Dietary Interventions for Weight Loss and Maintenance: Preference or Genetic Personalization?

Hongyu Wu · Judith Wylie-Rosett · Qibin Qi

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Abstract Obesity and related co-morbidities are major health problems throughout the world. Dietary interventions are the most common strategies employed for weight loss in overweight and obese individuals. A large body of evidence has shown that many diets varying in quantity and quality of macronutrients are effective in promoting weight loss, but there is still extensive debate about what types of diet are most effective for treating overweight and obesity. Likewise, long-term weight loss and maintenance are difficult for overweight and obese people. On the other hand, significant inter-individual variation in weight loss in response to dietary composition has long been noted, partly accounted for by an individual's genetic makeup. Identification of gene–diet interactions in weight loss may provide useful information for the development of personalized approaches to weight loss. This review summarizes dietary intervention studies for weight loss and maintenance, and recent studies of gene–diet interaction with regard to weight loss.

Keywords Dietary intervention · Gene–diet interaction · Obesity · Weight loss · Weight maintenance

Introduction

Obesity is a major health problem throughout the world. According to the World Health Organization, more than 1.4 billion adults worldwide are overweight, and of these, approximately 500 million are obese [1]. The total number of obese people is projected to rise to 700 million by the year 2015 [1]. Interactions between genetic predisposition and dietary and

lifestyle factors are believed to account for the recent obesity epidemic [2, 3]. An excess amount of body weight has been associated with increased risk of cardiovascular disease, diabetes, certain types of cancer, and mortality, and the obesity-associated co-morbidities are of major public health concern [4].

Energy-restricted diets are effective in achieving weight loss [5]. However, there is still extensive debate regarding the effectiveness of different weight-loss diets varying in quantity and quality, and in composition of macronutrients [6, 7•]. More importantly, many people can lose weight in the short term by following a number of different weight-loss diets, but most have difficulty in maintaining their weight loss and achieving weight stability [8].

On the other hand, significant inter-individual variation in weight loss in response to dietary composition has long been noted, suggesting that individual genetic makeup may contribute to such differential responses [9]. With the recent advent of genome-wide association studies (GWAS), a large number of genetic loci have been associated with obese phenotypes [10•]. Emerging evidence has demonstrated that GWAS-identified genetic variants might interact with diet and lifestyle factors in reducing adiposity levels and obesity risk [11•, 12]. There is increasing interest in the new field of personalized dietary intervention based on an individual's genetic makeup [10•, 13].

The aim of this article is to review dietary intervention studies for weight loss and maintenance. In addition, we also briefly summarize recent studies of gene–diet interactions in weight-loss trials.

Dietary Interventions for Weight Loss

Macronutrient Composition

In recent years, there has been substantial focus on the role of dietary macronutrient composition in optimizing weight loss. For instance, there is a great interest in low-carbohydrate,

H. Wu
Department of Nutrition, Harvard School of Public Health, Boston,
MA 02115, USA

J. Wylie-Rosett · Q. Qi (✉)
Department of Epidemiology and Population Health, Albert Einstein
College of Medicine, Bronx, NY 10461, USA
e-mail: qibin.qi@einstein.yu.edu

high-protein, high-fat ('Atkins') diets [14]. A number of studies have compared the effects of low-carbohydrate diets with traditionally high-carbohydrate, low-fat, energy-deficit diets on weight loss and yielded various results [15–20] (Table 1).

In a six-month, randomized controlled weight-loss trial, Samaha et al. [15] found that severely obese subjects lost more weight after six months of a low-carbohydrate diet as compared with a low-fat, energy-restricted diet. After a 1-year follow-up of this trial, weight loss was similar between these two diet groups [16]. Similar results were observed in another randomized controlled trial in which the low-carbohydrate diet produced a greater weight loss than the conventional low-fat diet for the first six months, while the differences in weight loss were not significant at 1 year [17]. In the A TO Z (Atkins, Traditional, Ornish, Zone) Weight Loss study, Gardner et al. [18] compared four diets, representing a spectrum of carbohydrate intake: Atkins (very-low-carbohydrate), Zone (low-carbohydrate), LEARN (high-carbohydrate), and Ornish (very-high-carbohydrate). After 1 year of dietary interventions, premenopausal overweight and obese women assigned to the Atkins diet lost more weight than those assigned to the other three diets.

