The American Journal of Clinical Nutrition 117 (2023) 599–606

The American Journal of CLINICAL NUTRITION

journal homepage: www.journals.elsevier.com/the-american-journal-of-clinical-nutrition

Original Research Article

Evidence for the carbohydrate–insulin model in a reanalysis of the Diet Intervention Examining The Factors Interacting with Treatment Success (DIETFITS) trial

Adrian Soto-Mota [1,2], Mark A. Pereira [3,†], Cara B. Ebbeling [4,5], Lucia Aronica [6], David S. Ludwig [4,5,*,†]

[1] *Metabolic Diseases Research Unit, National Institute for Medical Sciences and Nutrition Salvador Zubiran, Tlalpan, Mexico City, Mexico;* [2] *Monterrey Institute of Technology and Higher Education, Xochimilco, Mexico City, Mexico;* [3] *Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, MN, USA;* [4] *New Balance Foundation Obesity Prevention Center, Boston Children's Hospital, Boston, MA, USA;* [5] *Department of Pediatrics, Harvard Medical School, Boston, MA, USA;* [6] *Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, CA, USA*

A B S T R A C T

Background: The Diet Intervention Examining The Factors Interacting with Treatment Success (DIETFITS) trial demonstrated that meaningful weight loss can be achieved with either a "healthy low-carbohydrate diet" (LCD) or "healthy low-fat diet" (LFD). However, because both diets substantially decreased glycemic load (GL), the dietary factors mediating weight loss remain unclear.

Objectives: We aimed to explore the contribution of macronutrients and GL to weight loss in DIETFITS and examine a hypothesized relationship between GL and insulin secretion.

Design: This study is a secondary data analysis of the DIETFITS trial, in which participants with overweight or obesity (aged 18–50 y) were randomized to a 12-mo LCD ($N = 304$) or LFD ($N = 305$).

Results: Measures related to carbohydrate intake (total amount, glycemic index, added sugar, and fiber) showed strong associations with weight loss at 3-, 6-, and 12-mo time points in the full cohort, whereas those related to total fat intake showed weak to no associations. A biomarker of carbohydrate (triglyceride/HDL cholesterol ratio) predicted weight loss at all time points (3-mo: β [kg/biomarker z-score change] $= 1.1$, $P = 3.5 \times 10^{-9}$; 6-mo: $\beta = 1.7$, $P = 1.1 \times 10^{-9}$; and 12-mo: $\beta = 2.6$, $P = 1.5 \times 10^{-15}$), whereas that of fat (low-density lipoprotein cholesterol + HDL cholesterol) did not (all time points: $P =$ NS). In a mediation model, GL explained most of the observed effect of total calorie intake on weight change. Dividing the cohort into quintiles of baseline insulin secretion and GL reduction revealed evidence of effect modification for weight loss, with $P = 0.0009$ at 3 mo, $P = 0.01$ at 6 mo, and $P = 0.07$ at 12 mo.

Conclusions: As predicted by the carbohydrate–insulin model of obesity, weight loss in both diet groups of DIETFITS seems to have been driven by the reduction of GL more so than dietary fat or calories, an effect that may be most pronounced among those with high insulin secretion. These findings should be interpreted cautiously in view of the exploratory nature of this study.

Trial Registration: ClinicalTrials.gov (NCT01826591).

Keywords: obesity, low-carbohydrate diet, macronutrients, weight loss trial, insulin, reanalysis

Introduction

Measures of adiposity continue to increase worldwide [1, 2] despite a public health prevention campaign focused on calorie balance that was initiated a century ago [3], stimulating development of new pathophysiological explanations of obesity. In the carbohydrate–insulin model (CIM) [4, 5], hormonal responses to ingestion of rapidly digestible (high glycemic load, GL) starches and added sugars shift substrate partitioning toward fat deposition, thus reducing the availability of metabolic fuels to metabolically active and energy sensing

Abbreviations: CIM, carbohydrate–insulin model; DIETFITS, Diet Intervention Examining The Factors Interacting with Treatment Success (trial); GI, glycemic index; GL, glycemic load; HDLc, high-density lipoprotein cholesterol; insulin-30, insulin 30 min into an oral glucose tolerance test; LCD, low-carbohydrate diet; LDLc, low-density lipoprotein cholesterol; LFD, low-fat diet; TG, triglyceride; LASSO, least absolute shrinkage and selection operator.

* Corresponding author.
E-mail address: david.ludwig@childrens.harvard.edu (D.S. Ludwig).

† Mark Pereira and David Ludwig are associate editors of *the American Journal of Clinical Nutrition* and were not involved in the editorial evaluation of this manuscript.

https://doi.org/10.1016/j.ajcnut.2022.12.014
Received 16 September 2022; Received in revised form 21 December 2022; Accepted 23 December 2022
Available online 6 January 2023
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tissue (skeletal muscle, liver, and brain). The body compensates for the energy sequestered into the adipose tissue through hunger, leading to increased energy intake and reduced energy expenditure under some conditions. Thus, in the CIM, the chronic positive energy balance that de facto accompanies weight gain according to the first law of thermodynamics results from, rather than causes, obesity.

Evidence pertaining to the CIM – derived from laboratory animal studies, short-term feeding trials, and observational research – has been recently reviewed and debated [4–9]. These data provide at least some support for 2 predictions of the CIM: *1*) a low- vs. high-GL diet will produce greater reduction in body weight and *2*) individuals with high endogenous insulin secretion will be most susceptible to the adverse metabolic effects of a high-GL diet, consequently benefiting most from GL reduction. However, few large scale, longer-term trials have specifically tested these predictions.

