Supplementary Online Content

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eMethods

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

Participants

Participants were recruited using fliers, newspaper advertisements, and Internet postings that described the study as an opportunity for weight loss with provision of meals.

Inclusion criteria

1. Age between 18 and 40 years
2. Body mass index of 27 kg/m^2 or above
   Note. Body mass index is used to define overweight (25.0–29.9 kg/m^2) and obesity (≥30.0 kg/m^2) in adults, and weight loss is recommended for all overweight and obese adults.[1] Nevertheless, we chose a lower BMI of 27 kg/m^2 or above as an inclusion criterion, recognizing that weight loss corresponding to 10-15% of initial body weight may not be appropriate for some individuals with a lower BMI.
3. Medical clearance from a primary care provider
4. Willingness to eat and drink only the foods and beverages on the study menus during participation.

Exclusion criteria (men and women)

1. Body weight exceeding 160 kg
2. Change in body weight exceeding ±10% during the prior year
3. Current smoking
4. Recent adherence to a weight loss diet or vigorous physical activity regimen
5. Use of medications that could affect study outcomes
6. Diabetes mellitus (fasting plasma glucose ≥ 126 mg/dL)
7. Any other major illness as assessed by a medical history and laboratory screening tests (ALT, BUN, Creatinine, TSH, CBC).

Exclusion criteria for women

1. Irregular menstrual cycles
2. Pregnancy or lactation during the 12 months prior to enrollment
3. Any change in birth control medication during the 3 months prior to enrollment

Random Assignment

Preceding the test phase for each participant, a randomly assigned order of diets was retrieved from a sealed envelope. Thirty envelopes were prepared in advance, to be opened in sequence. To ensure balance, the six possible orders of diet were grouped into two complementary Latin Squares (see below), each diet appearing once in each position in each Latin Square.[2]

Diet sequences in 3-period crossover trial can be grouped into two Latin Squares. LF: Low-fat. LGI: low-glycemic index. VLC: very-low-carbohydrate.

	Period A	Period B	Period C
Latin Square 1	**LF**	**LGI**	**VLC**
	LGI	**VLC**	**LF**
	VLC	**LF**	**LGI**
Latin Square 2	**LF**	**VLC**	**LGI**
	LGI	**LF**	**VLC**
	VLC	**LGI**	**LF**

The sequence of thirty assignments consisted of three blocks of two Latin Squares (one of type 1, one of Type 2) and one block of four Latin Squares (two of each type). To ensure unpredictability, the orders of diet were randomly permuted within each Latin Square, and the Latin Squares were randomly permuted within each block. In three instances where a participant withdrew from the study after randomization but before completing the test phase, the prescribed order was not re-used. Among 21 subjects completing the study, the relative frequency of the six possible orders of diet did not differ significantly from a uniform distribution ($P>0.90$ by Fisher exact test).

Dietary Interventions

We provided participants with all of their food, prepared in a research kitchen, using menus that cycled every 14 days for the run-in diet and every 7 days for each test diet to ensure variety and avoid monotony. We used the Food Processor (v9.8, ESHA Research, Salem, Oregon) to compute macronutrient composition of the cycle menus. Dietary glycemic load was calculated as grams of available carbohydrate × GI for each food, using glucose as 100%,[3] and then summed over all foods to obtain daily values. Food was distributed across meals and snacks throughout the day as 25% of energy for breakfast, 30% for lunch, 30% for dinner, and 15% for an evening snack. During the test phase, the macronutrient composition of every meal reflected the composition of each respective diet. For production consistency and quality control, we standardized recipes and weighed all menu items to within 0.1 g for portions <10 g or within 0.5 g for portions ≥10 g using electronic scales. The diets were not composited and analyzed chemically for this study. However, prior comparative research showed good correlation between the calculated methods employed here and chemical analyses.[4]

We calculated individual energy needs as the arithmetic product of REE, estimated using a regression equation,[5, 6] and a physical activity factor derived from a questionnaire.[7] Energy intake was restricted to 60% of calculated needs to promote weight loss during the run-in phase, without feeding any participant <1,200 kcal/d. Energy needs for the weight stabilization period at the end of the run-in phase were estimated based on recent rate of weight loss during the energy-restricted diet: energy intake during weight loss (kcal/day) + [rate of weight loss (kg/day) × 7700 kcal/kg]. We noted that the conversion factor of 7700 kcal/kg is appropriate for calculations of short-term, but not long-term, energy balance.[8] During the transition from weight loss to stabilization, energy intake was ramped up over four days. More specifically, we calculated the difference between energy in the weight loss diet vs. estimated energy needs for weight stabilization and then increased energy intake by one-fourth of this difference over each of four days. The energy content of diets throughout the test phase remained constant, at the level required for weight stabilization at the end of the run-in phase.

