Genetic variation of fasting glucose and changes in glycemia in response to 2-year weight-loss diet intervention: the POUNDS Lost trial

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Abstract

Objective—Weight loss intervention through diet modification has been widely used to improve obesity-related hyperglycemia; however, little is known about whether genetic variation modifies the intervention effect. We examined the interaction between weight-loss diets and genetic variation of fasting glucose on changes in glycemic traits in a dietary intervention trial.

Research Design and Methods—The Preventing Overweight Using Novel Dietary Strategies (POUNDS LOST) trial is a randomized, controlled 2-year weight-loss trial. We assessed overall genetic variation of fasting glucose by calculating a genetic risk score (GRS) based on 14 fasting glucose-associated single nucleotide polymorphisms, and examined the progression in fasting glucose and insulin levels, and insulin resistance and insulin sensitivity in 733 adults from this trial.

Results—The GRS was associated with 6-month changes in fasting glucose (P<0.001), fasting insulin (P=0.042), homeostasis model assessment of insulin resistance (HOMA-IR, P=0.009) and insulin sensitivity (HOMA-S, P=0.043). We observed significant interaction between the GRS and dietary fat on 6-month changes in fasting glucose, HOMA-IR and HOMA-S after multivariable adjustment (P-interaction=0.007, 0.045, and 0.028, respectively). After further adjustment for weight loss, the interaction remained significant on change in fasting glucose (P=0.015). In the high-fat diet group, participants in the highest GRS tertile showed increased fasting glucose,

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whereas participants in the lowest tertile showed decreased fasting glucose (P-trend<0.001); in contrast, the genetic association was not significant in the low-fat diet group (P-trend=0.087).

Conclusions—Our data suggest that participants with a higher genetic risk may benefit more by eating a low-fat diet to improve glucose metabolism.

INTRODUCTION

Hyperglycemia, one of the criteria of type 2 diabetes, is closely related to obesity (1). Weight loss intervention through diet and lifestyle modification has been widely adopted as a mainstream approach to improve glycemia and mitigate obesity-related metabolic risk factors (2,3). Blood glucose level is affected not only by diet and lifestyle, but also by genetic variation. In the past decade, several genome-wide association studies (GWASs) have identified a group of genetic variants that determine the overall variation of fasting glucose levels (4-8). In clinical trials, it has been noted for long time that the changes in glycemic measures in response to diet or lifestyle interventions exhibit considerable inter-individual variation (9-12). We hypothesized that such diverse responses may be at least partly determined by the interaction between the interventions and genetic variation, especially which is related to blood glucose levels.

In this study, we calculated a genetic risk score, based on the 14 fasting glucose-associated single nucleotide polymorphisms (SNPs) identified by Meta-Analyses of Glucose and Insulin related traits Consortium (MAGIC) (7), and examined the interaction between the composition of macronutrients in weight-loss diets and genetic variation of fasting glucose in relation to changes in glycemic traits in the 2-year Preventing Overweight Using Novel Dietary Strategies (POUNDS Lost) trial.

RESEARCH DESIGN AND METHODS

Study participants

The POUNDS Lost trial is a 2-year randomized clinical trial to compare the effects of energy-reduced diets with different compositions of fat, protein and carbohydrate on reducing body weight (www.clinicaltrials.gov; NCT00072995). The study design and sample collection have been described in detail previously (10). Briefly, a total of 811 overweight or obese subjects (25 ≤ body mass index ≤ 40 kg/m^2) aged 30 to 70 years were randomly assigned to one of four diets. The targeted percentages of energy derived from fat, protein and carbohydrate in the 4 diets were 20%, 15%, and 65%; 20%, 25%, and 55%; 40%, 15%, and 45%; and 40%, 25%, and 35%. Major exclusion criteria were the presence of diabetes or unstable cardiovascular disease, the use of medications that affect body weight, and insufficient motivation. After 2 years, 645 participants (80%) completed the trial. The study was approved by the human subjects committee at the Harvard School of Public Health and Brigham and Women's Hospital, Boston, MA, by the Pennington Biomedical Research Center of the Louisiana State University System, Baton Rouge, LA, and by a data and safety monitoring board appointed by the National Heart, Lung, and Blood Institute. All participants provided written informed consent.