To address this knowledge gap, we tested the 2 CIM hypotheses specified above using data from the Diet Intervention Examining The Factors Interacting with Treatment Success (DIETFITS) trial [10], in which 609 participants were randomized to a "healthy low-carbohydrate diet" (LCD) or "healthy low-fat diet" (LFD) for 12 mo. Of note, both groups received similar instructions to minimize the intake of added sugars, refined flours, and trans fats; increase vegetable intake; and focus on minimally processed, nutrient-dense whole foods. As presented in the original trial results and subsequent analyses [10, 11], weight loss was greater in the LCD vs. LFD group at 3 and 6 mo, but not at 12 mo, and insulin secretion did not modify weight loss response to the diets. Although the findings of DIETFITS have been interpreted as opposing the CIM [7], the reduction in mean glycemic index (GI) and GL in both groups [10] complicates causal inference. The aim of this study was to explore the contribution of GL to weight loss and its interaction with high insulin secretion in DIETFITS, thereby examining the macronutrient intake based on self-reported data and objective biomarkers.

Methods

Original study design

The original DIETFITS trial was a single-site parallel randomized trial of 609 overweight or obese participants, conducted from January 2013 to May 2016, designed to test whether baseline genetic or metabolic factors would explain any of the differential weight loss for participants assigned to LFD vs. LCD [10]. The detailed study protocol has been reported elsewhere [12]. Briefly, participants were generally healthy adults (diabetes but not prediabetes was exclusionary) aged 18–50 y, with BMI of 28–40 kg/m^2. The weight loss intervention involved a 12-mo protocol of 22 small-group educational sessions focused on 3 central components for both LCD and LFD. During the first 8 wk of the Limbo phase, participants were instructed to cut back on fat or carbohydrate intake progressively until they achieved a daily intake of no more than 20 g of carbohydrate (LCD) or fat (LFD). During the titrate phase, participants were instructed to increase their fat or carbohydrate intake slowly, by 5–15 g increments each week, until they achieved a comfortable maintenance level that they could feasibly maintain for the 12-mo intervention period. In the high-quality intervention component, both groups received similar instructions to focus on home-cooked whole foods; maximize fresh, seasonal vegetables, and lean, grass-fed meats; and eliminate or minimize processed foods with added sugar, refined white flour, and trans fats. Dietary composition and adherence were assessed using the Nutrition Data System for Research at 3, 6, and 12 mo by 3 unannounced 24-h multiple-pass recall interviews (2 weekdays, 1 weekend day) [13]. The study was registered on Clinical Trials.gov with the identifier NCT01826591.

Data and variable definitions

Data used for the reanalyses were obtained from the public repository of the original DIETFITS trial at Open Science Framework (https://osf.io/ztysq). Weight loss was defined as both the absolute difference in kilograms against baseline and the percent change from baseline (available in the analysis code). As macronutrient data were available in grams, the energy content was calculated using conversion factors for energy density (carbohydrate: 4 kcal/g; protein: 4 kcal/g; and fat: 9 kcal/g). GL values were used as reported in the original dataset. We calculated and used the ratio of triglycerides to high-density lipoprotein cholesterol (TG/HDLc) as a biomarker of carbohydrate reduction and HDLc and low-density lipoprotein cholesterol (LDLc) (HDLc + LDLc) as a biomarker of fat reduction [14–19]. Blood concentration of insulin 30 min after a standard 75-g oral glucose challenge (insulin-30) was used as a proxy measure of insulin secretion, as previously described and validated [8, 20, 21].

Statistical analyses

Analyses were performed for the main assessment time points (3, 6, and 12 mo) with R version 4.0.3. Commented and indexed R code (R Studio version: 1.3.1093) was used for all analyses, with packages updated to their latest version as of November 10, 2022. As per the available code, a set seed number of 4321 was used in analyses involving random sampling and the reported results correspond to those random simulations with this seed number. The code is available at: (https://github.com/AdrianSotoM/DIETFITS_reanalysis/blob/main/paper_code.R).

To evaluate the impact of participant attrition on the primary outcome, we imputed data using the R function *mice::mice* with the least absolute shrinkage and selection operator (LASSO) with linear regression and predictive mean matching and 20 imputed datasets [22]. Consistent with the recommendation to use 5–10 donor variables [23], we chose the following in view of their potential relationship with weight: baseline weight, diet group, gender, GL, total calorie intake, BMI, and waist circumference. A monotonic visit sequence was implemented within the *mice::mice* settings because of the mostly monotonic missing data pattern (~95%). Convergence was evaluated visually for all models using *plot(.mids)*, and percentile distributions were used to evaluate the plausibility of the imputed values using *quantile(probs)*. Weight change was calculated for missing data at every time point with the imputed weight value. All mixed models used *lmer::lmer* and tested the interaction between diet and the time point with baseline weight as a covariate and a random effect for participants. Pooled estimated means and *P* values were obtained using *emmeans::emmeans* and *emmeans::pairs* for between-group comparisons, which employ the Kenward–Roger method for calculating the degrees of freedom.