Few studies have investigated the effects of the low-carbohydrate diets on weight loss beyond 1 year. In the Dietary Intervention Randomized Controlled Trial (DIRECT) involving 322 moderately obese subjects, a low-carbohydrate, non-restricted-calorie diet based on the Atkins diet was observed to be more effective in weight loss as compared with a low-fat, restricted-calorie diet over the 2-year intervention [19]. However, Foster et al. [20] did not find significant differences in weight loss at 2 years, comparing a low-carbohydrate diet (Atkins) with a low-fat, calorie-restricted diet in 307 obese participants. It should be noted that each diet was combined with a lifestyle modification program during the intervention [20]. A recent, large two-year randomized trial (POUNDS LOST) assigned 811 overweight and obese adults to one of four reduced-calorie diets ranging from 35 to 65 % of dietary carbohydrate and showed that there was no significant difference in weight loss at 2 years among diet groups at this level of carbohydrate intake [5].

Recently, Bueno et al. [21•] performed a meta-analysis to compare the effects of very-low-carbohydrate diets with those of low-fat diets on long-term weight loss (1 or more years of follow-up) based on data from 13 randomized controlled trials with a total of 1,415 participants. Individuals assigned to a very-low-carbohydrate diet showed greater weight loss than those assigned to a low-fat diet (-0.91 [95 % CI $-1.65, -0.17$] kg) [21•]. In another recent meta-analysis, Hu et al. [22•] summarized data from 23 randomized controlled trials with 6 or more months of follow-up, including a total of 2,788 participants, to compare the effects of low-carbohydrate diets (≤ 45 % of energy) with low-fat diets (≤ 30 % of energy) on weight loss. Compared with those on low-fat diets, participants on low-carbohydrate diets exhibited a

slightly but not statistically significantly lower reduction in body weight (-1.0 [95 % CI $-2.2, 0.2$] kg). Interestingly, after removing studies with relatively small sample size or studies among patients with chronic diseases in the meta-analysis, weight loss was significantly greater in low-carbohydrate diets compared with low-fat diets.

A number of studies have investigated other comparisons of macronutrient composition in weight-loss diets [6, 7••]. In the POUNDS LOST trial, using a two-by-two factorial design, investigators also compared the effects of low-fat (20 % of energy) and high-fat (40 % of energy) diets, or average-protein (15 % of energy) and high-protein (25 % of energy) diets on weight loss, but there was no significant difference among the diet groups [5]. Many studies have shown that compared with traditional low-fat, standard-protein diets, low-fat, high-protein diets may increase weight loss [23–25], body fat mass loss [23, 26, 27], and satiety [28–30], and mitigate reductions in fat-free mass [30, 31] and resting energy expenditure [24], though these effects were not consistently observed in all studies. For example, Flechtner-Mors et al. [23] found that obese subjects with metabolic syndrome following a protein-rich diet lost more body weight and fat mass compared to those on the conventional protein diet for 1 year, whereas the loss of fat-free mass was similar in both diet groups. In a 6-week trial including 20 healthy subjects, both low-fat, energy-restricted diets varying in protein content (15 or 30 % of energy) were equally effective in reducing weight and fat mass, but greater satiety was reported in the high-protein diet group [29]. In addition, Hochstenbach-Waelen et al. [28] have demonstrated that a high-protein diet (25 % of energy) resulted in a 2.6 % higher 24-h total energy expenditure and 33 % higher satiety than did a low-protein diet (10 % of energy).