In total, 733 participants with genotyping data available were included in the present study. There was no significant difference in the baseline characteristics between the participants with and without genotyping data.

Measurements

Body weight and waist circumference were measured in the morning before breakfast on 2 days at baseline, 6 months, and 2 years. Body mass index was calculated as weight by height squared (kg/m^2). Dietary intake was assessed by a review of the 5-day diet record at baseline, and by 24-hour recall during a telephone interview on 3 nonconsecutive days at 6 months and 2 years, in a random sample of 50% of the participants. Fasting blood samples, 24-hour urine samples, and measurement of resting metabolic rate were obtained on 1 day. Serum glucose, insulin, and urinary nitrogen were measured at the clinical laboratory at the Pennington Biomedical Research Center. Homeostasis model assessment (HOMA) models were used to estimate insulin resistance (HOMA-IR), insulin sensitivity (HOMA-S), and β-cell function (HOMA-B) (13,14), which were calculated by the following equations: HOMA-IR = [fasting insulin (μU/mL) × fasting glucose (mmol/L)] / 22.5, HOMA-S = 22.5 / [fasting insulin (μU/mL) × fasting glucose (mmol/L)], and HOMA-B = [20 × fasting insulin (μU/mL)] / [fasting glucose (mmol/L)-3.5].

Genotyping and genetic risk score calculation

DNA was extracted from the buffy coat fraction of centrifuged blood using the QIAmp Blood Kit (Qiagen, Chatsworth, CA). Fourteen fasting glucose-associated SNPs identified by MAGIC in European ancestry were selected and were genotyped successfully in 733 of 811 total participants using the OpenArray SNP Genotyping System (BioTrove, Woburn, MA). The genotype success rate was 99% in available DNA samples. Replicated quality control samples (10%) were included in every genotyping plate with greater than 99% concordance. The allele frequencies of all SNPs in total participants or in white participants were in Hardy-Weinberg equilibrium (all P > 0.05).

We assessed overall genetic variation of fasting glucose by calculating a genetic risk score (GRS). The GRS was calculated based on the 14 SNPs by summing risk allele's numbers, and weighted by their effect sizes (β coefficients) derived from genome-wide association meta-analyses data (**Supplementary Table 1**). The GRS was computed using the equation: GRS = $(\beta_1 \times SNP_1 + \beta_2 \times SNP_2 + \ldots + \beta_{14} \times SNP_{14}) \times$ (n/sum of the β coefficients), where β is the β coefficient of each SNP for higher levels of fasting glucose, SNP_1, SNP_2 … and SNP_{14} indicate the number of risk alleles (0, 1 or 2) for each SNP, and sum of the β coefficients is 0.424 in the current analysis. The GRS ranged from 8 to 24 among the study participants, and a higher score indicated a higher genetic risk of higher levels of fasting glucose.

Statistical analysis

The primary endpoints for this study were changes in glycemic traits including fasting glucose, fasting insulin, insulin resistance and insulin sensitivity over the intervention. Participants from the 4 diet groups were combined for the comparison of low-fat diet (20% fat) and high-fat diet (40% fat), and for the comparison of average-protein diet (15%) and high-protein diet (25%) in accordance to the two-factorial design of the original trial (10),