To construct spider graphs, linear models for weight loss as the dependent variable (with sex, baseline BMI, baseline energy intake, and diet group as covariates) were compared using web plots with the function *performance::compare_performance* [24] and default settings. Metrics for the spider graphs included Akaike information criterion weight (AICwt), Bayesian information criterion weight (BICwt), adjusted R^2 (to the number of predictors in the model), root mean square error, and Sigma (residual standard deviation of the errors). Correlation scatterplots were created with the function *ggstatsplot::ggscatterstats* and β values were produced with a univariate linear model for weight loss. Z values were used to standardize the x-axis between comparisons.

To assess mediation, we compared a multivariable linear model for weight loss as the dependent variable and calorie intake as the

TABLE 1
Daily dietary intakes by time from the study of Gardner et al. [10].

Time point	LFD		LCD	
Total energy intake (kcal)				
Baseline	$n = 304$	2148 ± 39	$n = 304$	2223 ± 38
3 mo	$n = 274$	1515 ± 28	$n = 275$	1581 ± 29
6 mo	$n = 240$	1624 ± 37	$n = 251$	1621 ± 33
12 mo	$n = 225$	1716 ± 35	$n = 224$	1697 ± 32
Total carbohydrate (g)				
Baseline	$n = 304$	242 ± 5	$n = 304$	247 ± 5
3 mo	$n = 274$	205 ± 4	$n = 275$	97 ± 3
6 mo	$n = 240$	211 ± 5	$n = 251$	113 ± 4
12 mo	$n = 225$	213 ± 5	$n = 224$	132 ± 4
Added sugar (g)				
Baseline	$n = 304$	49 ± 2	$n = 304$	52 ± 2
3 mo	$n = 274$	29 ± 1	$n = 275$	16 ± 1
6 mo	$n = 240$	32 ± 2	$n = 251$	19 ± 1
12 mo	$n = 225$	33 ± 2	$n = 224$	23 ± 2
Glycemic index (% glucose standard)				
Baseline	$n = 304$	58 ± 0.3	$n = 304$	58 ± 0.3
3 mo	$n = 274$	56 ± 0.3	$n = 275$	50 ± 0.4
6 mo	$n = 240$	56 ± 0.4	$n = 251$	51 ± 0.5
12 mo		56 ± 0.4	$n = 224$	53 ± 0.5
Glycemic load (g, % glucose standard)				
Baseline	$n = 304$	128 ± 3	$n = 304$	132 ± 3
3 mo	$n = 274$	102 ± 2	$n = 275$	43 ± 2
6 mo	$n = 240$	107 ± 3	$n = 251$	52 ± 3
12 mo	$n = 225$	108 ± 3	$n = 224$	63 ± 3
Total fat (g)				
Baseline	$n = 304$	87 ± 2	$n = 304$	93 ± 2
3 mo	$n = 274$	42 ± 1	$n = 275$	89 ± 2
6 mo	$n = 240$	50 ± 2	$n = 251$	87 ± 2
12 mo	$n = 225$	58 ± 2	$n = 224$	86 ± 2
Saturated fat (g)				
Baseline	$n = 304$	29 ± 0.7	$n = 304$	30 ± 0.7
3 mo	$n = 274$	13 ± 0.4	$n = 275$	29 ± 0.7
6 mo	$n = 240$	15 ± 0.7	$n = 251$	28 ± 0.7
12 mo	$n = 225$	18 ± 0.6	$n = 224$	28 ± 0.8
Protein (g)				
Baseline	$n = 304$	92 ± 2	$n = 304$	93 ± 2
3 mo	$n = 274$	80 ± 2	$n = 275$	97 ± 2
6 mo	$n = 240$	82 ± 2	$n = 251$	94 ± 2
12 mo	$n = 225$	85 ± 2	$n = 224$	93 ± 2
Fiber (g)				
Baseline	$n = 304$	22 ± 0.6	$n = 304$	22 ± 0.5
3 mo	$n = 274$	24 ± 0.7	$n = 275$	17 ± 0.8
6 mo	$n = 240$	24 ± 0.7	$n = 251$	17 ± 0.5
12 mo	$n = 225$	23 ± 0.6	$n = 224$	19 ± 0.5

Data expressed as mean ± SD.
LCD, low-carbohydrate diet; LFD, low-fat diet.

independent variable with a similar model that included GL reduction. Additionally, a structural equation model was developed [25]. Confidence intervals for the proportional mediated effect were calculated using the boot command in the function *mediation::mediate* with a quasi-Bayesian method as the default parameter [26].

To explore whether insulin secretion could modify the effect of reducing GL on body weight, a heatmap was created using *ggplot2* with *geom_tile* for the average weight loss in each quintile intersection between these 2 variables. We categorized GL reduction and insulin-30 into quintiles because the reduction in GL observed in both diet groups may mask effect modification analyzed with fewer categories. Evidence for the effect modification was evaluated by testing in a linear model a Boolean interaction variable defined as true if the case belonged to the highest quintile for both variables.