We instructed participants to eat only the foods and supplements provided and to consume one meal per day (Monday through Friday, either lunch or dinner) on-site, in a dining room at the research center. All remaining meals and the evening snack, including those for days during the weekend, were packaged for consumption off-site. Frozen meals were provided for unanticipated circumstances, such as severe weather, that might preclude travel to the research center. Moreover, we educated participants to consume their meals and snack at regularly scheduled times throughout the day and to drink non-caloric beverages ad libitum, including up to three servings per day of caffeinated beverages. We asked participants to use rubber spatulas to wipe their plates and thereby facilitate consumption of all provided food.

We tracked body weight and monitored adherence at daily (Monday through Friday) visits for lunch or dinner. When necessary, we made adjustments in energy intake to achieve weight loss and stabilization during the run-in phase. We allowed the duration of the run-in phase to vary among participants, to account for individual differences in the rate of weight loss. The energy intake required for weight stabilization at the end of the run-in phase was established as the energy intake for the entire test phase, with no further adjustments regardless of any weight fluctuation with the test diets. Participants completed a diary during daily visits to document deviations from

study protocols, such as not eating all study foods or consuming any foods or beverages not consistent with the assigned diet. When participants had challenges in complying with protocols, we initiated behavioral counseling. We neither prescribed nor restricted aerobic physical activity but asked participants not to take part in a weight-training program.

Assessment of Body Composition

Before and after the weight loss period, we assessed body composition by dual-energy x-ray absorptiometry (DXA, Discovery A, Hologic, Inc., Waltham, MA) during an outpatient visit. We instructed participants to fast for at least 4 hours prior to the DXA scan. Body fat percentage was calculated as the proportion of fat mass to total mass.

Inpatient Hospital Admissions

When possible, admissions for females were scheduled during the follicular phase of the menstrual cycle to minimize potential confounding of metabolic outcomes. On three consecutive days of each inpatient hospital admission, we awakened the participant at 6:30 am following a 10-hour overnight fast. We asked the participant to void and then measured body weight using an electronic scale, with the participant wearing only a hospital gown and undergarments. The participant returned to bed for assessment of REE and blood pressure, positioned with the head of the bed elevated to approximately a 45° angle. We collected a 24-hour urine sample, starting in the morning on the first full day of the admission. On the final day of the admission, we also obtained a fasting blood sample and conducted an oral glucose tolerance test (OGTT). Participants ate breakfast after assessment of REE, except on the morning of the OGTT, lunch between noon and 1:00 pm, dinner between 5:00 and 6:00 pm, and an evening snack at 8:00 pm. Under staff supervision, participants took two daily 20-minute walks in the research ward, one after lunch and another after dinner. Specimens collected during the admission were sent to the Harvard Catalyst Central Laboratory or Laboratory Corporation of America (LabCorp) for analysis.

Resting Energy Expenditure. We measured REE by indirect calorimetry using a dilution canopy system (VMAX, Encore 29n, Viasys Healthcare, Inc., Yorba Linda, CA). The system was calibrated according to the manufacturer's specifications. Room temperature was set at 21°C (70°F), and lighting and noise were minimized to limit variability in measurements. Oxygen consumption and carbon dioxide production were measured for 30 minutes, and REE (kcal/d) was calculated using the Weir equation9 with data averaged over the last 20 minutes.

Hormones. Serum leptin was measured by radioimmunoassay (LINCO Research, St. Charles, MS), thyroid stimulating hormone (TSH) by chemiluminescent immunoassay (Beckman Coulter, Fullerton, CA), and total triiodothyronine (T3) by electrochemiluminescence immunoassay (LabCorp, Test 002188). Free cortisol in a 24-hour urine sample was measured by liquid chromatography/tandem mass spectrometry (LabCorp, Test 004432).

