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PROCEEDINGS ARTICLE

Tailoring dietary approaches for weight loss

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Although the 'Low-Fat' diet was the predominant public health recommendation for weight loss and weight control for the past several decades, the obesity epidemic continued to grow during this time period. An alternative 'low-carbohydrate' (Low-Carb) approach, although originally dismissed and even vilified, was comparatively tested in a series of studies over the past decade, and has been found in general to be as effective, if not more, as the Low-Fat approach for weight loss and for several related metabolic health measures. From a glass half full perspective, this suggests that there is more than one choice for a dietary approach to lose weight, and that Low-Fat and Low-Carb diets may be equally effective. From a glass half empty perspective, the average amount of weight lost on either of these two dietary approaches under the conditions studied, particularly when followed beyond 1 year, has been modest at best and negligible at worst, suggesting that the two approaches may be equally ineffective. One could resign themselves at this point to focusing on calories and energy intake restriction, regardless of macronutrient distributions. However, before throwing out the half-glass of water, it is worthwhile to consider that focusing on average results may mask important subgroup successes and failures. In all weight-loss studies, without exception, the range of individual differences in weight change within any particular diet groups is orders of magnitude greater than the average group differences between diet groups. Several studies have now reported that adults with greater insulin resistance are more successful with weight loss on a lower-carbohydrate diet compared with a lower-fat diet, whereas adults with greater insulin sensitivity are equally or more successful with weight loss on a lower-fat diet compared with a lower-carbohydrate diet. Other preliminary findings suggest that there may be some promise with matching individuals with certain genotypes to one type of diet over another for increasing weight-loss success. Future research to address the macronutrient intake component of the obesity epidemic should build on these recent insights and be directed toward effectively classifying individuals who can be differentially matched to alternate types of weight-loss diets that maximize weight-loss and weight-control success.

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LOSING WEIGHT THROUGH DIETARY CHANGE—SIMPLY ELUSIVE

Mathematically, weight loss should be simple and achieved by an energy deficit, which in turn is achieved by a total energy intake that is less than total energy expenditure. Given that the energy intake portion of this equation is a combination of dietary fats, carbohydrates, proteins and alcohol consumed, it should follow that eating and/or drinking less fat or less carbohydrate or less protein or less alcohol, or any combination of these, will lead to weight loss. Although seemingly straightforward, this has proven to be behaviorally and psychologically daunting for many of the millions of Americans and of the billion people worldwide who are overweight or obese and have tried to lose weight and then maintain that weight loss.[1] Health professionals have tried for decades to improve on the dismal success rates of 'eating less' by providing more specific guidance on what to eat less of—particularly fat vs carbohydrates. The past decade has generated an extensive set of trials that were designed to address the impact of manipulating fat and carbohydrate content and, to a lesser extent, protein content. The objective of this paper will be to critically review the data from those studies and provide current evidence-based conclusions and recommendations regarding optimal macronutrient composition(s) of weight-loss diets, practical perspectives and suggestions for further research needed.

THE TOPPLING OF THE REIGN OF THE LOW-FAT DYNASTY

A prominent feature of the dietary recommendations for weight loss in the NIH 1998 clinical guidelines for obesity prevention and treatment was a low-fat diet.[2] This recommendation was based on an evaluation of the controlled trial and observational epidemiological data available at the time.[3] The publication of these guidelines reinforced what was already the public health Low-Fat mantra being used ubiquitously to describe the essence of a healthful diet. Despite widespread, if not universal, adoption of the Low-Fat mantra among health professionals, the obesity epidemic in the US that began in the 1980s continued to spread and rise through the 1990s and into the new millennium. At least two overviews in the early 2000s of available evidence for the Low-Fat recommendation concluded that the evidence for superior weight loss with Low-Fat diets vs other alternatives, particularly low-carbohydrate diets (Low-Carb), was weak and was of limited value for making practical recommendations to the general population, because most of the trials in this area involved short-term (that is, 12 weeks or less), tightly controlled studies in small numbers of subjects.[4,5] A call for further studies led to a decade of longer, larger studies in free-living populations.