and such analytical strategy would have better power than analyzing the four groups. Levels of insulin, HOMA-IR and HOMA-S were log-transformed before analysis to improve the normality of their distributions. General linear models for continuous variables and chi-square test for categorical variables were applied for the comparison according to tertiles of the GRS. We used general linear models to test means (standard deviations, SEs) of changes in glycemic traits in high-fat and low-fat diets groups according to tertiles of the GRS with adjustment for age, sex, ethnicity, baseline values of the respective outcomes, and weight loss at each intervention time. To test for interaction, we examined the GRS, dietary fat or protein intake, and an interaction product term of the GRS-diet intervention as independent predictors of changes in glycemic traits, with adjustment for age, sex, ethnicity, baseline values of the respective outcomes, and weight loss at each intervention time in the general linear models. We excluded individuals with missing measures at each time point in the analysis. Because our analysis is hypothesis driven and primarily focused on the genetic risk score (rather than individual SNPs), we did not adjust for multiple testing. As the majority of the participants were white (80%), we also examined the genetic effects and gene-diet interaction in white participants in a sensitivity analysis. We used Quanto 1.2.4 (http://hydra.usc.edu/gxe/; University of Southern California, Los Angeles) to estimate the detectable effect sizes of gene-diet interactions. The study had 80% power to detect gene-diet interaction effect sizes of 0.05 and 0.01 mmol/L for changes in fasting glucose, 0.15 and 0.12 for log-transformed units for changes in HOMA-IR, and 0.15 and 0.12 log-transformed units for changes in HOMA-S at 6 months and 2 years, respectively. All reported P values are nominal and 2-side, and a P value less than 0.05 was considered statistically significant. Statistical analyses were performed with SAS version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

Baseline characteristics

Table 1 presents the baseline characteristics of participants according to the tertiles of the GRS of fasting glucose. Mean age, proportions of sex and four diet groups were similar, while the ethnicity proportion was different across the tertiles of the GRS. After adjustment for age, sex and ethnicity, a higher GRS was associated with higher fasting glucose and lower HOMA-B levels (both P < 0.001). The GRS was not significantly associated with body mass index, dietary intervention groups assignment, or other baseline characteristics.

Dietary nutrient intake and biomarkers of adherence by tertiles of the GRS

The reported dietary intakes (total energy, fat, protein, and carbohydrate) and changes in biomarkers of adherence (urinary nitrogen and respiratory quotient) confirmed that participants modified their intake of macronutrients in the direction of the intervention goals, although the targets were not fully achieved (10). At 6 months, there were no significant differences in mean values of nutrient intake and biomarkers of adherence across the tertiles of GRS (all P > 0.05). At 2 years, fat intake was significantly decreased (P = 0.040), and urinary nitrogen was significantly increased (P = 0.027) across the tertiles of GRS. No other differences in nutrient intake and biomarkers of adherence at 2 years were found across the GRS tertiles (all P > 0.05) (**Table 2**).

The GRS and changes in glycemic traits

As shown in **Supplementary Figure 1**, one unit higher GRS was significantly associated with 0.03 mmol/L greater increase in fasting glucose (P < 0.001), 0.01 μU/mL less decrease in fasting insulin (P = 0.042), 0.02 less decrease in HOMA-IR (P = 0.009), and −0.01 less increase in HOMA-S (P = 0.042) at 6-month, independent of age, sex, ethnicity, diet groups, and baseline values of the respective outcomes. After further adjustment for weight loss at 6 months, the association of the GRS with changes in fasting glucose and HOMA-IR remained significant, but the association with changes in fasting insulin and HOMA-S were attenuated.

Genetic risk, dietary fat intervention and changes in glycemic traits

At 6 months, we also observed significant interaction between the GRS and dietary fat intake (high-fat v.s. low-fat) on changes in fasting glucose, HOMA-IR and HOMA-S (P for interaction = 0.007, 0.045, and 0.028, respectively), after adjustment for age, sex, ethnicity, and baseline values of the respective outcomes. After further adjustment for weight loss at 6 months, the interaction between the GRS and change in fasting glucose remained significant (P = 0.015). In the high-fat diet group, participants in the highest tertile of the GRS showed increased fasting glucose compared to the baseline levels, whereas participants in the lowest tertile of the GRS showed decreased fasting glucose (P for trend < 0.001). In the low-fat diet group, no significant association between the GRS and changes in glucose was observed (all P for trend   0.087). At 2 years, the association between the GRS and the glycemic measures, and GRS-diet interaction were attenuated to be not significant (**Table 3**). No significant interaction between the GRS and dietary protein was observed across the 2-year intervention.