Insulin Sensitivity. We conducted an OGTT using a standard 75-gram dose of dextrose (Trutol, Thermo Fisher Scientific Inc., Waltham, MA), instructing the participants to drink the dextrose solution within 2 minutes. Blood for determination of plasma glucose and serum insulin was obtained by indwelling venous catheter at −10, −5, 0, 10, 20, 30, 60, 90, and 120 minutes relative to the time at which the participant starting consuming the dextrose. The hand and forearm were placed in a warming box set at 65°C (150°F), starting 15 minutes before the

first blood draw and throughout the OGTT, to arterialize venous blood samples. Glucose concentration was measured using an enzymatic reference method (LabCorp, 001818), and serum insulin was measured by chemiluminescent immunoassay (Beckman Coulter, Chaska, MN). Using plasma glucose and serum insulin data from the OGTT, we calculated indexes of peripheral and hepatic insulin sensitivity according to the method of Abdul-Ghani et al.[10]

Other Metabolic Syndrome Components. Serum levels of high-density lipoprotein cholesterol (HDL-C), total cholesterol, and triglycerides were measured by enzymatic reference methods (LabCorp, Tests 001925, 001065, and 001172). Non-HDL-C, calculated by subtracting HDL-C from total cholesterol, was assessed as an indicator of atherogenic particle concentration.[11, 12] Plasminogen activator inhibitor-1 (PAI-1) activity and high sensitivity C-reactive protein (CRP) in plasma were measured by enzyme-linked immunosorbent and immunochemiluminometric assays, respectively (LabCorp, Tests 146787 and 120766). We obtained three blood pressure readings per day at the right arm using an automated system (Dinamap, Criticon Inc, Tampa, Fla). All readings for each admission were averaged to obtain mean values for systolic and diastolic blood pressures.

Hunger and Well-being. Prior to breakfast during each hospital admission conducted as part of the test phase, we asked participants to rate level of hunger using a 10-cm visual analog scale, anchored with the descriptors "not at all hungry" and "extremely hungry." To assess well-being, we asked participants, "How do you feel right now?" Responses were obtained using a visual analog scale, anchored with the descriptors "really terrible" and "really great." A rating of 10 would represent the highest level of hunger and the best sense of well being on these two scales, respectively.

Assessments Under Free-Living Conditions

Total Energy Expenditure. TEE under free-living conditions was measured using the doubly labeled water (DLW) method. Following oral administration of the stable isotopes of hydrogen (^2H) and oxygen-18 (^{18}O) in the form of $^2H_2{}^{18}O$, the ^{18}O is eliminated from the body as both carbon dioxide and water, and the ^2H is excreted exclusively as water. The difference between the urinary elimination rates of ^{18}O and ^2H provides a measure of carbon dioxide production (rCO_2) which is used to estimate TEE. In the present study, the dose of DLW was 183.3 g (10.8 g of 99.9% ^2H_2O, 172.5 g of 10% $H_2{}^{18}O$) for a participant weighing ≤125 kg and 199.4 g (11.7 g of 99.9% ^2H_2O, 187.7 g of 10% $H_2{}^{18}O$) for a participant weighing >125 kg. Urine samples were collected before each dose and at regular intervals over 14 days following each dose. Isotopic enrichment data were obtained by gas-isotope-ratio mass spectrometry,[13] converted to "tracer-to-tracee" ratios,[14, 15] and used to model rCO_2 as described below. TEE was calculated from rCO_2 using the equation of Ravussin et al,[16] with the food quotient (FQ) as an estimate of respiratory quotient (RQ).[17]

When determining rCO_2 for each DLW study (1 at baseline, 3 during the test phase), we used multi-dose compartmental modeling to correct for residual tracer and possible variations in dilution spaces and water kinetics among study periods. We used separate compartments for ^2H and ^{18}O tracer data, because the volume of dilution (V_d) and elimination rate constant (k_{out}) differ between hydrogen and oxygen,[18] and set V_d and k_{out} for each DLW study as computationally adjustable parameters in the compartmental model. All four DLW studies were analyzed as

a single, linear steady state compartmental model during the fitting process using the "CompWin" module of the SAAM II program (v1.1).[19, 20] Subsequently, we decoupled the baseline study from the other studies, modeling the studies conducted during the test phase as a single entity. The model was refitted at the dose transition points to determine new optimal values of V_d and k_{out} for each study using the "Condition Change" feature of SAAM II. The coefficient of variation (CV) on the adjustable parameters was typically 0.8% to 1.5% (V_d) and 0.7% to 3% (k_{out}). The CV on the derived parameter TEE was typically 3% to 6%.