Low-Fat vs Low-Carb diets

Between 2003 and the current year, a series of studies from a variety of investigators contrasted Low-Fat vs Low-Carb weight-

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loss diets head to head.[6–18] As would be expected, these studies involved a range of sample sizes, duration and study populations, as well as a range of different approaches to defining, achieving and assessing Low-Fat vs Low-Carb diets. Despite all the variability in these design features, the general conclusion across this set of studies was relatively consistent—those assigned to the Low-Carb diet were at least as, and sometimes more, successful with weight loss compared with those assigned to the Low-Fat diet. This trend also held true for several metabolically related variables (for example, triglycerides, HDL-cholesterol, blood pressure).

Although the conclusion above appears to overturn what had been several decades of promoting the superiority of a Low-Fat diet over a Low-Carb diet as a dietary strategy for successful weight loss, it is important to recognize that the average weight loss in these trials, over durations of 6 months to 2 years, was always modest for both diet groups—typically in the range of 5–10 pounds. This was particularly true in the trials of longer duration, as there was a fairly consistent pattern that maximal weight loss was achieved after ~6 months, followed by varying degrees of recidivism.[16,17] The general response to the evidence generated in this recent set of studies has been to conclude that recommendations to favor a Low-Fat approach to weight loss over other macronutrient distributions were not as well founded as previously believed, and to shift the focus more simply to overall calorie restriction as the driver of weight loss, regardless of macronutrient content.[17] Given that the *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults* have not been formally updated since 1998,[2] this would appear to be an important, evidence-based shift in clinical recommendations. However, it is likely that the shift in emphasis from Low Fat to simply calories is an oversimplification of what the total body of current evidence suggests, and fails to capture what may be important differential impacts in population subgroups. Low-Fat vs Low-Carb diets may not yield substantially different responses on average, but not everyone is average.

NOT EVERYONE IS AVERAGE

The heterogeneity of individual responsiveness to weight-loss diets is substantial. As is standard in scientific publications, most weight-loss studies present average group responses with some measure of variance (for example, s.d., s.e.m., 95% CI), rather than presenting individual raw data. When presenting data this way, it is easy to fail to appreciate the magnitude of the typical range of individual variability in these weight-loss studies. In a two-arm weight-loss trial among 146 overweight or obese adults comparing a Low-Carb ketogenic diet to a Low-Fat diet plus orlistat, after 48 weeks the average weight loss in both groups was approximately 10% of baseline weight and not different between groups, but within both groups the individual weight loss ranged from small amounts of weight gain to approximately 30% weight loss (a range of >40 kg (>90 lbs) of weight change within each group).[19] In a four-arm weight-loss trial among 160 overweight and obese adults comparing Atkins, Zone, Weight Watchers and Ornish, after 12 months the average weight loss across all four groups was 4–7 kg (excluding drop-outs), but within all four groups the range included some individuals who gained $\geqslant 5$ kg and some who lost $\geqslant 15$ kg (a range of ~23 to ~40 kg (~50 to ~90 lbs) of weight change within each diet group).[8] The individual results for 12-month completers in our own A TO Z Study (80% retention at 12 months) are presented in Figure 1. In the A TO Z Study, the average weight loss at 12 months among the 311 overweight or obese women assigned to Atkins, Zone, LEARN or Ornish was 2–5 kg (~4–11 lbs; carrying baseline forward for drop-outs and missing data), but within all four groups the range of weight change was from gaining $\geqslant 5$ kg to losing $\geqslant 15$ kg (a range of ~30 to ~35 kg (~65 to ~75 lbs) of weight change within each diet group). Therefore, although the magnitude of the average weight loss in the Low-Fat vs Low-Carb diet studies and the differences between assigned groups have been modest, the tremendous variability of results within each assigned diet group suggests that these substantially different individual responses to the same diets merit further investigation.

