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Personalized nutrition: pretreatment glucose metabolism determines individual long-term weight loss responsiveness in individuals with obesity on low-carbohydrate versus low-fat diet

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Abstract

Background/Objectives: The interaction between fasting plasma glucose (FPG) and fasting insulin (FI) concentrations and diets with different carbohydrate content were studied as prognostic markers of weight loss as recent studies up to six month of duration have suggested the importance of these biomarkers.

Subjects/Methods: This was a retrospective analysis of a clinical trial where participants with obesity were randomized to an *ad libitum* low-carbohydrate diet or a low-fat diet with low energy content (1200-1800 kcal/d [$\approx$ 5.0-7.5 MJ/d]; 30% calories from fat) for 24 months. Participants were categorized (pretreatment) as normoglycemic (FPG<5.6 mmol/L) or prediabetic

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Author Contributions: GDF, HRW, JOH and SK conceived and carried out the original experiments. MFH, YZ, and AA conceived the idea of the current analysis. BWP performed insulin sensitivity analyses. MFH analyzed the data and wrote the first draft of the paper. All authors have reviewed the manuscript critically and approved the final manuscript.

Conflicts of Interest: MFH, YZ, and AA are co-inventors on a pending provisional patent application on the use of biomarkers for prediction of weight-loss responses. AA is co-inventor of other related patents/patent applications owned by UCPH, in accordance with Danish law. AA and JOH are consultants for Gelesis Inc. concerning scientific advice unrelated to the current paper. AA is furthermore consultant/member of advisory boards for Groupe Éthique et Santé, France, Nestlé Research Center, Switzerland, Weight Watchers, USA, BioCare Copenhagen, Zaluvida, Switzerland, Basic Research, USA, Novo Nordisk, Denmark, & Saniona, Denmark. MFH & AA are co-authors of the book “Spis dig slank efter dit blodsukker” (Eat according to your blood sugar and be slim)/Politikens Forlag, Denmark, and of other books about personalized nutrition for weight loss. AA is co-owner and member of the Board of the consultancy company Dentacom Aps, Denmark, & co-founder and co-owner of UCPH spin-out Mobile Fitness A/S, Flaxslim ApS. MFH & AA are co-founder and co-owner of UCPH spin-out Personalized Weight Management Research Consortium ApS (Glucodiet.dk). SK is a shareholder of Aspire Bariatrics, receives research support from Johnson & Johnson and Merck, and has served as a consultant for Pfizer and Janssen.

Clinical trial registry: [ClinicalTrials.gov](https://clinicaltrials.gov) number: NCT00143936

(FPG 5.6-6.9 mmol/L) and further stratified by median FI. Linear mixed models were used to examine outcomes by FPG and FI values.

Results: After 2 years, participants with prediabetes and high FI lost 7.2 (95%CI 2.1;12.2, $P=0.005$) kg more with the low-fat than low-carbohydrate diet, whereas those with prediabetes and low FI tended to lose 6.2 (95%CI -0.9;13.3, $P=0.088$) kg more on the low-carbohydrate diet than low-fat diet [Mean difference: 13.3 kg (95%CI 4.6;22.0, $P=0.003$)]. No differences between diets were found among participants with normoglycemia and either high or low FI (both $P=0.16$).

Conclusions: Fasting plasma glucose and insulin are strong predictors of the weight loss response to diets with different macronutrient composition and might be a useful approach for personalized weight management.

Introduction

Efforts to identify a single optimal diet for the treatment of obesity have largely failed. This has given rise to numerous fad diets that confuse the public, and has led to the conclusion that macronutrient composition does not affect weight loss [1]. While true, on average, less is known about biomarkers that could identify which types of macronutrient mixes are best for different types of people.

Several studies containing small number of subjects have attempted to establish whether fasting plasma insulin concentration or indices of insulin secretion predict the weight loss response to low carbohydrate (low glycemic load) and low fat (high glycemic load) diets, but results have been equivocal [2–6]. A recent re-analysis of four randomized dietary intervention studies have proposed the combination of fasting glucose and insulin to be an important determinant of individual dietary responsiveness to diets with different carbohydrate and fat contents [7,8]. However, these four studies were less than 6 months in duration and did not include very low carbohydrate diets.