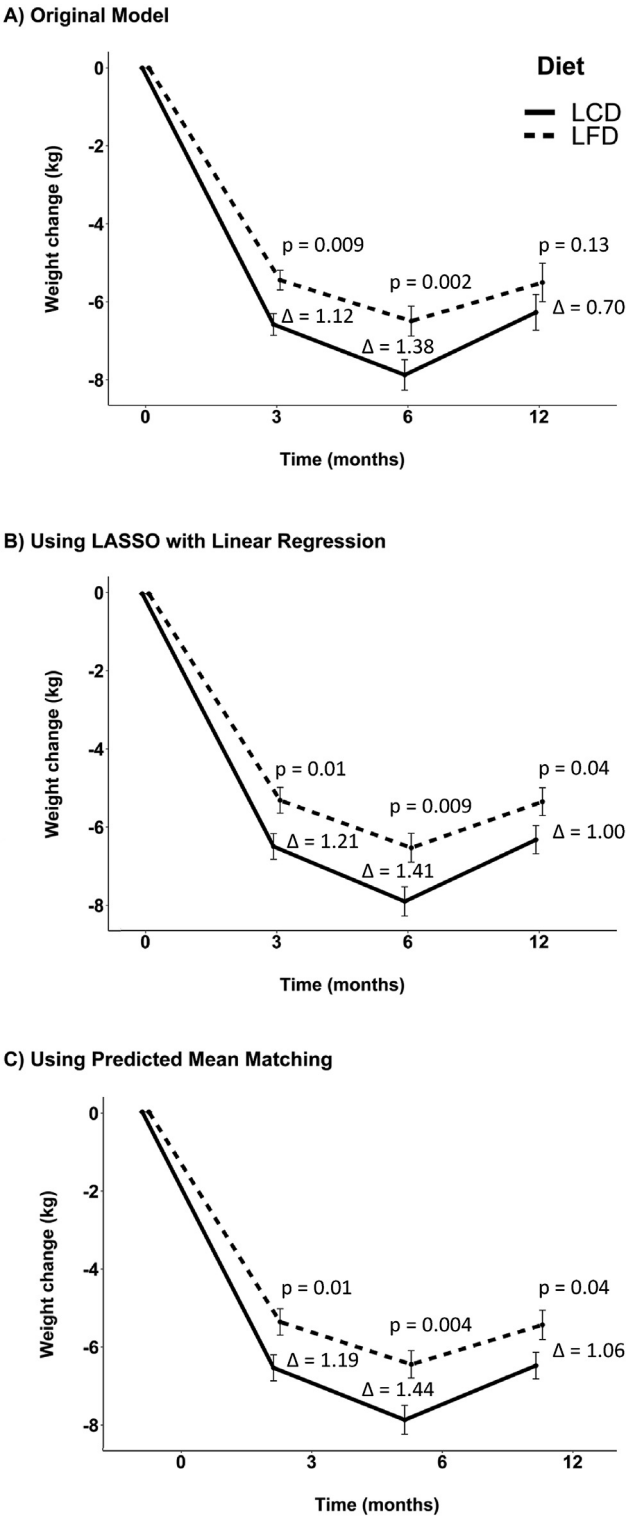

FIGURE 1. Primary outcome of the trial. (A) With the original analytic approach, the diet groups differed significantly at 3 and 6 mo, but not at 12 mo (sample sizes [LCD vs. LFD]: 3 mo, 275 vs. 274; 6 mo, 251 vs. 240; and 12 mo, 224 vs. 225). (B) Using LASSO with linear regression and (C) using predictive mean matching to impute missing data, the difference at 12 mo strengthened ($n = 304$ vs. 305). These imputations used a change model adjusted for baseline weight (see Methods). Δ indicates the weight difference between groups. LCD, low-carbohydrate diet; LFD, low-fat diet; LASSO, least absolute shrinkage and selection operator.

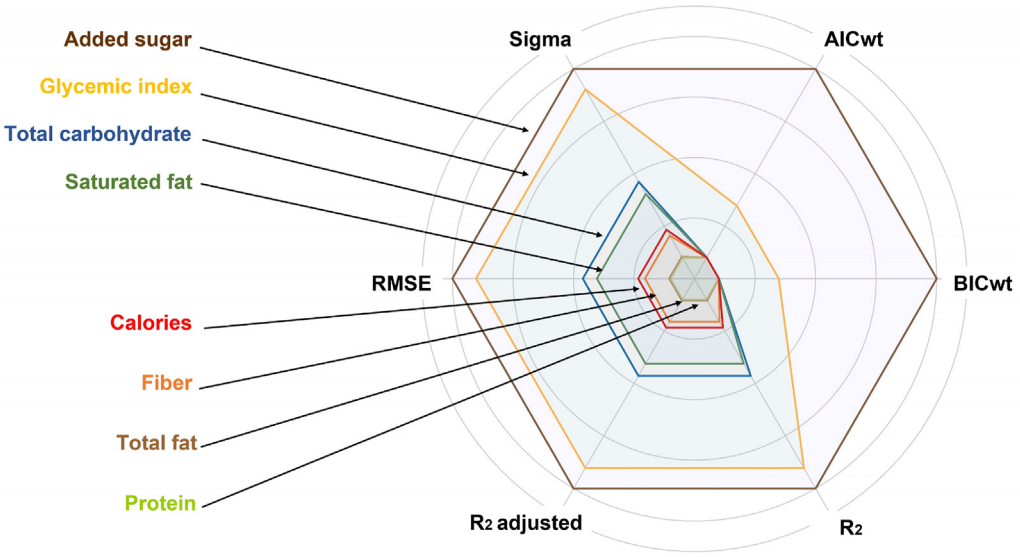

FIGURE 2. Spider graph of dietary factors and weight change at 3 mo (n = 522). Adjusted R^2 (to the number of predictors in the model); AICwt, BICwt, RMSE, and Sigma (residual standard deviation of the errors). Larger areas indicate better predictive performance in the full cohort. Macronutrients expressed in kcal (to facilitate direct comparisons), fiber in g, and GI in percentage (glucose standard). AICwt, Akaike information criterion weight; BICwt, Bayesian information criterion weight; RMSE, root mean square error.