The results were similar in the sensitivity analyses only including white participants. At 6 months, there was significant interaction between the GRS and dietary fat intake on changes in fasting glucose (P = 0.011) and HOMA-S (P = 0.043) after adjustment for age, sex, and baseline values of the respective outcomes. The GRS-diet interaction on change in HOMA-IR was attenuated (P = 0.068), while the interaction on change in fasting glucose remained significant (P = 0.024) after further adjustment for weight loss at 6 months. At 2 years, the results did not remain significant (**Supplementary Table 2**).

Dietary fat intervention on change in fasting glucose by GRS

We further assessed the effect of the high-fat and low-fat diets on changes in fasting glucose by tertiles of the GRS with multivariable adjustment (**Figure 1**). At 6 months, in tertile 1 (the lowest) and tertile 2 of the GRS, no significant difference in fasting glucose was observed among these two diet groups. In tertile 3 (the highest) of the GRS, participants eating the high-fat diet had a greater increase in fasting glucose than those eating the low-fat diet (P = 0.014). At 2 years, fasting glucose levels rebounded, and in tertile 2 and 3 of the GRS, participants eating high-fat diet showed significantly higher increment in fasting glucose compared with those eating low-fat diet (both P < 0.05), whereas no significant difference was observed among the two diet groups in tertile 1 of the GRS.

DISCUSSIONS

In the POUNDS Lost trial, the fasting glucose GRS was significantly associated with 6-month changes in fasting glucose, fasting insulin, HOMA-IR and HOMA-S. In addition, we found that the genetic variation of fasting glucose interacted with the dietary fat intake in relation to 6-month changes in glycemic traits, especially fasting glucose.

In the present study, a higher fasting glucose GRS was associated with greater increase in fasting glucose and less decrease in HOMA-IR at 6 month, independent of concurrent weight loss. Many of the established fasting glucose loci included in the GRS contain biological candidate genes with plausible causality, such as *PROX1* and *GLIS3* encode transcription factors that play crucial roles in beta-cell ontogeny, and *SLC2A2* and *GCK* involve in glucose-mediated insuiln secretion cascade and beta-cell function (15-18). The significant association of the GRS with changes in fasting insulin and HOMA-S was diminished after adjustment for weight loss, suggesting that the genetic effect on changes in glycemic traits might be mediated by weight loss, which has been considered as a cornerstone for improvement of insulin resistance and insulin sensitivity (19,20).

In addition, we found significant gene-dietary fat interaction on changes in several glycemic measures at 6 months. Our data indicated that only the interaction on change in fasting glucose was independent of weight loss, whereas the interaction on changes in HOMA-IR and HOMA-S were likely mediated by weight change. An interesting finding is that in the high-fat diet group, participants with different genetic risk showed directionally opposite changes in fasting glucose: participants with higher genetic variation to fasting glucose showed increased fasting glucose, whereas those with lower genetic variation showed decreased fasting glucose. While no such genetic effect was observed in the low-fat diet group. The potential mechanisms underlying these results might be related to fatty acid-induced glucose intolerance. Animal studies have showed compelling evidence that high-fat diet and increased circulating free fatty acid levels induce glucose intolerance by disrupting gene expression in signaling pathways of glucose metabolism (21,22), decreasing basal and insulin-stimulated glucose utilization (23,24), and causing adipose chronic inflammation and ectopic lipid deposition in the liver and brown fat (25). Moreover, it has been suggested that individuals with a higher genetic risk to diabetes or its risk factors may be more susceptible to glucose intolerance upon exposure to high-nutrient diets (26,27). These findings raise the possibility that dietary fat-induced fasting glucose elevation may be enhanced in participants with a higher genetic risk to higher levels of fating glucose. From another perspective, the low-fat/high-fat diets are the same as the high-carbohydrate/low-carbohydrate diets in the present trial, therefore possible modifications of the varying percentages of carbohydrates on the genetic effect should also be taken into account. That is, the genetic effect on changes in fasting glucose was more significant in the low-carbohydrate diet group than in the high-carbohydrate diet group.