Therefore, the purpose of this study was to re-analyze data from a previously published clinical trial to investigate fasting plasma glucose (FPG) and fasting insulin (FI) as prognostic markers for long-term weight loss in diets differing in carbohydrate and fat content. In the original 24-month intervention, subjects were randomly assigned to either a low-carbohydrate diet (Atkins) or an energy-restricted low-fat diet. The protocol stated primary end-points of this trial have been published elsewhere [9] as have secondary outcomes.

Materials and Methods

In the original trial, 307 participants were randomized to an *ad libitum* low-carbohydrate diet ($n=153$) or a hypocaloric low-fat diet ($n=154$) for 24 months. The intent with the low carbohydrate diet was to follow recommendations provided in *Dr. Atkins' New Diet Revolution* [10]. During the first three months the *ad libitum* low-carbohydrate diet contained 20 g of carbohydrates/day, consisting of low glycemic index vegetables, followed by a 5g/day increase per week by consuming more vegetables, fruits and whole grain until a stable desired weight was achieved. Limiting carbohydrate intake was the primary target for

this group. The low-fat diet consisted of 55, 30, and 15 energy percentage from carbohydrate, fat, and protein, respectively. Energy intakes were prescribed at 1200 to 1500 kcal/day [≈ 5.0 - 6.3 MJ/day] for women and 1500 to 1800 kcal/day [≈ 6.3 - 7.5 MJ/day] for men. Limiting the overall energy intake by decreasing fat intake was the primary goal for this group. All participants received comprehensive, in-person group instructions weekly for 20 weeks, every other week for 20 weeks, and then every other month for the remainder of the 2-year study period. Each treatment session lasted 75 to 90 minutes. Topics included self-monitoring, stimulus control, and relapse management. Group sessions reviewed participants' completion of their eating records. At baseline, fasting plasma glucose (FPG) and insulin (FI) were assessed after a 12-hour overnight fast, and insulin sensitivity (SI) measured by an intravenous glucose tolerance test [11]. Whole blood was drawn into EDTA-containing tubes, centrifuged, and plasma was stored at -80°C until use. Plasma glucose concentration was measured by using an automated glucose analyzer (Yellow Spring Instruments Co) and plasma insulin concentration was measured by using electrochemiluminescence technology (Elecsys 2010, Roche Diagnostics). Body weights were measured at baseline and after 3, 6, 12, and 24 months of intervention. Detailed information about the study has been published [9]. The study was conducted according to the Declaration of Helsinki guidelines and written informed consent was obtained from the participants after receiving oral and written information about study procedures. The study was registered on clinicaltrials.gov with the identifier: [NCT00143936](https://clinicaltrials.gov/ct2/show/study?term=NCT00143936).

For this re-analysis, baseline FPG levels were used to stratify subjects as being normoglycemic ($\text{FPG} < 5.6$ mmol/L) or having prediabetes ($\text{FPG} = 5.6$ - 6.9 mmol/L) according to previous procedures [7]. Furthermore, median FI (76 pmol/L) as well as median SI (2.47×10^{-4} pools/min per mU/L) were used to dichotomize subjects into low and high FI as well as SI groups according to previous procedures where the FI cut-off has varied between 72.9 and 90.3 pmol/L [7]. Subjects were included in the current study if they had baseline measures of FPG, FI, and body weight, and at least one follow-up measurement of body weight.

Statistics

Baseline characteristics were summarized as mean $\pm$ standard deviation (SD), median (interquartile range) or as proportions. Linear mixed models, with subject as a random effect with the use of all available weight measurements (without imputation but including those from non-completers), were used to compare differences in weight change between the two diets at each time point. Differences in weight change between FPG and insulinemic groups (and the combination of the two using an interaction term) were analyzed by means of linear mixed models. The linear mixed models comprised fixed effects including age, gender, and baseline BMI as well as random effects for participants and site. Results are shown as mean weight change from baseline with 95% confidence interval (CI). Using 24-month data, we conducted post hoc t-tests using pairwise comparisons to analyzed differences in weight change between diets both within and between each blood marker group. The level of significance was set at $P < 0.05$, with no adjustment for multiple testing, and statistical analyses were conducted using STATA/SE 14.1 (Houston, USA).