Sample size

Due to the exploratory, post-hoc nature of this study, no outcome-based sample size was established a priori. However, the available sample size was sufficient to detect f^2 differences as small as 0.05, with $\alpha = 0.05$ and a statistical power of 0.8 in linear multiple regressions with as many as 5 predictors and R^2 as low as 0.1. Statistical power and sample size assessments were performed using G*Power version 3.1.9.4 (open access software by the University of Dusseldorf) [27]. One participant was excluded because of improbable lipid data.

Results

Table 1 provides descriptive data on change in dietary intakes at all 3 time points. The greatest differentiation among groups for GL, total carbohydrate, and total fat was observed at 3 mo, with diminishing magnitudes of difference thereafter.

Imputation of the primary outcome

Figure 1 depicts the primary outcome of the original trial. With the original analytic approach (Figure 1A), weight loss was significantly greater in the LCD vs. LFD at 3 and 6 mo, but not at 12 mo, as previously reported [10, 11]. With imputation for missing data in a change model adjusted for baseline (Figure 1B, C), the difference between diet groups strengthened at 12 mo.

Dietary predictors of weight loss

As shown in spider graphs (Figure 2, Supplemental Figures 1 and 6), measures related to carbohydrate intake performed better than those

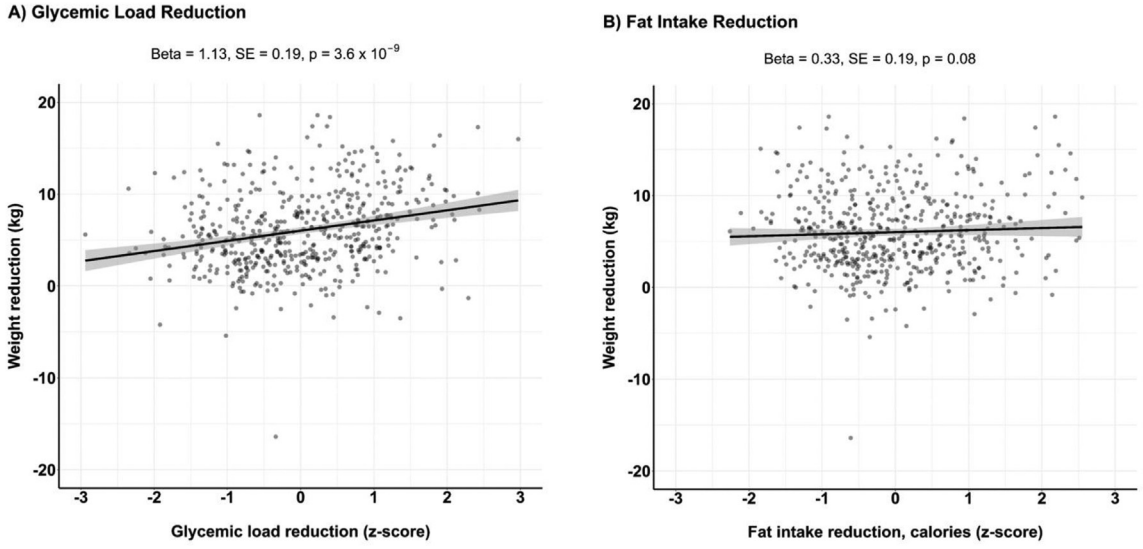

FIGURE 3. Correlation between reduction in glycemic load (A) or dietary fat (B) and weight change at 3 mo in the full cohort (n = 522). Positive values indicate the magnitude of weight loss.

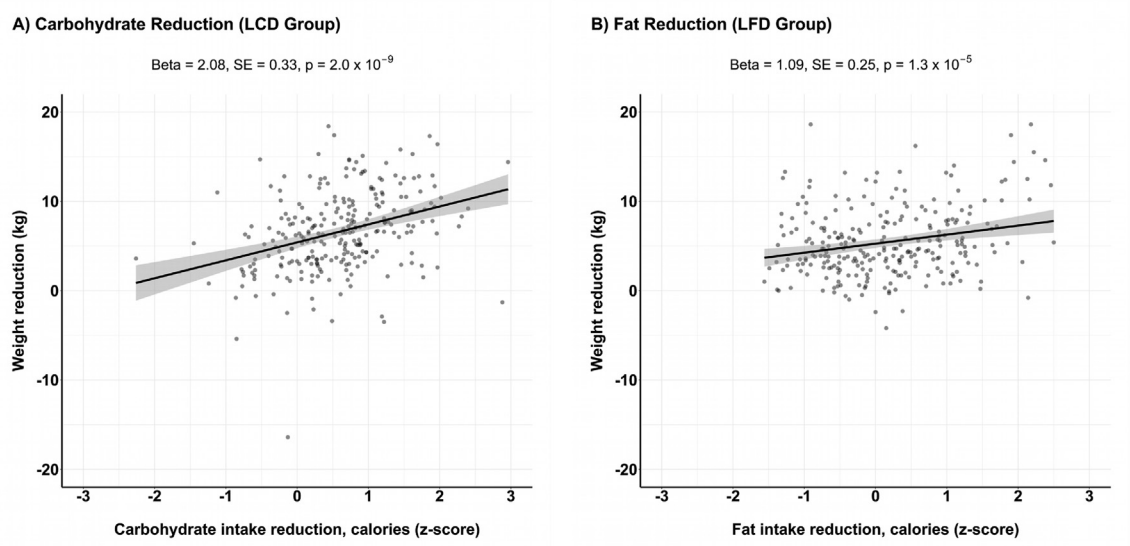

FIGURE 4. Correlation between adherence measures and weight change at 3 mo by diet group. (A) Carbohydrate reduction in the LCD group ($n = 259$) and (B) dietary fat reduction in the LFD group ($n = 263$). Positive values indicate the magnitude of weight loss. LCD, low-carbohydrate diet; LFD, low-fat diet.