A systematic review and meta-analysis summarized data from 24 weight-loss trials that compared energy-restricted diets matched for fat intake but varied in protein and carbohydrate intakes [32•]. It showed that compared with standard-protein, low-fat diets, high-protein, low-fat diets provided a modest benefit for weight loss (-0.79 [95 % CI $-1.50, -0.08$] kg). This meta-analysis also indicated that the high-protein diets have positive effects on body composition, satiety and resting energy expenditure during weight loss. However, most of the trials included in this meta-analysis had less than 6 months of follow-up, and the long-term effects of high-protein, low-fat diets on weight loss remain unclear.

Glycemic Index

Besides the quantity of macronutrient composition, another interesting aspect of dietary interventions for weight loss is the quality of carbohydrates in the diets. The glycemic index (GI) of foods is considered as an important dietary factor in weight-loss diets, though the efficacy of low-GI diets for weight loss

Table 1 Selected dietary interventions for weight loss and maintenance

Study	Participants	Dietary interventions	Duration	Major findings
Samaha et al. 2003 [15]; Stern et al. 2004 [16]	132 severely obese men and women	Low-carbohydrate diet and energy-restricted, low-fat diet	6 months; 1 year	At 6 months, subjects on the low-carbohydrate diet lost more weight than those on the low-fat diet (-5.8 ± 8.6 kg vs. -1.9 ± 4.2 kg; $P=0.002$). At 1 year, difference in weight loss between two diet groups was not significant (-5.1 ± 8.7 kg vs. -3.1 ± 8.4 kg; $P=0.20$)
Foster et al. 2003 [17]	63 obese men and women	Low-carbohydrate diet and energy-restricted, low-fat diet	1 year	Participants on the low-carbohydrate diet lost more weight than those on the low-fat diet at 3 months (-6.8 ± 5.0 vs. -2.7 ± 3.7 percent of body weight; $P=0.001$) and 6 months (-7.0 ± 6.5 vs. -3.2 ± 5.6 percent of body weight; $P=0.02$), but the difference at 12 months was not significant (-4.4 ± 6.7 vs. -2.5 ± 6.3 percent of body weight; $P=0.26$)
Gardner et al. 2007 [18]	311 premenopausal overweight or obese women	Atkins (very-low-carbohydrate), Zone (low-carbohydrate), LEARN (high-carbohydrate), and Ornish (very-high-carbohydrate)	1 year	Weight loss was greater in the Atkins diet (-4.7 [95 % CI -6.3 , -3.1] kg) compared with the other diet groups (Zone: -1.6 [-2.8 , -0.4] kg; LEARN: -2.6 [-3.8 , -1.3] kg; and Ornish: -2.2 [-3.6 , -0.8] kg) ($P<0.05$)
Shai et al. 2008 [19]; Schwarzfuchs et al. 2010 [56]	322 moderately obese men and women	Low-carbohydrate diet, energy-restricted Mediterranean diet, and energy-restricted low-fat diet	2 years; 4 years of follow-up	Weight loss was greater in the low-carbohydrate diet group (-4.7 ± 6.5 kg) and the Mediterranean diet group (-4.4 ± 6.0 kg) than in the low-fat diet group (-2.9 ± 4.2 kg) ($P<0.001$ for both comparisons with the low-fat diet). During 4-year follow-up period, participants had regained 2.7 kg of weight lost in the low-fat group, 1.4 kg in the Mediterranean group, and 4.1 kg in the low-carbohydrate group ($P=0.004$ for all comparisons). There was a significant difference in total 6-year weight loss between the Mediterranean group and the low-fat group ($P=0.01$)
Foster et al. 2010 [20]	307 obese men and women	Low-carbohydrate diet and energy-restricted, low-fat diet	2 years	No significant difference in weight loss between the low-carbohydrate diet (-6.3 [-28.1 , -4.6] kg) and the low-fat diet (-7.4 [-9.1 , -5.6] kg) ($P=0.41$)
Sacks et al. 2009 [5]	811 overweight or obese men and women	Percentages of energy derived from fat, protein, and carbohydrates in the four diets were 20, 15, and 65 %; 20, 25, and 55 %; 40, 15, and 45 %; and 40, 25, and 35 %. (Two-by-two factorial comparisons of low-fat vs. high-fat and average-protein vs. high-protein, and in the comparison of highest and lowest carbohydrate content)	2 years	No significant difference in weight loss between the low-fat (20 %) and high-fat (40 %) diet groups (3.3 kg for both groups); between the average-protein and high-protein diet groups (3.0 and 3.6 kg, respectively), or between the lowest and highest carbohydrate diet groups (3.4 and 2.9 kg, respectively) ($P>0.20$ for all comparisons)
McMillan-Price et al. 2006 [39]	129 overweight or obese young adults	Four reduced-fat, high-fiber diets: Diets 1 and 2 were high-carbohydrate (55 % of total energy intake), with high and low GLs, respectively; diets 3 and 4 were high-protein (25 % of total energy intake), with high and low GLs, respectively. The glycemic load was highest in diet 1 and lowest in diet 4.	12 weeks	No significant difference in weight loss (percent of body weight) among diet groups (diet 1: -4.2 ± 0.6 %; diet 2: -5.5 ± 0.5 %; diet 3: -6.2 ± 0.4 %; and diet 4: -4.8 ± 0.7 %; $P=0.09$), but the proportion of subjects in each group who lost 5 % or more of their body weight varied significantly by diet (diet 1: 31 %; diet 2: 56 %; diet 3: 66 %; and diet 4: 33 %; $P=0.01$)
Das et al. 2007 [41]	34 healthy overweight adults	High-GL diet and low-GL diet	1 year	No significant difference in weight loss (percent of body weight) between the high-GL diet group (-8.04 ± 4.1 %) and low-GL diet group (-7.81 ± 5.0 %) ($P=0.59$)