Results

Dropout among the 307 randomized subjects was higher in the low-carbohydrate group compared to the low-fat group (44% vs. 32%, $P=0.031$). This higher dropout in the low-carbohydrate group compared to the low-fat group was particularly seen among subjects with both high FPG and high FI (47% vs. 10%, $P=0.018$). The 251 subjects used for these analyzes included participants (low-carbohydrate, $n=122$; low-fat, $n=129$) 46 ± 10 years of age, with a BMI of 36.1 ± 3.5 . Overall, 70% of these were women. Baseline BMI was higher among patients with prediabetes and high FI compared to patients with prediabetes and low FI whereas no difference was found between these two phenotypes for age, body fat mass percentage or sex distribution ($P=0.76$) (Table 1).

As previously reported [9] no difference in weight change was observed between the two diets at any time-points (all $P \geq 0.17$) (Figure 1).

At baseline, Pearson correlation coefficients between FPG and FI, FPG and SI, as well as FI and SI were $r=0.22$ ($P<0.001$), $r=0.003$ ($P=0.96$), and $r=-0.38$ ($P<0.001$), respectively.

No differences in body weight changes between the two diets were observed for participants who were normoglycemic ($P=0.19$) or had prediabetes ($P=0.77$) (Table 2).

Participants with high FI lost 3.4 kg (95%CI 0.7;6.0, $P=0.012$) more weight on the low-fat compared with the low-carbohydrate diet, whereas no difference in weight loss between diets was observed among participants with low FI [-0.4 (95%CI -3.1 ;2.3, $P=0.79$). Consequently, participants with high compared to low FI lost borderline 3.7 kg (-0.03 ;7.51, $P=0.052$) more on the low-fat compared to low-carbohydrate diet (Table 2). Using SI revealed that subjects with greater insulin resistance (low SI group) showed greater weight loss with the low-fat than low-carbohydrate diet (Table 2).

Body weight change on the low-fat and low-carbohydrate diet for each of the four combined groups of FPG and FI are presented in Figure 2. Subjects with prediabetes and high FI lost 7.2 (95%CI 2.1;12.2, $P=0.005$) kg more on the low-fat diet ($n=17$) than the low-carbohydrate diet ($n=8$), whereas subjects with prediabetes and low FI tended to lose 6.2 (95%CI -0.9 ;13.3, $P=0.088$) kg more on the low-carbohydrate diet ($n=7$) than low-fat diet ($n=6$). Therefore, from the interaction analysis, differences in response between subjects with prediabetes and high FI and subjects with prediabetes and low FI is 13.3 kg (95%CI 4.6;22.0, $P=0.003$) (Table 2). Among those having body-composition at baseline and after 2 years ($n=27$) this corresponded to a 10.7 kg (0.4;21.1, $P=0.042$) difference in body fat mass. Furthermore, results were similar when using low SI, instead of high FI, as the measure of insulin resistance (Table 2). No differences between diets were found for individuals who were normoglycemic having either high or low FI (both $P \geq 0.16$).

Combining FI and SI revealed that individuals with high FI and low SI lost 5.1 (95%CI 1.9;8.3, $P=0.002$) kg more on the low-fat ($n=38$) than low-carbohydrate diet ($n=22$). No significant differences were found among the three remaining combinations of FI and SI (all $P \geq 0.12$).

Discussion

The results from this study confirm that the combination of FPG and FI is an important biomarker of the weight loss response to diets varying in macronutrient composition and extend this also to include studies with long time follow-up and very low carbohydrate diets. Despite two profoundly different diets eliciting nearly identical changes in body weight at all time-points, substantial long-term, diet-specific body weight responses were observed when subjects were stratified according to their pretreatment FPG and FI levels.