TAILORING DIETS TO MAXIMIZE SUCCESS

Insulin resistance

At least three groups of investigators have reported that the weight-loss response to Low-Fat vs Low-Carb diets is different for insulin-resistant vs insulin-sensitive individuals. Two of these involved feeding studies with small sample sizes. In the first of the two feeding studies, 32 overweight women and men (body mass index 25–30 kg m^{-2}) were divided into two groups split at the median of serum insulin concentrations at the 30-min blood collection (INS-30) during an oral glucose tolerance test (OGTT). The 16 participants with the lowest INS-30 and the 16 with the highest INS-30 were then randomized, separately, to either a high-glycemic-load diet (60:20:20 carb:fat:protein) or a low-glycemic-load diet (40:30:30 carb:fat:protein). Therefore, a 2×2 study design was used, with 4 cells and $n = 8$ per cell. After 6 months, the group with the highest INS-30 lost more weight on the low-glycemic-index diet compared with the high-glycemic-index diet ($P = 0.047$). Among the group with the lowest INS-30, the absolute difference in weight loss was in the opposite direction although not statistically significant ($P = 0.3$); the interaction of INS-30 $\times$ Glycemic Load, however, was statistically significant ($P = 0.03$).[20]

The study design for the second of the two feeding studies was a similar 2×2 design with two diets—Low-Fat (60:20:20 carb:fat:protein) vs Low-Carb (40:40:20 carb:fat:protein) diets—and with participants selected as having a fasting insulin level either below 10 μIU ml^{-1} or above 15 μIU ml^{-1}. After 4 months, among the 21 obese, nondiabetic women enrolled ($n = 4$–6 per group), those in the lower fasting insulin group lost significantly more weight on the Low-Fat diet ($P < 0.01$), whereas those in the higher fasting insulin group lost significantly more weight on the Low-Carb diet ($P < 0.05$); the diet group X fasting insulin interaction was statistically significant ($P < 0.05$).[21] A third related study was conducted in a free-living population of 73 overweight young adults with body mass index >30 kg m^{-2} who were instructed to follow one of the two study diets for 18 months—Low Fat (55:20:25 carb:fat:protein) or Low Glycemic Load (40:35:25). Throughout the study duration, the average weight-loss trajectory was parallel for the two diet groups, and by 18 months both groups had lost small but similar amounts of weight on average; that is, 2–3 kg. An OGTT had been performed at baseline for most of the study participants, and the investigators analyzed the data after splitting each diet group into those above and below the median INS-30 of 57.5 μIU ml^{-1}. The investigators observed a significant difference in weight loss among those with the higher INS-30 values, favoring those assigned to the Low-Glycemic-Load diet relative to the Low-Fat diet ($P = 0.02$).[22] With these reported findings in mind, we recently conducted secondary analyses in our A TO Z Study data set examining possible weight-loss differences in the same 2×2 manner (data unpublished). For these exploratory analyses, we focused on just the Ornish and Atkins diet groups as being the clearest choices for Low-Fat vs Low-Carb diets. We then tested for a possible differential weight-loss response among those with higher vs lower baseline fasting insulin, TG/HDL-C ratios, HOMA-IR or QUICKI values (all indirect measures of insulin resistance),[23,24] and observed the same trend as reported by others—those assigned to the Low-Fat diet (that is, High Carb) who were likely more insulin resistant at baseline had significantly less success with weight loss than those who were more likely insulin sensitive at baseline. In all of the four studies described above, the weight loss by diet group assignment alone