Table 1 (continued)

Study	Participants	Dietary interventions	Duration	Major findings
Sichieri et al. 2007 [42]	203 healthy women (BMI: 23–30 kg/m ²)	High-GI diet and low-GI diet	18 months	No significant difference in weight loss between the high-GI diet group (-0.41 kg) and low-GI diet group (-0.26 kg) (P=0.93)
Ebbeling et al. 2007 [43]	73 obese young adults	Low-GI diet (40 % carbohydrate and 35 % fat) and low-fat (55 % carbohydrate and 20 % fat) diet	18 months	No significant difference in weight loss between the low-GI diet group and low-fat diet group (P=0.99). Insulin concentration at 30 minutes after a dose of oral glucose was a significant effect modifier (P=0.022 for interaction). In the high-insulin concentration stratum, the low-GI diet group lost more weight than the low-fat diet group (-5.8 vs. -1.2 kg; P=0.004)
Esposito et al. 2003 [47]	120 premenopausal obese women	Low-energy, Mediterranean-style diet and increased physical activity and a control group with general information about health food choices and exercise	2 years	Weight loss was greater in the Mediterranean-style diet group (-14 kg) than the control group (-3 kg) (P<0.001)
Esposito et al. 2004 [48]	180 patients with metabolic syndrome	Mediterranean-style diet and low-fat diet	2 years	Body weight decreased more in patients in the Mediterranean-style diet group (-4.0 [1.1] kg) than in those in the low-fat diet group (-1.2 [0.6] kg) (P<0.001)
Delbridge et al. 2009 [52]	141 healthy overweight or obese men and women	Very-low-energy diet (weight-loss phase); high-protein diet and high-carbohydrate diet (maintenance phase)	3 months (weight-loss phase); 1 year (maintenance phase)	Participants lost an average weight of 16.5 kg at 3 months and maintained a mean weight loss of 14.5 kg for 12 months. No significant differences between diet groups were observed (P=0.84)
Due et al. 2008 [53]	131 nondiabetic overweight or obese men and women	Low-calorie diet (weight-loss phase); moderate amount of fat diet (35–45 % of energy; and >20 % of fat as monounsaturated fatty), a low-fat (20–30 % of energy) diet, or a control diet (35 % of energy as fat) (maintenance phase)	8 weeks (weight-loss phase); 6 months (maintenance phase)	Participants with an initial weight loss of ≥ 8 % in all three diet groups regained weight (2.5, 2.2, and 3.8 kg, respectively), and there was no significant difference among diet groups (P=0.31)
Larsen et al. 2010 [54••]	773 overweight or obese men and women	Low-calorie diet (weight-loss phase); five diets (using a two-by-two factorial design): low-protein and low-GI diet, low-protein and high-GI diet, high-protein and low GI diet, high-protein and high-GI diet, and control diet (maintenance phase)	8 weeks (weight-loss phase); 26 weeks (maintenance phase)	The weight regain during the maintenance period was 0.93 kg (95 % CI, 0.31 to 1.55) higher in the low-protein groups than in the high-protein groups (P=0.003) and 0.95 kg (95 % CI, 0.33 to 1.57) higher in the high-GI groups than in the low-GI groups (P=0.003)
Dale et al. 2009 [55]	200 overweight or obese women	Two-by-two factorial design: high-carbohydrate diet and intensive support; high-monounsaturated-fat diet and intensive support; high-carbohydrate diet and nurse support; high-monounsaturated-fat diet and nurse support	2 years	Participants further reduced their body weight (average weight loss: ~2 kg), and there were no significant differences between the two support programs or the two diets