Although based on small numbers of subjects we found a large 13.3 kg difference in 24-month weight loss between participants with prediabetes (determined by impaired fasting blood glucose) and a high vs low FI. Specifically, subjects with prediabetes and lower FI were more responsive to a low-carbohydrate *ad libitum* diet, whereas subjects with prediabetes and higher FI were more responsive to a low-fat hypocaloric diet. In addition, participants with prediabetes and low insulin sensitivity (SI), assessed by using the intravenous glucose tolerance test, lost more weight with a low-fat than a low-carbohydrate diet. Changes in body weight among participants who were normoglycemic, regardless of FI or SI, did not differ by diet assignment.

The results from our study are consistent with and extend the results from previous studies that have found low glycemic index/load diets and a high-fat/low-carbohydrate diet to cause greater weight loss than high glycemic index/load diets or a low-fat/high-carbohydrate diet specifically in people with prediabetes and low FI [7]. In contrast, there is not strong support that pretreatment FI alone is a reliable predictor of diet-induced weight loss. Some studies have found that a diet lower in glycemic load is an important predictor among subjects with high FI (insulin resistant subjects) and/or that diets lower in fat is an important predictor among subjects with low FI (insulin sensitive subjects) [2,5,7,8,12–14]. However, other studies found no evidence for this difference [7,15]. In the present study, individuals with high FI and low SI, that was found to be negatively correlated, were found to lose more weight on the low-fat than the low-carbohydrate diet.

While additional data are certainly needed and the reasons for our observed differences deserve further examination, the combined use of pretreatment FPG and FI as predictors of weight loss and weight loss maintenance on different diets appears to have great promise. In addition SI seems promising although less feasible to implement in clinical practice. It is useful to consider why aspects of glycemic control might impact weight loss differently on different diets. One possible mechanism relates to insulin resistance in the brain since cellular glucose uptake in the brain is important to achieve satiety [16]. Furthermore, the combination of high FPG and low FI could indicate reduced beta-cell mass and thus a reduced ability to dispose a glucose load. The microbiome may also be involved in determining how glycemic control impacts weight change on different diets and might work through production of short chain fatty acids. Highlighting a potential important genus, *Prevotella* is known to be an efficient degrader of dietary fiber [17] and producer of SCFA [18], while being associated with improvements in blood glucose and insulin [19] and weight loss [20,21] when consuming a fiber rich diet.

This study has several limitations. First, we do not have accurate measures of dietary intake throughout the intervention and thus cannot ensure compliance to the randomized diets at 24 months. During the first 3 to 6 months the magnitude of weight loss appeared almost the same among the four different phenotypes. As caloric intake was suppressed during this period, there might have been only a narrow opportunity for the differences in satiety to be expressed. As time passed and caloric restriction was no more imposed, the differences in satiety may have become more prominent. Nevertheless, as previously reported [9], LDL cholesterol concentrations increased at 3 and 6 month in the low-carbohydrate group but decreased in the low-fat group, such that the differences between groups were statistically significant. This was not the case at the subsequent visits. As isocaloric replacement of dietary carbohydrate with fat increases plasma LDL cholesterol concentration [22] this indicate that the compliance to the diets dropped after 6 month – specifically the difference in carbohydrate and fat percentage diminished. However, as the difference in weight loss according to glycemic and insulinemic status started only after 6 month, other changes between the diets might have occurred from this point and forward. Those in the low-carbohydrate group gradually added more vegetables, fruits, and whole grains, so that at the end of the study, the diet may have contained more fiber and wholegrains. Dietary fiber is regarded as important for weight regulation [23] as diets including more fruits, vegetables and whole grains have been found to lower body weight in randomized dietary studies [24,25] as well as observational studies [23]. Therefore the results among the patients with prediabetes and low FI could be consistent with recent re-analysis of dietary intervention studies finding a high fiber diet [7], a low glycemic index/load diet [7] and a high fat/low carbohydrate diet [7] to be particular effective among the patients with prediabetes and low FI – also more effective compared to patients with high FPG and high FI. However, without dietary intake data, we are unfortunately not able to investigate if the differential weight loss response observed between subjects with prediabetes and high FI and subjects with prediabetes and low FI was driven by differences in dietary fiber intake.