We also conducted a sensitivity analysis to assess whether the observed effect of dietary composition on TEE could be explained by the sensitivity of the method to slight differences in calculated FQ. In this analysis, TEE values were computed using experimental data from a typical DLW tracer study in which the FQ was incremented over the range of 0.7 to 1.0. FQ is a linear parameter derived independently from food composition tables,[17] and the analysis revealed that a 0.01 unit change in FQ causes ~1% change in TEE. To further enhance the interpretation of our findings, we measured RQ by indirect calorimetry before and during a 6-hour postprandial period for test meals reflecting the LF, LGI, and VLC diets, respectively. Resting RQ was measured for 20 minutes before each test meal, and postprandial RQ was measured for the final 20 minutes of each hour during the postprandial period. To adjust RQ, we assumed that one-third of a day would reflect resting RQ and two-thirds of the day would reflect postprandial RQ. The difference in measured RQ and calculated FQ for the LF, LGI, and VLC diets was 0.01, 0.00, and 0.04, respectively.

Physical Activity. We assessed physical activity with an accelerometer (GT1M, Actigraph, Pensacola, FL), positioned at the right hip using an elastic belt, and software available from the manufacturer (ActiLife v4.1.1). The device measures the magnitude of accelerations and sums magnitudes within a specified time interval, or epoch, and data are expressed as intensity counts per epoch. A one-minute epoch was used in the present study.

We asked each participant to wear the accelerometer for 7 days per assessment, except when sleeping, bathing, or participating in water activities such as swimming. If intensity counts were equal to zero for more than 60 minutes, we assumed that the participant was not wearing the monitor. We defined moderate- to vigorous-intensity physical activity (MVPA) using a cut point of ≥2,020 activity counts per minute, consistent with methodology for analyzing accelerometer data from the National Health and Nutrition Examination Survey (2003-2004).[21] Daily physical activity was quantified as total counts and minutes of MVPA. Data for any given day were considered valid when the participant wore the monitor for at least 8 hours.

Statistical Analysis

Our primary outcome was REE, assessed by indirect calorimetry. The estimated statistical power for this trial was based on data from a prior two-arm parallel-group study of adults after weight loss,[22] indicating a difference of 80 kcal/d in REE between a low-glycemic load diet and a conventional low-fat diet. The crossover design with the originally planned sample size of 24 provided 88% power to detect a difference of that magnitude between any two diets, using a Bonferroni-corrected Type I error rate to compensate for the three pairwise comparisons. The attained sample size of 21 provided 83% power.

Analytic procedures appropriate for the three-period crossover design were based on the factorial analysis of variance (ANOVA) methods described by Senn.[2] For each outcome variable obtained during the four inpatient admissions, we fitted a repeated-measures mixed-effects model with measurement period (baseline, LF, LGI, VLC) as the primary independent variable. The model was adjusted for sex, age at baseline, weight after run-in, and order of diets (6 possible sequences). The model was additionally adjusted for two time-varying covariates: mean weight during the measurement period and order of the measurement period (baseline always first; test-phase diets second, third, or fourth). For analysis of weight, the weight covariates were omitted. To account for within-subject correlation, the model included an unstructured covariance matrix relating the four measurement periods. In cases where the outcome was measured daily, the model also included a compound-symmetric covariance matrix relating the three measurement days per diet period. Because the independent variables in this model include both discrete factors and continuous measures, we use the terms 'ANOVA' and 'regression' interchangeably, both being special cases of the general linear model.

We tested two closely related null hypotheses for each outcome variable. The first test addressed the 'overall' null hypothesis that the mean outcome was equal in all three test-phase diet periods (H_0: LF=LGI=VLC). The second was a test for linear trend across diets, proceeding from highest to lowest glycemic load (H_0: slope=0 with equal spacing from LF to LGI to VLC). Both hypotheses addressed differences among the three diets, rather than changes from the common baseline period. Contrasts addressing these two hypotheses were constructed from parameters of the fitted ANOVA. A significance criterion of $P<0.05$ was employed for each test, making the expected number of Type I errors for each test close to 1 for the 22 outcome variables reported here.