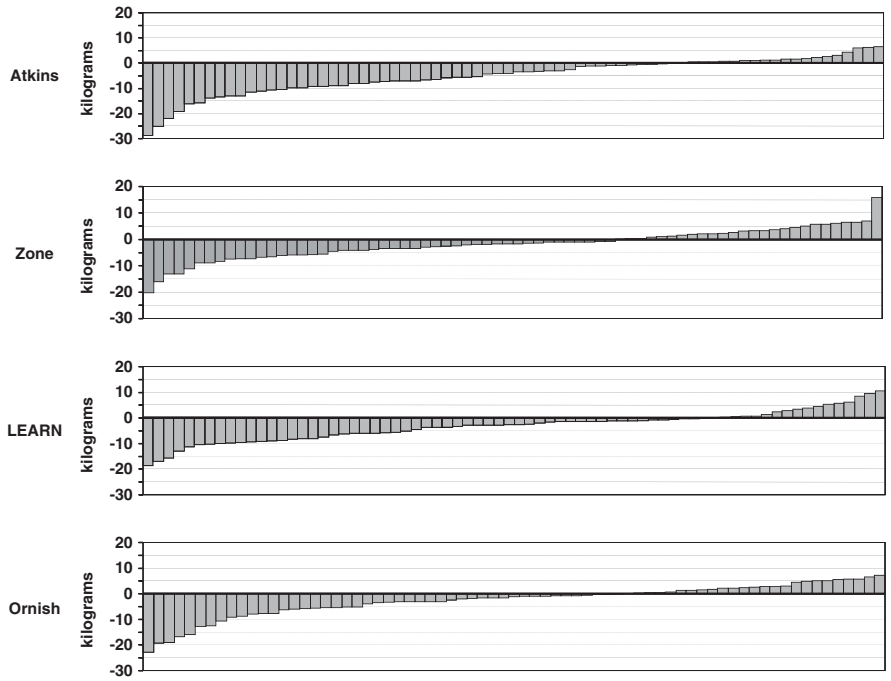

Figure 1. The 12-month weight change of individual study participants who completed the full study protocol of the A TO Z Study, by diet group, ordered from greatest loss to greatest gain. Each bar represents an individual study participant. Missing data for 12, 23, 24 and 22% for the Atkins, Zone, LEARN and Ornish groups, respectively.

(that is, collapsing the high and low INS-30 or fasting insulin groups together) was similar and neither clinically nor statistically significant for Low-Fat vs Low-Carb diets. However, when separating the study groups into those likely to be more insulin sensitive and those more insulin resistant, it was consistently observed that a Low-Carb assignment was superior for weight loss compared with a Low-Fat assignment among the more insulin-resistant groups, and that the opposite was true (although more inconsistently) for those who were more insulin sensitive.

This pattern of findings appears to reopen the case for taking into consideration the usefulness of a Low-Fat vs a Low-Carb dietary approach to weight loss. However, rather than suggesting that there is one diet that is superior to the other on average, in the general population, what is likely more true is that some individuals may be more successful with a Low-Fat diet, whereas others may be more successful with a Low-Carb diet. In this case, guiding an individual to a tailored weight-loss diet would involve assessing their insulin-resistance status. Although there are no standard clinical measures or cutoff points for this diagnosis, there are a number of surrogate or proxy measures that can be used (for example, fasting insulin, QUICKI, HOMA-IR, TG/HDL ratio and OGTT insulin concentrations).[23,24] Given the ongoing obesity epidemic and the strong association between obesity and insulin resistance, it is likely that future research and expert discussion will soon yield a consensus on clinically useful cutoff points of readily accessible variables to use as a basis for a diagnosis of insulin resistance.