Although the low-fat diet, in theory, was calorie-restricted throughout the 24 months, this was likely not the case, as is evidenced from regain occurring after 6 months. This emphasizes the need for more carefully controlled and planned dietary intervention studies with good compliance markers of dietary intake. Second, the number of participants in the high and low FI and high and low SI in the subgroups with prediabetes were small. Dropout was larger in the low-carbohydrate group, primarily due to participants with prediabetes and high FI dropping out of the low-carbohydrate diet arm. These participants with prediabetes and high FI that managed to complete the trial were also the ones having the worst weight development on the low-carbohydrate diet arm, which further underlines that the low carbohydrate diet did not work for this phenotype. Therefore, this skewed drop-out between diets for this particular phenotype most likely did not affect our findings, as both completion rate and weight loss were lower on the low-carbohydrate diet, and therefore pointing in the same direction. Furthermore, assuming subjects were eating typical high fat ($\approx 35\%$) American diet before the study, our results could potentially explain why subjects with prediabetes and high FI compared to subjects with prediabetes and low FI had a higher initial BMI.

Finally, our study is not able to determine the potential mechanism(s) responsible for the differences in weight loss responses to low-fat and low-carbohydrate diet therapy among participants with prediabetes. However, the differences we observe in weight change responsiveness to different diets between obese individuals with normoglycemia and prediabetes are likely attributed to effects mediated through changes in energy intakes driven by different satiety effects as similar effects have been observed in diets with ad libitum intake [7,8]. However, we cannot rule out that differences in resting energy expenditure could have made a contribution as low glycemic load diets stimulate thermogenesis [26], and it is possible that this effect might be more pronounced among individuals with obesity and prediabetes. In the parent study, there was not an attempt to ensure that the degree of caloric restriction was equivalent between diets. Hall et al. [27] have described energetic difference between low carbohydrate and low fat diets when the degree of caloric restriction is the same. Under these conditions, there was more fat loss with low fat vs low carbohydrate diets. Because it is likely that subjects in the present analysis were not very calorically restricted after 6 months, we cannot determine whether FPG and FI are more predictive under conditions of caloric restriction or under conditions refeeding following caloric restriction. It will be important to answer this question in future prospective studies.

These data further support the notion that the optimum diet for weight management may differ between individuals. Maybe it is time to stop the debate about which diet is optimum for the population and begin to understand how to provide the optimum diet to the individual. The combination of pre-treatment glucose and insulin seems to be one factor that can help do this as recently reviewed [28]. It is likely that other aspects of an individual's metabolism may impact response to different diets. It is even possible that as aspects of metabolism are changed (e.g. by weight loss or exercise), the composition of the optimum diet may change. The concepts of personalized nutrition or personalized lifestyle may drive some innovative new research in the area of weight management.

The strengths of our study include the 2-year duration and that replacing SI with FI produced complementary findings. Moreover, the post-hoc analyses of the study ensured a completely unbiased observation and neither the investigators nor the participants knew about the background and aim of the current re-analysis.

Conclusions

In conclusion, pre-treatment fasting plasma insulin is associated with long-term weight loss on *ad libitum* low-carbohydrate or caloric restricted low-fat diets among people with obesity and impaired fasting glucose, but not those with normoglycemia. Our results suggest that easily accessible biomarkers, namely fasting plasma glucose and plasma insulin are strong predictors of the weight loss response to diets with different macronutrient composition. Additional prospective randomized controlled trials in large numbers of participants are needed to further evaluate the use of these baseline markers of metabolic function for effective personalized weight management.

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Figure 1: Changes in bodyweight during the 2 year intervention with low fat and low carbohydrate diets.