When the overall comparison yielded a significant difference among the three diets (H_0: LF=LGI=VLC rejected at $P<0.05$), we performed pairwise comparisons among the three diets with a Bonferroni-adjusted criterion of $P<0.05/3$. These comparisons were equivalent to comparing changes from baseline because the design incorporated a common baseline period, preceding all test diet periods, rather than new baseline periods interspersed between diets.

For descriptive purposes we constructed an adjusted mean for each diet period, with standard error, as well as contrasts between baseline and each diet period and a contrast between baseline and the mean of the three diet periods. Variables demonstrating a skewed distribution were log-transformed for analysis, and the adjusted mean logs were re-transformed to natural units for reporting. One variable with extreme skew (CRP) was rank-transformed for analysis,[23] and in place of adjusted means we report the median with 95% confidence limits.[24]

To prevent undue influence of anomalous measurements, we applied a technique of 'robust' regression with M-estimation.[25] In contrast to ordinary least-squares regression, the M-estimation method calls for iterative re-fitting of the data, with lower weight applied at each iteration to those data points with larger residuals in the prior iteration. We employed the Talworth (step-function) weighting formula, which assigns unit weight to all data points lying within 2.795 residual standard deviations of the fitted model and zero weight to all data points lying farther away. The iterative weighting procedure is thus equivalent to an algorithm for discarding outliers until none remain. The value of 2.795 is chosen to provide 95% asymptotic efficiency in relation to ordinary least-squares estimation. For this report we conducted robust regression analysis on 22 outcome measures, as tabulated in Results. Each

analysis comprised 84 data points (21 subjects × 4 measurement periods), or 252 data points in the case of daily measurements. Among those 22 analyses, the number of discarded outliers ranged from 0 to 3, with median 1. Inclusion of outliers did not materially affect study outcomes.

We did not impute outcome data for the drop-outs. Failure to consider drop-outs in a study with a parallel design may produce selective bias favoring one specific diet over another; however, this risk is reduced in a crossover study with diets assigned in random order. Of the 33 participants enrolled in this study, 8 (25%) dropped out during the run-in phase and only 3 (9%) after random assignment. Two of these 3 participants never started a test diet, and one of them (3%) dropped-out after beginning one of the test diets, but before collection of any outcome data. Thus, our analyses did not discard or ignore any valid data for any participant. Moreover, non-completers did not differ from completers with respect to any of the characteristics listed in Table 2. Although the characteristics of the study group may nonetheless have changed as a result of drop-outs, participants represented a convenience sample, selected for likelihood to comply with the rigors of a 7-month feeding study (**see Comment**) and the risk of bias favoring a specific diet is therefore small.

Missing data were uncommon in this study. The 21 subjects whose data were included in analysis each completed and provided data for all three diet test phases. Among the 22 analyses reported in Results, each comprising 84 or 252 potential data points as described above, the median number of missing data points was 1. We consequently made no attempt to impute missing values, as our analytical tool, mixed-effects regression, provides unbiased estimates for incomplete data so long as the absent data are missing at random ('non-informative missingness,' unrelated to treatment or outcome).[26] With our short measurement periods, all analyzed subjects completing all diet test phases, and so few missing points, we considered the possibility of informative missingness to be remote and of little conceivable impact on results.

We compared baseline characteristics between subjects who completed the trial and those who dropped out using Fisher's Exact Test for dichotomies and Student's t-test for continuous measures, corroborated by the Wilcoxon rank-sum test in cases of skewed distribution. All tests were two-tailed. SAS software (version 9.2, Cary, NC) was used for all computations.