Genotyping for increased weight-loss success

The unraveling and mapping of the human genome has led to an explosion of findings linking common single-nucleotide polymorphisms to obesity.[25] This raises the possibility that specific genotypes might be identified that could be used to classify individuals into those who were more responsive vs less responsive to various weight-loss diets. This hypothesis was tested in a secondary analysis of the POUNDS LOST Study when Qi *et al*.[26] explored whether the insulin-resistant substrate 1 (IRS-1) variant modified the long-term changes in insulin resistance and body weight in response to weight-loss diets. In that analysis, individuals with the IRS1 rs2943641 CC genotype experienced better weight-loss success when they were assigned to a high-carbohydrate and low-fat diet compared with a higher-fat and lower-carbohydrate diet.[26] Our research group conducted similar exploratory *post hoc* analyses with genotypes in the A TO Z Study and observed a significant multi-locus genotype X diet assignment interaction for weight loss (manuscript in progress; data not presented here). Although these exploratory observations of gene X diet interactions will need to be replicated to confirm their potential usefulness, it is not difficult to imagine that there are sources of genetic variation that might predispose individuals to be more successful on one type of weight-loss diet than another, and that significant gene–diet interactions may someday provide an important step forward to realizing personalized nutrition strategies for weight loss.

'LOW-CARB' DIET—POTENTIALLY AS PRONE TO MISUNDERSTANDING AND MANIPULATION AS 'LOW-FAT' DIET HAS BEEN

A brief word of caution is in order regarding the likelihood of oversimplifying a 'Low-Carb' recommendation so as to undermine its potential usefulness, similar to what has happened to 'Low-Fat' recommendations. The term 'Low Carb' provides little specificity, leaving it open to a wide range of interpretation and misinterpretation. Low Carb could be 10, 20, 30 or 40% of energy intake, each of which would involve different food choices (anything higher than 40% carbohydrate would be too similar to the current American Diet to merit a distinction as 'low'). The term 'Low Carb' also fails to address the wide range of specific types and sources of dietary carbohydrates, and surely not all of these types and sources should be lowered equally. Priorities for choosing high energy density and low nutrient density carbohydrate-rich food and beverage sources as the first place to cut back would be a

practical approach for reducing carbohydrate intake. In that regard, items high in added sugars, particularly those in sodas, would be a likely group to limit,[27] whereas the carbohydrates in leafy greens and nutrient-dense vegetables should probably be increased in the context of an overall lowering of total carbohydrate. Products made with white wheat flour are items that generally fall into the high energy density and low nutrient density category of carbohydrate-rich foods. Therefore, this would be another category of carbohydrates that might be targeted for limiting. Whole-wheat flour products are more nutrient dense than their white flour counterparts, but have a virtually identical glycemic index, and therefore might also be a carbohydrate-rich category to limit. In contrast, there might still be a place for modest portions of whole wheat berries (the true whole grain of either white wheat flour or whole-wheat flour) in an overall Low-Carb diet. However, everything is relative, and in terms of prioritizing the most nutrient- and energy-dense carbohydrate food sources, the wheat berries would probably fall behind bell peppers.

Surely the lessons learned from decades of unintended responses to the 'Low-Fat' public health mantra should be kept in mind here. Although the original intent of a 'Low-Fat' diet was to promote nutrient-dense, low-energy foods, such as dark green leafy vegetables and butternut squash, the response of the food industry was to produce a staggering selection of Low-Fat snack foods and desserts with so much added sugar as to be energy-dense/low-nutrient foods, flipping part of the original intent on its head. It is easy to imagine that the food industry would be just as successful at finding ways to make inexpensive, great-tasting Low-Carb junk food. Americans got a taste of this when the Atkins diet craze hit a recent peak, back in the 2000s. Therefore, if the case for a useful role of 'Low-Carb' diet continues to be strengthened, which will likely be true for some subsets of the population more than others, it will be critical to be aware of and effectively translate the important distinctions mentioned above to the target population.

WHAT ABOUT PROTEIN?