Similar to our previous studies, the gene-diet interaction became attenuated at 2 years. Between 6 months to 2 years, both body weight and glucose levels rebounded (10), partially due to a diminished adherence to the diet intervention, which was similar to other weight-loss trials (28,29). These results suggest that the modification of dietary fat on the

association between genetic variation and changes in glycemic traits might be more prominent in a short-term intervention. Moreover, the rebound in glycemic traits, especially fasting glucose, may also partly explain the attenuated gene-diet interaction; however.

To the best of our knowledge, this is the first study assessing interaction between the overall genetic variation of fasting glucose and dietary interventions on changes in glycemic measures in a large and long-term randomized clinical trial. Several limitations also warrant consideration. First, we applied HOMA models rather than a gold standard such as hyperglycemic clamp technique or intravenous glucose tolerance test to assess insulin resistance and beta-cell function. Although HOMA models have been validated as robust and feasible epidemiological tools (30), the data need to be interpreted carefully. Second, even though our study is thus far the largest diet intervention weight-loss trial, the relatively small sample size of the subgroups may limit the power to detect very moderate interactions. Third, most of the participants (80%) in our trial are white, and the replications in other ethnic populations are warranted to verify our findings.

In conclusion, we found a significant interaction between the genetic variation of fasting glucose and dietary fat intervention on changes in glycemic traits, suggesting that overweight or obese patients with a higher genetic risk may benefit more by taking a low-fat weight-loss diet to improve glucose metabolism. Our findings provide supportive evidence for the concept of genetic risk-stratified nutrition intervention in preventing disease related to glucose metabolism, such as type 2 diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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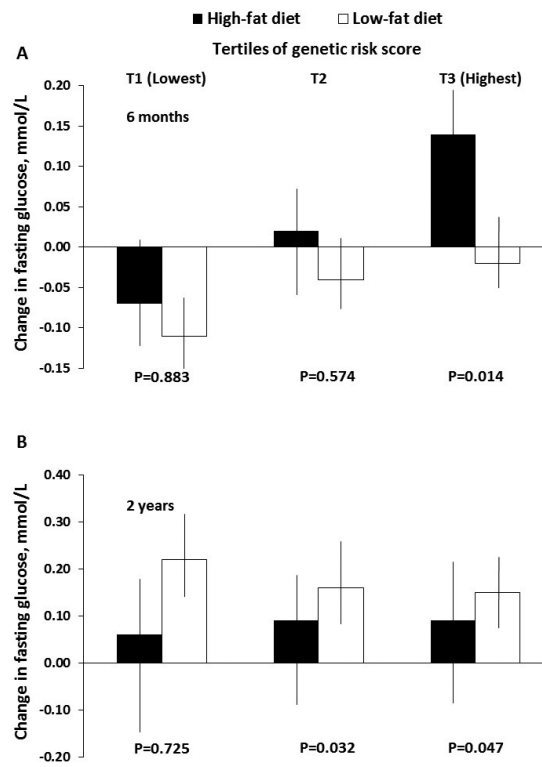
Figure 1. The effects of high-fat and low-fat diets on changes in fasting glucose by tertiles of fasting glucose genetic risk score over 2 years

A. 6 months, B. 2 years. Data are expressed as mean (SE) after adjustment for age, sex, ethnicity, and baseline values of the respective outcomes. P values are for comparisons between the two diet groups.