REFERENCES

1. Klein S, Sheard NF, Pi-Sunyer X, et al. Weight management through lifestyle modification for the prevention and management of type 2 diabetes: rationale and strategies. A statement of the American Diabetes Association, the North American Association for the Study of Obesity, and the American Society for Clinical Nutrition. *Am J Clin Nutr.* 2004;80:257-263.
2. Senn S. *Cross-over Trials in Clinical Research*. 2nd ed. New York: Chichester, UK: John Wiley & Sons; 2002.
3. Atkinson FS, Foster-Powell K, Brand-Miller JC. International tables of glycemic index and glycemic load values: 2008. *Diabetes Care.* 2008;31:2281-2283.
4. McCullough ML, Karanja NM, Lin PH, et al. Comparison of 4 nutrient databases with chemical composition data from the Dietary Approaches to Stop Hypertension trial. DASH Collaborative Research Group. *J Am Diet Assoc.* 1999;99:S45-53.
5. Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. *Am J Clin Nutr.* 1990;51:241-247.
6. Frankenfield D, Roth-Yousey L, Compher C. Comparison of predictive equations for resting metabolic rate in healthy nonobese and obese adults: a systematic review. *J Am Diet Assoc.* 2005;105:775-789.
7. Pereira MA, FitzerGerald SJ, Gregg EW, et al. A collection of Physical Activity Questionnaires for health-related research. *Med Sci Sports Exerc.* 1997;29:S1-205.
8. Katan MB, Ludwig DS. Extra calories cause weight gain--but how much? *Jama.* 2010;303:65-66.
9. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. *J Physiol.* 1949;109:1-9.
10. Abdul-Ghani MA, Matsuda M, Balas B, DeFronzo RA. Muscle and liver insulin resistance indexes derived from the oral glucose tolerance test. *Diabetes Care.* 2007;30:89-94.
11. Miller M, Ginsberg HN, Schaefer EJ. Relative atherogenicity and predictive value of non-high-density lipoprotein cholesterol for coronary heart disease. *Am J Cardiol.* 2008;101:1003-1008.
12. Di Angelantonio E, Sarwar N, Perry P, et al. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA.* 2009;302:1993-2000.
13. Wong WW, Lee LS, Klein PD. Deuterium and oxygen-18 measurements on microliter samples of urine, plasma, saliva, and human milk. *Am J Clin Nutr.* 1987;45:905-913.
14. Cobelli C, Toffolo G, Bier DM, Nosadini R. Models to interpret kinetic data in stable isotope tracer studies. *Am J Physiol.* 1987;253:E551-564.
15. Cobelli C, Toffolo G, Foster DM. Tracer-to-tracee ratio for analysis of stable isotope tracer data: link with radioactive kinetic formalism. *Am J Physiol.* 1992;262:E968-975.
16. Ravussin E, Harper IT, Rising R, Bogardus C. Energy expenditure by doubly labeled water: validation in lean and obese subjects. *Am J Physiol.* 1991;261:E402-409.
17. Black AE, Prentice AM, Coward WA. Use of food quotients to predict respiratory quotients for the doubly-labelled water method of measuring energy expenditure. *Hum Nutr Clin Nutr.* 1986;40:381-391.
18. Bluck LJC. Doubly labelled water for the measurement of total energy expenditure in man - progress and applications in the last decade. *Nutr Bull.* 2008;33:80-90.
19. Barrett PH, Bell BM, Cobelli C, et al. SAAM II: Simulation, Analysis, and Modeling Software for tracer and pharmacokinetic studies. *Metabolism.* 1998;47:484-492.
20. Cobelli C, Foster DM. Compartmental models: theory and practice using the SAAM II software system. *Adv Exp Med Biol.* 1998;445:79-101.
21. Metzger JS, Catellier DJ, Evenson KR, Treuth MS, Rosamond WD, Siega-Riz AM. Patterns of objectively measured physical activity in the United States. *Med Sci Sports Exerc.* 2008;40:630-638.
22. Pereira MA, Swain J, Goldfine AB, Rifai N, Ludwig DS. Effects of a low-glycemic load diet on resting energy expenditure and heart disease risk factors during weight loss. *JAMA.* 2004;292:2482-2490.
23. Iman RL, Conover WJ. The use of the rank transform in regression. *Technometrics.* 1979;21:499-509.
24. Hahn GJ, Meeker WQ. *Statistical Intervals: A Guide for Practitioners*. New York: John Wiley & Sons, Inc.; 1991.
25. Rousseeuw PJ, Leroy AM. *Robust Regression and Outlier Detection*. New York: John Wiley & Sons, Inc.; 1987.
26. Gadbury GL, Coffey CS, Allison DB. Modern statistical methods for handling missing repeated measurements in obesity trial data: beyond LOCF. *Obes Rev.* 2003;4:175-184.