related to total energy intake in the full cohort, consistent with a dominant effect of GL. GI and added sugar were consistently among the top 3 positions. Total fat intake was among the weakest measures at all time points. Similarly, reduction in GL strongly predicted the weight change (3 mo: $\beta = 1.1$, $P = 3.6 \times 10^{-9}$; 6 mo: $\beta = 1.0$, $P = 0.0003$; and 12 mo: $\beta = 0.9$, $P = 0.008$), whereas the change in total fat intake was not significantly associated with weight change at any time point (Figure 3, Supplemental Figures 2 and 7).

Reported adherence and biomarkers of dietary intake

Considering diet groups separately (Figure 4, Supplemental Figures 3 and 8), weight change was associated with the change in carbohydrate intake in the LCD group and change in fat intake in the LFD group. To examine whether these reported adherence measures (i.e., involving main recommendations specific to each diet group) mediated weight loss, we employed TG/HDLc ratio as a biomarker of carbohydrate restriction and LDLc + HDLc as a biomarker of fat restriction [14–19] (Figure 5, Supplemental Figures 4 and 9). Among the full cohort, the TG/HDLc ratio strongly predicted weight loss at 3 mo ($\beta = 1.1$, $P = 3.5 \times 10^{-9}$), 6 mo ($\beta = 1.7$, $P = 1.1 \times 10^{-9}$), and 12 mo ($\beta = 2.6$, $P = 1.5 \times 10^{-15}$), whereas LDLc+HDLc showed no significant associations at any time point, again supporting a causal role of GL reduction, more so than fat reduction, in weight loss.

Effect mediation by glycemic load

As shown in Table 2 and Supplemental Tables 1 and 2, the effect of caloric reduction on weight loss is almost entirely mediated by GL reduction. When GL reduction was added to the model, the effect of energy intake on weight loss was markedly attenuated and no longer statistically significant. The lower 95% CI for the proportion of the

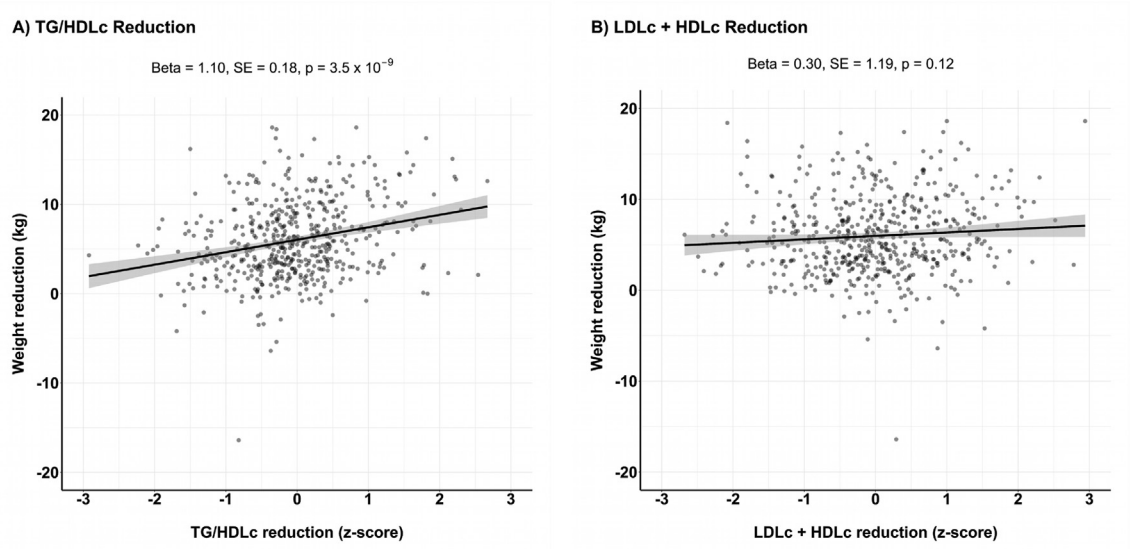

FIGURE 5. Correlation between dietary biomarkers and weight change at 3 mo in the full cohort ($n = 531$). (A) Change in TG/HDLc ratio (biomarker of carbohydrate reduction and (B) change in LDLc + HDLc (biomarker of dietary fat reduction). Positive values indicate the magnitude of weight loss. HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; TG, triglyceride.

TABLE 2
Effect mediation analyses for weight change at 3 mo ($n = 522$).