CI confidence interval, GL glycemic load, GI glycemic index

remains controversial [33]. High-GI food, such as refined grains and starchy foods may cause overeating and promote weight gain, while low-GI diets that are based on large amount of fruits, vegetable, legumes and whole grains tend to promote satiety, minimize postprandial insulin secretion and maintain insulin sensitivity [34].

Many trials have evaluated the effectiveness of low-GI or low-glycemic load (GL) diets for weight loss with inconsistent findings [33] (Table 1). Some short-term (6 months or less) weight-loss trials found that participants assigned to follow low-GI/GL diets had greater weight loss than those assigned to follow high-GI/GL diets [35, 36], while others did not [37–39]. A Cochrane meta-analysis of six short-term (5 weeks to 6 months in duration, with up to 6 months follow-up), randomized controlled trials (a total of 202 participants) showed that there was a 1.1-kg greater weight loss with low-GI/GL diets compared to high-GI/GL diets [40].

However, the beneficial effect of low-GI/GL diets on weight loss was not observed in two long-term, randomized controlled trials. Das et al. [41] found that weight losses were similar between high-GL and low-GL diet groups (both were 30 % energy-restricted) among 34 healthy overweight adults after a 1-year intervention. After a 6-week run-in period, 203 healthy women were assigned to a high-GL or a low-GL, mildly energy-restricted diet, and weight loss was similar between diet groups after 18 months [42]. In addition, in a randomized trial of 73 obese young adults, after a 6-month intensive intervention period and a 12-month follow-up period, there was no significant difference in weight loss between the low-GL (40 % carbohydrate and 35 % fat) and low-fat (55 % carbohydrate and 20 % fat) diet groups [43].

Mediterranean Diet

In recent years, the Mediterranean-style diet has been widely applied in dietary interventions to modify cardiovascular risk factors as well as to lose weight [44•, 45]. In general, a traditional Mediterranean-style diet is characterized by a high intake of monounsaturated fat, plant proteins, whole grains, and fish; moderated intake of alcohol, and low consumption of red meat, refined grains, and sweets [46].