With the bulk of the weight-loss diet literature focusing on manipulations of fat and carbohydrate content, it has most commonly been the case that protein levels, typically the smallest contributor of the three major macronutrients, are held constant across diet plans to keep the study design more cleanly focused on the two largest contributors. However, it is worth noting in this overview that the 2000s did yield a set of studies that specifically addressed the separate and distinct role of protein manipulations in weight-loss response. One set of studies chose designs that held fat levels constant between diets and contrasted manipulations of protein vs carbohydrate.[28–31] Other studies held carbohydrate levels constant between diets and contrasted manipulations of protein vs fat.[32,33] In general, the results of this set of studies focusing on protein manipulations suggest that a higher-protein diet, regardless of whether it is used to substitute primarily for fats or carbohydrates, leads to greater appetite suppression and weight loss, as well as greater decreases in blood pressure and triglyceride concentrations. An important follow-up to these findings may be to investigate the extent to which the food sources of the protein (for example, plant-based protein vs animal-based protein) might influence these results—if not due to the differences specifically in the protein itself, then perhaps due to the differences in fiber or other constituents typical of certain high-protein food sources. However, the protein manipulations achieved in the relatively short and tightly controlled studies cited above may have limited generalizability; in the POUNDS LOST weight-loss study, which targeted a free-living population and included diets intended by design to have 25 vs 15% protein, participant diet assessment revealed that at 2 years the actual protein intake levels achieved in the different groups were virtually indistinguishable, at 21 vs 20%.[17] In a large European Study (Diogenes project), among 773 overweight and obese participants who had lost $\geqslant$8% body weight after 8 weeks on a low-calorie diet, those randomized to a diet of modestly increased protein intake and modestly decreased glycemic index had improved weight-loss maintenance relative to those randomized to lower protein and higher glycemic index treatment arms.[34]

SUMMARY/CONCLUSION

After decades of health professionals promoting a Low-Fat dietary approach for weight loss and weight control, a series of studies conducted in the past decade pitting Low-Fat vs Low-Carb diets have provided evidence that the Low-Fat diet is not a superior approach; a Low-Carb, and possibly a High-Protein, diet is equally, if not modestly more, effective. Taking a glass-half-full perspective, this suggests that many dietary approaches may be equally effective, thus suggesting a range of viable options to choose from for individuals interested in weight loss. In contrast, the glass half empty perspective would be that when these different dietary approaches are tested on the average study participant, the magnitude of average success is modest at best and perhaps even trivial or negligible—that is, the different dietary approaches are equally ineffective. Before throwing out the half-glass of water and putting that energy into the search for the next promising drug or wondering whether it will all come to bariatric surgery as a population-level approach to the obesity epidemic, there remains room for optimism and a need for further research into tailoring different dietary approaches for different classifications of overweight and obese individuals. Given the heterogeneity and complexity of the causes and manifestations of obesity, it would be overly simplistic and even arrogant to think that there could be one dietary approach to weight loss that would be superior to all other approaches, for all individuals. It is clear that any given dietary approach yields a wide range of responses among individuals. Individuals who are insulin resistant appear more likely to be successful in losing weight with a Low-Carb diet rather than a Low-Fat diet. The likely possibility that there is genetic predisposition to greater success with weight loss on one type of diet over another is emerging, and there may soon be inexpensive tests to classify individuals by genotype. The next generation of dietary weight-loss studies should address the exciting possibility of tailoring weight-loss diets to individual predisposition for greater weight-loss success. Expectations of the degree to which this dietary tailoring could contribute to halting and reversing the obesity epidemic should be tempered by a realistic appreciation of the many complex factors that have additively and synergistically caused the obesity epidemic, many of which are not directly dietary. With that very complexity in mind, any and every advantage that can be established and added to the tool chest of strategies to address obesity should be vigorously pursued. It would be difficult to imagine any long-term solution that did not include dietary modification in the equation. Tailoring dietary approaches by appropriately matching different types of individuals with different dietary strategies is likely to have a role in increasing individual success with weight loss and weight-loss maintenance, and in finding solutions to the obesity epidemic.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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REFERENCES

