. and B.I. performed laboratory and metabolomic analysis. N.K. performed the proteomic analysis. A.Y.M., G.T., and I.Shai verified the underlying data, analyzed all findings, and take responsibility for the integrity and accuracy of the data analysis. A.Y.M., G.T., and I.Shai wrote the manuscript. All authors contributed to data interpretation, revised, and approved the manuscript. A.Y.M., G.T., and I.Shai take final responsibility for the decision to submit the study for publication.

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Conflict of interest: None declared.

Data availability

Upon request from the corresponding author, deidentified participants' data will be available to others after publication, as will the study protocol and the statistical analysis plan. DNA methylation raw data are available in the ArrayExpress repository: tables https://www.ebi.ac.uk/biostudies/arrayexpress/studies/E-MTAB-8956 and https://www.ebi.ac.uk/biostudies/arrayexpress/studies/E-MTAB-12527.

Disclaimer

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