		Estimate	Std. error	T value	P
M1	Intercept	5.97	0.33	18.06	$< 2 \times 10^{-16}$
	Calorie reduction	−0.001	0.0003	−3.33	0.0009
	Diet group	−1.05	0.37	−2.81	0.005
M2	Intercept	4.63	0.46	9.99	$< 2 \times 10^{-16}$
	GL reduction	−0.02	0.006	−4.06	5.71×10^{-5}
	Calorie reduction	0.0001	0.0004	0.26	0.80
	Diet group	0.38	0.51	0.75	0.45
Quasi-Bayesian 95% CIs ($n = 522$ over 100 simulations)					
		Estimate	Low 95% CI	Up 95% Cl	P
Proportion mediated		97%	93%	100%	$< 2 \times 10^{-16}$

Structural equation model for estimating the proportion mediated by glycemic load (GL) reduction. Estimates of the mediated proportion of the effect of glycemic load >100% are reported as 100%. For simulations, the seed value was set at 4321.

effect mediated by GL reduction yielded a lower limit of 93% at 3 mo, 92% at 6 mo, and 83% at 12 mo.

Effect modification by insulin secretion

Participants in the highest quintile of both insulin-30 and GL reduction lost more weight than those in any of the other 24 quantiles for all time points (Figure 6, Supplemental Figures 5 and 10). The P value for this interaction was 0.0009 at 3 mo, 0.01 at 6 mo, and 0.07 at 12 mo (without imputation for missing data). The statistical strength of the findings was weaker when dividing the cohort into quartiles of insulin-30 and GL reduction: $P = 0.004$, 0.13, and 0.17, respectively.

Discussion

The original DIETFITS findings show that, with attention to a healthful eating pattern including reduction of processed carbohydrates, meaningful weight loss can be achieved with diets varying substantially in macronutrients [10]. However, the nature of the specific dietary changes mediating weight loss remains an issue of major scientific and public health importance.

To address this issue, we first reanalyzed the primary outcome using imputation for missing data and found that the weight change difference between the LCD and LFD groups strengthened at 12 mo. This result raises the possibility that the lack of significance in the original report [10] may involve some combination of loss of power with increasing dropout rate and convergence of diets between groups over time (Table 1).

For this reason, we examined the predictors of weight loss response in the full cohort using dietary factors obtained from the same assessment methodology (i.e., 24-h multiple-pass recall interviews). GI, added sugar, and total carbohydrate performed well, whereas dietary fat performed poorly. Furthermore, GL reduction strongly predicted weight change at all time points, whereas dietary fat reduction was not significantly associated at any time point. Although the change in both carbohydrate and fat predicted response within the LCD and LFD groups, respectively, these relations may reflect the adherence to main group-specific intervention messages, rather than mediating influences. We also explored objective biomarkers of dietary change and found that the TG/HDLc ratio (which decreases with carbohydrate reduction) predicted weight loss, but LDLc + HDLc (which decreases with fat reduction) [14–19] did not. In view of the strong focus on

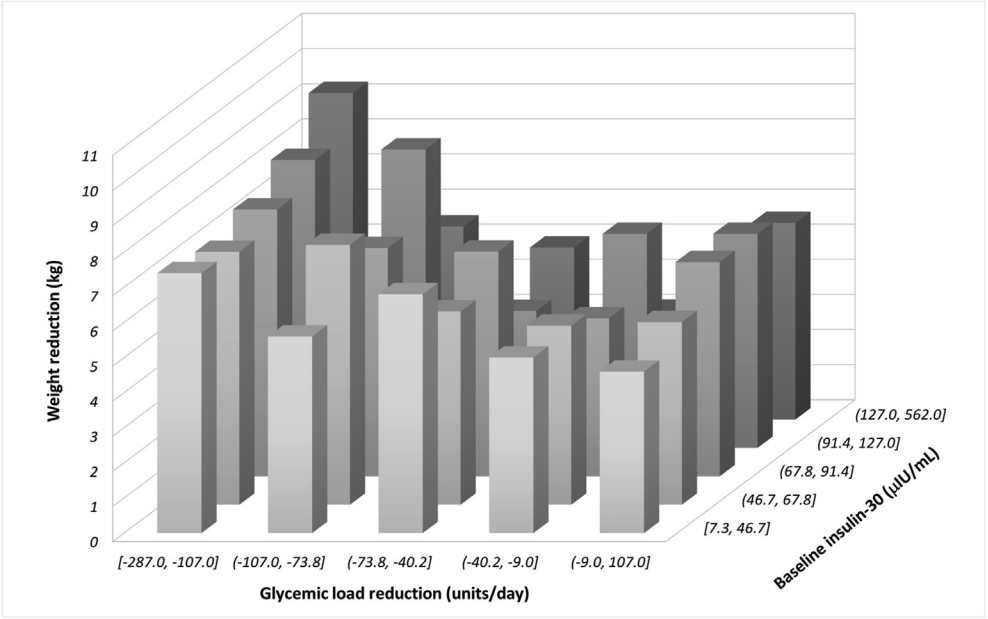

FIGURE 6. Interaction (effect modification) of baseline insulin secretion and glycemic load reduction on weight change at 3 mo ($n = 530$). Both variables are categorized into quintiles of change and analyzed with an interaction variable in a linear model. For the X and Z axes, brackets indicate that the numerical value is included in the quintile, whereas parentheses indicate that the value is excluded. Positive values on the Y axis indicate the magnitude of weight loss for each quintile intersection. $n = 20$ for the highest quintile intersection. For effect modification, $P = 0.0009$.

added sugar in both groups, and lack of a specific biomarker, we cannot exclude the possibility that associations involving this dietary factor may primarily reflect adherence to an intervention target.