1 Mann T, Tomiyama AJ, Westling E, Lew AM, Samuels B, Chatman J. Medicare's search for effective obesity treatments: diets are not the answer. *Am Psychol* 2007; **62**: 220–233.
2 Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—the evidence report. National Institutes of Health. *Obes Res* 1998; **6** (Suppl 2): 51S–209S.
3 Astrup A, Grunwald GK, Melanson EL, Saris WH, Hill JO. The role of low-fat diets in body weight control: a meta-analysis of *ad libitum* dietary intervention studies. *Int J Obes Relat Metab Disord* 2000; **24**: 1545–1552.
4 Bravata DM, Sanders L, Huang J, Krumholz HM, Olkin I, Gardner CD *et al.* Efficacy and safety of low-carbohydrate diets: a systematic review. *JAMA* 2003; **289**: 1837–1850.
5 Freedman MR, King J, Kennedy E. Popular diets: a scientific review. *Obesity Res* 2001; **9** (Supp): 1S–40S.
6 Aude YW, Agatston AS, Lopez-Jimenez F, Lieberman EH, Marie A, Hansen M *et al.* The national cholesterol education program diet vs a diet lower in carbohydrates and higher in protein and monounsaturated fat: a randomized trial. *Arch Intern Med* 2004; **164**: 2141–2146.
7 Brehm BJ, Seeley RJ, Daniels SR, D'Alessio DA. A randomized trial comparing a very low carbohydrate diet and a calorie-restricted low fat diet on body weight and cardiovascular risk factors in healthy women. *J Clin Endocrinol Metab* 2003; **88**: 1617–1623.
8 Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA* 2005; **293**: 43–53.
9 Foster GD, Wyatt HR, Hill JO, McGuckin BG, Brill C, Mohammed BS *et al.* A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med* 2003; **348**: 2082–2090.
10 Maki KC, Rains TM, Kaden VN, Raneri KR, Davidson MH. Effects of a reduced-glycemic-load diet on body weight, body composition, and cardiovascular disease risk markers in overweight and obese adults. *Am J Clin Nutr* 2007; **85**: 724–734.
11 McAuley KA, Hopkins CM, Smith KJ, McLay RT, Williams SM, Taylor RW *et al.* Comparison of high-fat and high-protein diets with a high-carbohydrate diet in insulin-resistant obese women. *Diabetologia* 2005; **48**: 8–16.
12 Samaha FF, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J *et al.* A low-carbohydrate as compared with a low-fat diet in severe obesity. *N Engl J Med* 2003; **348**: 2074–2081.
13 Stern L, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J *et al.* The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. *Ann Intern Med* 2004; **140**: 778–785.
14 Truby H, Baic S, deLooy A, Fox KR, Livingstone MB, Logan CM *et al.* Randomised controlled trial of four commercial weight loss programmes in the UK: initial findings from the BBC 'diet trials'. *BMJ* 2006; **332**: 1309–1314.
15 Yancy Jr WS, Olsen MK, Guyton JR, Bakst RP, Westman EC. A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: a randomized, controlled trial. *Ann Intern Med* 2004; **140**: 769–777.
16 Gardner CD, Kiazand A, Alhassan S, Kim S, Stafford RS, Balise RR *et al.* Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A TO Z Weight Loss Study: a randomized trial. *JAMA* 2007; **297**: 969–977.
17 Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD *et al.* Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N Engl J Med* 2009; **360**: 859–873.
18 Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I *et al.* Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med* 2008; **359**: 229–241.
19 Yancy WS, Westman EC, McDuffie JR, Grambow SC, Jeffreys AS, Bolton J *et al.* A randomized trial of a low-carbohydrate diet vs orlistat plus a low-fat diet for weight loss. *Arch Intern Med* 2010; **170**: 136–145.