Table 1

Baseline characteristics of study participants

	Tertiles of genetic risk score to fasting glucose			
	1 (n=241)	2 (n=245)	3 (n=247)	P
Age, years	51 ± 10	51 ± 9	51 ± 9	0.852
Sex, n (%)				
Female	134 (55.6)	154 (62.9)	158 (64.0)	0.124
Male	107 (44.4)	91 (37.1)	89 (36.0)	
Race or ethnicity, n (%)				
White	206 (85.5)	173 (70.6)	206 (83.4)	< 0.001
Black	22 (9.1)	59 (24.1)	31 (12.6)	
Hispanic	10 (4.2)	10 (4.1)	5 (2.0)	
Asian or other	3 (1.2)	3 (1.2)	5 (2.0)	
Diet groups (%fat/ protein/ carbohydrate), n (%)				
Group 1 (20/15/65)	65 (27.0)	58 (23.7)	58 (23.5)	0.827
Group 2 (20/25/55)	55 (22.8)	66 (26.9)	67 (27.1)	
Group 3 (40/15/45)	59 (24.5)	56 (22.9)	64 (25.9)	
Group 4 (40/25/35)	62 (25.7)	65 (26.5)	58 (23.5)	
Height, cm	169 ± 9	168 ± 8	168 ± 9	0.800
Weight, kg	94 ± 16	93 ± 15	93 ± 16	0.795
Body mass index, kg/m^2	32.7 ± 3.8	32.7 ± 3.8	32.6 ± 4.0	0.990
Waist circumference, cm	105 ± 13	103 ± 13	103 ± 13	0.581
Glucose, mmol/L	5.0 ± 0.6	5.1 ± 0.6	5.2 ± 0.7	<0.001
Insulin, μU/mL	10.5 (7.1-15.2)	11.1 (6.8-16.1)	10.0 (6.6-14.9)	0.649
HOMA-IR	2.31 (1.53-3.39)	2.55 (1.48-3.63)	2.24 (1.49-3.67)	0.612
HOMA-S	0.43 (0.30-0.65)	0.39 (0.28-0.68)	0.45 (0.27-0.67)	0.612
HOMA-B	145 (105-210)	134 (94-210)	123 (86-180)	<0.001
Weight loss at 6 months, kg	−7.4 ± 5.7	−6.0 ± 5.7	−6.6 ± 5.8	0.159
Weight loss at 2 years, kg	−4.6 ± 7.8	−3.7 ± 6.9	−4.0 ± 7.5	0.585
Dietary intake per day				
Energy, kcal	1993 ± 626	1903 ± 503	2007 ± 545	0.364
Carbohydrate, %	45 ± 8	45 ± 7	45 ± 8	0.748
Fat, %	37 ± 6	37 ± 6	37 ± 6	0.767
Protein, %	18 ± 4	18 ± 3	18 ± 3	0.625
Biomarkers of adherence				
Urinary nitrogen, g/day	12.3 ± 4.6	12.0 ± 4.2	12.4 ± 4.5	0.272
Respiratory quotient	0.84 ± 0.04	0.85 ± 0.04	0.84 ± 0.05	0.312

Data are expressed as mean ± SD, median (95% CI), or % (n) as appropriate. P values were calculated by using the chi-square test for categorical variables and F tests in general linear models for continuous variables after adjustment for age, sex and ethnicity.

Table 2

Nutrient intake and biomarkers of adherence according to tertiles of the genetic risk score at 6 months and 2 years

	At 6 months				At 2 years			
	T1	T2	T3	P	T1	T2	T3	P
Dietary intake per day [*]								
Energy, kcal	1671 ± 520	1575 ± 541	1615 ± 505	0.978	1596 ± 558	1457 ± 404	1522 ± 487	0.906
Carbohydrate, %	50 ± 11	52 ± 10	50 ± 10	0.757	47 ± 10	51 ± 11	49 ± 10	0.412
Fat, %	31 ± 8	29 ± 8	31 ± 9	0.818	32 ± 8	31 ± 9	29 ± 9	0.040
Protein, %	20 ± 4	21 ± 5	20 ± 4	0.461	21 ± 5	20 ± 5	21 ± 4	0.752
Biomarkers of adherence								
Urinary nitrogen, g/day[†]	11.5 ± 4.3	11.5 ± 4.6	11.8 ± 4.7	0.193	11.9 ± 4.4	11.7 ± 3.9	12.4 ± 5.1	0.027
Respiratory quotient[‡]	0.84 ± 0.04	0.84 ± 0.04	0.84 ± 0.04	0.102	0.83 ± 0.04	0.83 ± 0.04	0.83 ± 0.04	0.669

Data are expressed as mean ± SD. P values were calculated by F tests in general linear models after adjustment for age, sex and ethnicity.