Data are presented as mean change from baseline and 95% CI using a linear mixed model adjusted for subject as random effect with the use of all available weight measurements (including those from noncompleters). Observations (n) on the low fat diet were 145, 136, 115 and 105 at 3, 6, 12 and 24 month, respectively. Observations (n) on the low carbohydrate diet were 139, 128, 114, 86 at 3, 6, 12 and 24 month, respectively.

Figure 2: Bodyweight change among four different phenotypes on a low fat and low carbohydrate diet

Data are presented as mean change from baseline and 95% CI using a linear mixed model with the diet-FPG-FI-time interaction adjusted for age, sex and baseline BMI as fixed effects and subject and site as random effects with the use of all available weight measurements (including those from non-completers). Low and high fasting insulin (FI) is <76 and ≥76 pmol/L, respectively. Low and high fasting plasma glucose (FPG) is <5.6 and ≥5.6-6.9 mmol/L. * indicate significant difference between diets ($P < 0.05$).

Table 1:

Baseline characteristics of the 251 study populations stratified by fasting plasma glucose and fasting insulin

	FPG<5.6 mmol/L & FI<76 pmol/L (n=104)	FPG<5.6 mmol/L & FI 76 pmol/L (n=97)	FPG 5.6-6.9 mmol/L & FI<76 pmol/L (n=15)	FPG 5.6-6.9 mmol/L & FI 76 pmol/L (n=35)
Age	45.1±9.6 ^a	44.1±10.1 ^a	48.8 ± 10.3 ^{ab}	49.9 ± 9.5 ^b
Gender (%female / male) ¹	84.6/15.4	63.9/36.1	46.7/53.3	51.4/48.6
Body weight (kg)	98.5±14.0 ^a	105.5±14.3 ^{bc}	100.8±15.4 ^{ab}	111.0±15.3 ^c
BMI (kg/m ²)	35.5±3.3 ^a	36.7±3.7 ^b	34.4±2.3 ^a	37.1±3.5 ^c
Body fat mass (%)	42.2±5.6 ^a	39.1±6.5 ^b	38.6±5.1 ^b	37.6±7.2 ^{b2}
FPG (mmol/L)	4.8 (4.5;5.1) ^a	5.1 (4.7;5.3) ^b	5.7 (5.6;6.0) ^c	5.8 (5.6;6.0) ^c
FI (pmol/L)	47 (37;61) ^a	99 (87;127) ^b	44 (28;61) ^a	127 (90;172) ^c
SI (10 ⁻⁴ pools/min per mU/L)	3.2 (2.4;4.6) ^{a3}	2.0 (1.4;2.6) ^{b3}	3.3 (2.4;3.7) ^a	2.0 (1.4;2.8) ^{b2}

Abbreviations: BMI, Body mass index; FI, Fasting insulin; FPG, Fasting plasma glucose; SI, Insulin sensitivity. Data are presented as mean ± standard deviation, median (interquartile range) or proportions (%) and differences between four phenotypes were tested using one-way ANOVA with post-hoc tests (some variables transformed before analysis) or Pearson's chi-squared test. Different alphabets within a row (a, b, c) indicate significant differences (P < 0.05). Different alphabets within a row (a,b,c) indicate significant differences (P<0.05).

¹ Overall difference between groups tested by chi-squared, P<0.001.

² Missing data for one individual

³ Missing data for two individuals

Table 2:

Change in body weight on different diets when stratified on pre-treatment biomarkers