20 Pittas AG, Das SK, Hajduk CL, Golden J, Saltzman E, Stark PC *et al.* A low-glycemic load diet facilitates greater weight loss in overweight adults with high insulin secretion but not in overweight adults with low insulin secretion in the CALERIE Trial. *Diabetes Care* 2005; **28**: 2939–2941.
21 Cornier MA, Donahoo WT, Pereira R, Gurevich I, Westergren R, Enerback S, Eckel PJ *et al.* Insulin sensitivity determines the effectiveness of dietary macronutrient composition on weight loss in obese women. *Obes Res* 2005; **13**: 703–709.
22 Ebbeling CB, Leidig MM, Feldman HA, Lovesky MM, Ludwig DS. Effects of a low-glycemic load vs low-fat diet in obese young adults: a randomized trial. *JAMA* 2007; **297**: 2092–2102.
23 McLaughlin T, Abbasi F, Cheal K, Chu J, Lamendola C, Reaven G. Use of metabolic markers to identify overweight individuals who are insulin resistant. *Ann Intern Med* 2003; **139**: 802–809.
24 Pittas AG, Roberts SB. Dietary composition and weight loss: can we individualize dietary prescriptions according to insulin sensitivity or secretion status? *Nutr Rev* 2006; **64**: 435–448.
25 Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU *et al.* Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet* 2010; **42**: 937–948.
26 Qi Q, Bray GA, Smith SR, Hu FB, Sacks FM, Qi L. Insulin receptor substrate 1 gene variation modifies insulin resistance response to weight-loss diets in a 2-year randomized trial: the preventing overweight using novel dietary strategies (POUNDS LOST) trial. *Circulation* 2011; **124**: 563–571.
27 Johnson RK, Appel LJ, Brands M, Howard BV, Lefevre M, Lustig RH *et al.* Dietary sugars intake and cardiovascular health: a scientific statement from the American Heart Association. *Circulation* 2009; **120**: 1011–1020.
28 Due A, Toubro S, Skov AR, Astrup A. Effect of normal-fat diets, either medium or high in protein, on body weight in overweight subjects: a randomised 1-year trial. *Int J Obes Relat Metab Disord* 2004; **28**: 1283–1290.
29 Farnsworth E, Luscombe ND, Noakes M, Wittert G, Argyiou E, Clifton PM. Effect of a high-protein, energy-restricted diet on body composition, glycemic control, and lipid concentrations in overweight and obese hyperinsulinemic men and women. *Am J Clin Nutr* 2003; **78**: 31–39.
30 Layman DK, Evans E, Baum JI, Seyler J, Erickson DJ, Boileau RA. Dietary protein and exercise have additive effects on body composition during weight loss in adult women. *J Nutr* 2005; **135**: 1903–1910.
31 Noakes M, Keogh JB, Foster PR, Clifton PM. Effect of an energy-restricted, high-protein, low-fat diet relative to a conventional high-carbohydrate, low-fat diet on weight loss, body composition, nutritional status, and markers of cardiovascular health in obese women. *Am J Clin Nutr* 2005; **81**: 1298–1306.
32 Luscombe-Marsh ND, Noakes M, Wittert GA, Keogh JB, Foster P, Clifton PM *et al.* Carbohydrate-restricted diets high in either monounsaturated fat or protein are equally effective at promoting fat loss and improving blood lipids. *Am J Clin Nutr* 2005; **81**: 762–772.
33 Weigle DS, Breen PA, Matthys CC, Callahan HS, Meeuws KE, Burden VR *et al.* A high-protein diet induces sustained reductions in appetite, *ad libitum* caloric intake, and body weight despite compensatory changes in diurnal plasma leptin and ghrelin concentrations. *Am J Clin Nutr* 2005; **82**: 41–48.
34 Larsen TM, Dalskov SM, van Baak M, Jebb SA, Papadaki A, Pfeiffer AF *et al.* Diets with high or low protein content and glycemic index for weight-loss maintenance. *N Engl J Med* 2010; **363**: 2102–2113.