Several dietary intervention trials have suggested that the Mediterranean diet was beneficial for weight loss [19, 47, 48] (Table 1). In a 2-year, randomized, single-blind trial, 120 premenopausal obese women were randomly assigned to an intervention group with a low-energy Mediterranean-style diet and increased physical activity or a control group with general information about health food choices and exercise [47]. After 2 years of follow-up, women in the Mediterranean diet group had greater weight loss than those in the control group. In another randomized trial involving 180 patients with the metabolic syndrome, conducted by the same research group, the Mediterranean diet was found to be more effective in reducing

the prevalence of the metabolic syndrome as well as weight loss when compared with a traditional low-fat diet [48]. In the DIRECT study, investigators also evaluated the effects of the Mediterranean diet on weight loss, and found that an energy-restricted Mediterranean diet may be superior to a conventional energy-restricted, low-fat diet [19].

Other studies did not confirm the beneficial effects of the Mediterranean diet on weight loss [49–51]. In the Prevención con Dieta Mediterránea (PREDIMED) Study, a large, randomized controlled clinical trial on the primary prevention of cardiovascular disease, there were no significant differences in short-term or long-term weight changes between the Mediterranean and low-fat diets [49, 50]. Tuttle et al. did not observe beneficial effects of the Mediterranean diet on weight loss as compared with a low-fat diet among 101 patients who had all experienced a first myocardial infarction [51]. However, these trials were primarily designed for cardiovascular disease prevention, and not for weight loss.

A recent meta-analysis compared the Mediterranean diet to low-fat diets for modification of cardiovascular risk factors using data from 6 randomized trials with a total of 2,650 participants [44•]. After 2 years of follow-up, participants assigned to the Mediterranean diet had more favorable changes in weighted mean differences of body weight than those assigned to low-fat diets (-2.2 [95 % CI -3.9, -0.6] kg). In addition, this meta-analysis also indicated that the Mediterranean diet was more effective than low-fat diets in the long-term improvement of blood pressure, lipids, glucose and inflammatory markers [44•].

Dietary Interventions for Weight-Loss Maintenance

Although many of the aforementioned dietary interventions have been suggested as effective tools for weight loss, their long-term effects, especially on weight-loss maintenance have not been well established. Very few dietary intervention trials have been specifically designed to investigate weight maintenance, and the results are inconsistent [52, 53, 54•, 55] (Table 1).

Two randomized dietary intervention trials reported that diets varying in macronutrient composition had similar effects on weight-loss maintenance [52, 53]. After an 8-week weight-loss phase using low-calorie diet, 131 nondiabetic overweight or obese subjects with an initial weight loss of ≥ 8 % were randomly assigned to one of three diets: moderate amount of fat diet (35–45 % of energy; and >20 % of fat as monounsaturated fatty), a low-fat (20–30 % of energy) diet, or a control diet (35 % of energy as fat) for 6-months of weight-loss maintenance [53]. Participants in all three of the diet groups regained weight (2.5, 2.2, and 3.8 kg, respectively), and there were no significant differences among the diet groups. In another two-phase, randomized, dietary intervention trial,

Delbridge et al. [52] compared the effects of a low-fat, high-protein diet with a low-fat, high-carbohydrate diet on 12 months of weight maintenance in 141 healthy, overweight or obese subjects. In phase 1, all subjects were provided with a very-low-energy diet for 3 months, and they lost an average weight of 16.5 kg. During phase 2, subjects were randomly assigned to the high-protein or high-carbohydrate dietary groups and maintained a mean weight loss of 14.5 for 12 months, and no significant differences between groups were observed.