[*] At 6 months, data were included from 109, 108, and 111 across tertiles of genetic risk score, respectively; and at 2 years, data were included from 50, 57, and 62 across tertiles of genetic risk score, respectively.

[†] At 6 months, data were included from 184, 177, and 173 across tertiles of genetic risk score, respectively; and at 2 years, data were included from 139, 114, and 118 across tertiles of genetic risk score, respectively.

[‡] At 6 months, data were included from 201, 194, and 195 across tertiles of genetic risk score, respectively; and at 2 years, data were included from 163, 145, and 154 across tertiles of genetic risk score, respectively.

Table 3

Changes in glycemic traits in high-fat and low-fat diets groups according to tertiles of the genetic risk score, based on general linear models

	At 6 months				At 2 years			
	T1 (Lowest)	T2	T3 (Highest)	P for trend	T1 (Lowest)	T2	T3 (Highest)	P for trend
Change in glucose, mmol/L *								
High-fat diet	−0.07 ± 0.09	0.02 ± 0.09	0.14 ± 0.09	< 0.001	0.06 ± 0.17	0.09 ± 0.16	0.09 ± 0.16	0.694
Low-fat diet	−0.11 ± 0.06	−0.04 ± 0.06	−0.02 ± 0.06	0.087	0.22 ± 0.07	0.16 ± 0.07	0.15 ± 0.07	0.233
P for interaction Model 1				0.007				0.169
P for interaction Model 2				0.015				0.266
Change in log-insulin, μU/mL †								
High-fat diet	−0.18 ± 0.12	−0.10 ± 0.12	−0.04 ± 0.12	0.020	−0.14 ± 0.13	−0.14 ± 0.13	−0.07 ± 0.13	0.268
Low-fat diet	−0.23 ± 0.07	−0.20 ± 0.07	−0.22 ± 0.07	0.884	−0.19 ± 0.07	−0.10 ± 0.08	−0.17 ± 0.08	0.732
P for interaction Model 1				0.093				0.398
P for interaction Model 2				0.309				0.800
Change in log-HOMA-IR †								
High-fat diet	−0.21 ± 0.13	−0.10 ± 0.13	−0.02 ± 0.13	0.006	−0.13 ± 0.15	−0.11 ± 0.14	−0.04 ± 0.14	0.227
Low-fat diet	−0.24 ± 0.07	−0.20 ± 0.08	−0.23 ± 0.08	0.822	−0.15 ± 0.08	−0.08 ± 0.08	−0.14 ± 0.08	0.893
P for interaction Model 1				0.045				0.305
P for interaction Model 2				0.160				0.631
Change in log-HOMA-S †								
High-fat diet	0.18 ± 0.13	0.08 ± 0.13	0.02 ± 0.12	0.014	0.11 ± 0.15	0.09 ± 0.14	0.03 ± 0.14	0.328
Low-fat diet	0.26 ± 0.07	0.24 ± 0.08	0.27 ± 0.08	0.908	0.18 ± 0.08	0.11 ± 0.08	0.17 ± 0.08	0.899
P for interaction Model 1				0.028				0.342
P for interaction Model 2				0.112				0.708

Data are expressed as mean ± SE. Mean (SE) values and P values are calculated from general linear models, after adjustment for age, sex, ethnicity, and baseline values of the respective outcomes (Model 1). Model 2 is based on Model 1 with further adjustment for weight loss at each intervention time.

*
At 6 months, data were included from 307 and 319 for high-fat diet and low-fat diet groups, respectively; and at 2 years, data were included form 261 and 274 for high-fat diet and low-fat diet groups, respectively.

†
At 6 months, data were included from 297 and 304 for high-fat diet and low-fat diet groups, respectively; and at 2 years, data were included from 255 and 266 for high-fat diet and low-fat diet groups, respectively.