Fasting plasma glucose				
<i>Cut-offs</i>	<i>FPG<5.6</i>	<i>FPG 5.6-6.9</i>		
Low fat diet	(n=71)	(n=23)		
Weight (kg)	-7.5 (-9.0;-6.1)	-8.2 (-10.9;-5.5)		
Low carb diet	(n=62)	(n=15)		
Weight (kg)	-6.1 (-7.6;-4.6)	-7.5 (-10.7;-4.4)		
Fasting insulin				
<i>Cut-offs</i>	<i>FI<76</i>	<i>FI 76</i>		
Low fat diet	(n=37)	(n=58)		
Weight (kg)	-7.6 (-9.7;5.6)	-7.5 (-9.2;-5.9)		
Low carb diet	(n=44)	(n=33)		
Weight (kg)	-8.0 (-9.8;-6.2) ^a	-4.1 (-6.2;-2.1) ^b		
Insulin sensitivity				
<i>Cut-offs</i>	<i>SI<2.47</i>	<i>SI 2.47</i>		
Low fat diet	(n=53)	(n=39)		
Weight (kg)	-7.8 (-9.5;-6.1)	-7.8 (-9.7;-5.8)		
Low carb diet	(n=32)	(n=43)		
Weight (kg)	-3.2 (-5.3;-1.1) ^a	-8.5 (-10.4;-6.7) ^b		
Fasting plasma glucose and fasting insulin				
<i>Cut-offs</i> ³	<i>FPG<5.6 & FI<76</i>	<i>FPG<5.6 & FI 76</i>	<i>FPG 5.6-6.9 & FI<76</i>	<i>FPG 5.6-6.9 & FI 76</i>
Low fat diet	(n=30) [n=47]	(n=41) [n=56]	(n=6) [n=6]	(n=17) [n=20]
Weight (kg)	-7.6 (-9.8;-5.4)	-7.5 (-9.4;-5.6)	-9.6 (-15.0;-4.3)	-7.6 (-10.7;-4.6)
Low carb diet	(n=37) [n=57]	(n=25) [n=41]	(n=7) [n=9]	(n=8) [n=15]
Weight (kg)	-6.5 (-8.5;-4.6) ^a	-5.3 (-7.7;-3.0) ^a	-15.8 (-20.5;-11.1) ^b	-0.5 (-4.5;3.6) ^c
Fasting plasma glucose and insulin sensitivity				
<i>Cut-offs</i>	<i>FPG<5.6 & SI<2.47</i>	<i>FPG<5.6 & SI 2.47</i>	<i>FPG 5.6-6.9 & SI<2.47</i>	<i>FPG 5.6-6.9 & SI 2.47</i>
Low fat diet	(n=40)	(n=29)	(n=13)	(n=9)
Weight (kg)	-6.6 (-8.6;-4.7) ^a	-9.1 (-11.3;-6.9) ^{ab}	-11.4 (-14.8;-7.9) ^b	-4.4 (-8.7;-0.01) ^a
Low carb diet	(n=26)	(n=34)	(n=6)	(n=9)
Weight (kg)	-3.8 (-6.1;-1.5) ^a	-7.6 (-9.6;-5.5) ^b	-0.6 (-5.3;4.1) ^a	-12.1 (-16.1;-8.1) ^c

Fasting plasma glucose				
Cut-offs	FPG<5.6	FPG 5.6-6.9		
Fasting insulin and insulin sensitivity				
Cut-offs	FI<76 & SI<2.47	FI<76 & SI 2.47	FI 76 & SI<2.47	FI 76 & SI 2.47
Low fat diet	(n=15)	(n=21)	(n=38)	(n=18)
Weight (kg)	-9.6 (-12.9;-6.4)	-6.6 (-9.2;-4.0)	-7.1 (-9.0;-5.1)	-9.1 (-12.2;-6.1)
Low carb diet	(n=10)	(n=33)	(n=22)	(n=10)
Weight (kg)	-5.7 (-9.5;-2.0) ^{ab}	-8.4 (-10.5;-6.3) ^a	-2.0 (-4.5;0.6) ^b	-8.8 (-12.4;-5.1) ^a

Abbreviations: Carb, Carbohydrate; FI, Fasting insulin (unit: pmol/L); FPG, Fasting plasma glucose (unit: mmol/L); SI, Insulin sensitivity (unit: $\times 10^{-4}$ pools/min per mU/L). Data are presented as estimated mean weight change from baseline and 95% confidence intervals for each combination of the diet-FPG-FI/SI strata interaction after 2 years in the linear mixed models, which were additionally adjusted for age, gender, BMI as fixed factors as well as subjects and sites as random effects. Number of observations (n) is completers and number of observations [n] is at baseline. Different alphabets within a row (a,b,c) indicate significant differences ($P<0.05$). Cut-offs for FI and SI represented the median value.