In the Diet, Obesity, and Genes study (Diogenes) [54•], a large dietary intervention trial conducted in eight European countries, 773 participants who had lost at least 8 % of their initial body weight after a low-calorie-diet phase were randomly assigned, using a two-by-two factorial design, to one of five diets over a 26-week period: a low-protein and low-GI diet, a low-protein and high-GI diet, a high-protein and low-GI diet, a high-protein and high-GI diet, or a control diet. The weight regain during the maintenance period was 0.93 kg (95 % CI, 0.31 to 1.55), higher in the low-protein groups than in the high-protein groups (~5 percent of protein intake difference between groups) and 0.95 kg (95 % CI, 0.33 to 1.57) higher in the high-GI groups than in the low-GI groups (~5 GI-unit difference between groups). Of note, no significant weight regain was observed in the high-protein and low-GI diet group, and the study completion rate was significantly better in this diet group compared to the other groups. These data suggested that diets with a modest increase in protein content and a modest reduction in glycemic index are more effective in weight-loss maintenance.

In a randomized controlled trial with support programs, Dale et al. [55] have shown that participants maintained their weight and even lost more weight over 2 years. Using a two-by-two factorial design, 200 overweight or obese women who had lost 5 % or more of their initial body weight were randomly assigned to an intensive support program or to a nurse-led program with advice about high-carbohydrate diets or relatively high-monounsaturated-fat diets. After 2 years, participants further reduced their weight (average weight loss: ~2 kg), and there were no significant differences between the two support programs or the 2 diets.

Recently, investigators from the DIRECT study reported their 4-year follow-up data after a 2-year dietary intervention for weight loss [56]. At 6 years after study initiation, 67 % of the participants had continued with their originally assigned diet. During the 4-year follow-up period, participants had regained 2.7 kg of the weight they had lost in the low-fat group, 1.4 kg in the Mediterranean group, and 4.1 kg in the low-carbohydrate group ($P=0.004$ for all comparisons). There was a significant difference in total 6-year weight loss between the low-fat group and the Mediterranean group ($P=0.01$), but not between the low-fat group and the low-carbohydrate group or between the Mediterranean group and the low-carbohydrate group.

Gene–Diet Interactions in Weight-Loss Trials

A personalized dietary intervention based on an individual's genetic background might be an efficient strategy for weight loss, but reliable genetic markers of successful weight loss are poorly understood [9]. Several previous reviews have evaluated gene–diet interaction studies on weight loss for candidate genes; however, these results have not been replicated and remain inconclusive [2•, 3]. In the current review, we summarize recently published studies investigating interactions between GWAS-identified, obesity-related genetic variants, such as variants in fat mass and the obesity-associated (*FTO*) gene, insulin receptor substrate 1 (*IRS1*), and glucose-dependent insulinotropic polypeptide receptor (*GIPR*), and dietary interventions for weight loss [57–60, 61•, 62•, 63] (Table 2).

FTO is the first and strongest obesity susceptibility gene identified through GWAS so far [64–66]. The *FTO* gene is highly expressed in the hypothalamus, a region involved in the regulation of food intake and energy expenditure [67, 68]. Several short-term dietary intervention studies have investigated whether *FTO* genetic variation modified weight loss in response to energy-restricted diets [57–60]. In a 3-month intervention with a hypocaloric diet including 106 obese subjects, the carriers of the *FTO* rs9939609 variant were observed to experience greater weight loss than non-carriers [57]. Among 204 overweight or obese Japanese women following a calorie-restricted diet after 14 weeks, there were no significant differences in weight loss between the *FTO* rs9939609 genotype groups [58]. In a 10-week dietary intervention study, 771 obese subjects were randomly assigned to a high-fat, low-carbohydrate diet or a low-fat, high-carbohydrate diet, and no significant effect of the *FTO* rs9939609 genotype on weight loss in response to these two diets was observed [59]. Results were similar in another 3-month dietary intervention trial, and there was no significant interaction between the *FTO* rs9939609 genotype and dietary interventions on weight loss after two hypocaloric diets with different macronutrient composition in 305 obese subjects [60].