In a quasi-Bayesian model with GL and caloric intake, GL explained most of the observed variation in weight loss at all time points, whereas caloric intake explained none of the observed variation in weight loss. This finding, although seemingly in conflict with the law of conservation of energy, may be understood in view of the putative effects of GL on both components of energy balance. According to the CIM, reduction in GL not only reduces hunger and energy intake but also increases energy expenditure. A recent meta-analysis reported that total energy expenditure increased with low- vs. high-carbohydrate diets by ~50 kcal/d per 10% decrease in the proportion of energy from dietary carbohydrate after 2.5 wk (i.e., allowing time for physiological adaptation to the change in macronutrients) [28]. This effect, if translated to the 30% difference in carbohydrate intake between diet groups at 3 mo, could account for > 1 kg of body fat loss – representing a substantial component of the average loss at this time point. Thus, the change in GL and added sugar could better predict long-term weight change than energy intake, which involves only 1 energy balance component.

We found additional evidence in support of the CIM from possible effect modification. The CIM predicts that individuals with high insulin secretion in response to carbohydrate, due to genetic or acquired influences, will be most sensitive to the adverse effects of a high-GL diet and benefit the most from GL reduction [8]. Although an interaction between insulin-30 and dietary group assignment was not originally observed [10], power for this analysis would be reduced because of the reduction in GL in the LFD group. To address this challenge, we examined a greater number of subgroups by dividing the full cohort into quintiles of insulin-30 and GL reduction. We found that individuals with the highest insulin-30 and greatest GL reduction lost more weight than those in all 24 other subgroups with nominal significance for effect modification at 3 and 6 mo. The statistical strength of this effect was marginal at 12 mo, possibly due to diminishing adherence to the original dietary targets (related in part to study design) and dropouts.

These findings suggest that dietary intervention strategies targeting high-GL carbohydrates, rather than total fat or calories, may be advantageous for the long-term treatment of obesity. Although meta-analyses of clinical trials suggest only a modestly greater weight loss with low-carbohydrate vs. low-fat diets [15, 29–31], interpretation of these data commonly conflates biological efficacy with implementation. In a food environment awash in highly processed carbohydrates – reflecting to some degree the persistent legacy of the low-fat diet campaign of the late 20th century [32, 33], maintenance of a low-GL diet may be difficult for many people. However, this difficulty does not imply an insurmountable barrier to long-term adherence. If additional research confirms these findings, more effective behavioral and environmental interventions might be designed, as suggested by Diogenes [34] and the DIRECT study [35]. In these 2 trials, intensive behavioral support was provided, and differences in GL and body weight were maintained between treatment groups for the duration of the interventions.

This focus on GL could be combined with the attention to dietary fat quality (including saturated fat, as was the case in the LFD group) to maximize cardiovascular benefits. However, the adverse effects of saturated fat on LDLc, as observed in the general population, may be attenuated with the consumption of a reduced-GL diet [36]. Interestingly, in a prior analysis of DIETFITS, the relationship between the change in saturated fat intake and LDLc was significant on the LFD but not the LCD [37].

A major limitation of this study is the exploratory nature of the design, presenting the risk for false discovery. This concern would apply especially to findings of borderline statistical significance (most notably effect modification at the later time points) rather than the associations with dietary factors and biomarkers, many of which have sufficient strength to withstand multiple hypothesis testing for all practical purposes. Despite the use of the same assessment methodology to estimate intakes, comparison of dietary factors could be biased if systematic error occurred at any stage of dietary reporting or analysis. Although the biomarkers have demonstrated validity for the macronutrient exposures of interest, they could be affected by other dietary exposures and by weight loss, possibly biasing these associations. Greater dropout rate and convergence of diets within and between groups over time limit the power to assess long-term relationships and distinguish biological mechanisms from adherence. In addition, all models that address or disregard missing data involve implicit assumptions that may bias outcomes; our reanalyses of the primary outcome may not be more correct than those in the original report.

In conclusion, we found evidence that aspects of carbohydrate intake relate more strongly to weight loss in both diet groups of DIETFITS than other dietary factors and that fat intake had little relevance, even in the LFD group. This reanalysis provides qualified support for the CIM and highlights the potential efficacy for obesity treatment of reducing processed carbohydrates consumption, rather than the conventional targets of dietary fat and calories. Finally, we would emphasize that these findings extend, not oppose, the original conclusions of DIETFITS and highlight the value of full open access to data in clinical trials [38, 39].

Author disclosures

DSL reported receiving royalties from books on nutrition and obesity that recommend a carbohydrate-modified diet; and his spouse owns a nutrition education and consulting business. All other authors report no competing interests.

Acknowledgments

We thank Christopher Gardner for helpful discussion, Stephanie Dickinson for statistical advice, and Shui Yu for verifying the analyses.

Author contribution

ASM, MAP, and DSL designed and carried out the analyses. CBE and LA participated in data interpretation. LA, as a coinvestigator of the original trial, also helped ensure accurate representation of the intervention and data. All authors revised and approved the final version of this manuscript.

Funding

This study was funded by New Balance Foundation.

Data Availability

Data from the original trial are available at https://osf.io/ztysq. The analysis code used in the current study is available at https://github.com/AdrianSotoM/DIETFITS_reanalysis/blob/main/paper_code.R.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2022.12.014.

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