In the POUNDS LOST trial, Zhang et al. [61•] evaluated whether *FTO* variants modified the long-term effects of diets with different protein contents on weight loss and found significant gene–diet interaction patterns. Carriers of the *FTO* rs1558902 risk allele (minor allele) had a greater reduction in weight, body composition, and fat distribution in response to a high-protein diet at 2 years, whereas an opposite genetic effect was observed on changes in fat distribution in response to a low-protein diet. These data suggested that individuals with the risk allele of the *FTO* variant rs1558902 who choose a high-protein diet might obtain more benefits in terms of weight loss, and improvement of body composition and fat distribution, than non-carriers.

Table 2 Selected gene–diet interaction studies on weight loss for GWAS-identified genetic loci

Study	Locus (SNP)	Participants	Dietary interventions	Duration	Major findings
de Luis et al. 2013 [57]	<i>FTO</i> (rs9939609)	106 obese men and women	Low-fat hypocaloric diet	3 months	The A carriers of <i>FTO</i> rs9939609 had greater weight loss than non-carriers ($P<0.05$)
Matsuo et al. 2013 [58]	<i>FTO</i> (rs9939609)	204 overweight or obese women	Low-calorie diet	14 weeks	No significant difference in weight loss among AA genotype, TA and TT genotype groups ($P=0.36$)
Grau et al. 2009 [59]	<i>FTO</i> (rs9939609)	771 obese men and women	High-fat, low-carbohydrate diet and low-fat, high-carbohydrate diet	10 weeks	No significant influence of <i>FTO</i> rs9939609 genotype on weight loss in response to these two diets (P for interaction= 0.55)
de Luis et al. 2013 [60]	<i>FTO</i> (rs9939609)	305 obese men and women	High-fat, low-carbohydrate diet and low-fat, high-carbohydrate diet	3 months	No significant difference in weight loss between <i>FTO</i> rs9939609 genotypes in low-carbohydrate diet or in low-fat diet groups (both $P>0.05$)
Zhang et al. 2012 [61•]	<i>FTO</i> (rs1558902)	742 overweight or obese men and women	High-protein diet and low-protein diet	2 years	The risk allele (A) of <i>FTO</i> rs1558902 was significantly associated with a 1.51-kg greater weight loss in the high-protein group ($P=0.010$), but not in the low-protein group ($P=0.43$; P for interaction= 0.08). Significant <i>FTO</i> -diet interaction on 2-year changes in fat-free mass, whole body total percentage of fat mass, total adipose tissue mass, visceral adipose tissue mass, and superficial adipose tissue mass (All P for interaction <0.05)
Qi et al. 2011 [62•]	<i>IRS1</i> (rs2943641)	738 overweight or obese men and women	High-carbohydrate, low-fat diet and low-carbohydrate, high-fat diet	2 years	Individuals with the CC genotype of <i>IRS1</i> rs2943641 had greater weight loss at 6 months than those without this genotype in response to a high-carbohydrate, low fat diet ($P=0.018$). No significant genotype effect or gene-diet interaction on weight loss at 2 years
Qi et al. 2012 [63]	<i>GIPR</i> (rs2287019)	737 overweight or obese men and women	High-carbohydrate, low-fat diet and low-carbohydrate, high-fat diet	2 years	The T allele of <i>GIPR</i> rs2287019 was marginally associated with greater weight loss at 6 months in the high-carbohydrate, low-fat diet group ($P=0.06$), whereas no significant genotype effect was observed in the low-carbohydrate, high-fat diet ($P=0.57$) (P for interaction= 0.08). No significant genotype effect or gene-diet interaction on weight loss at 2 years

SNP single nucleotide polymorphism, GWAS genome-wide association study

Investigators from the same research group also tested effects of several other obesity- and diabetes-related genetic variants on weight loss in response to dietary intervention in the POUNDS LOST trials [62•, 63]. They found that participants with the CC genotype of *IRS1* rs2943641, associated with insulin resistance and abdominal adiposity [69, 70], had greater weight loss and improvement of insulin resistance than those without this genotype in response to a high-carbohydrate, low-fat diet [62•]. In addition, the T-allele carriers of the *GIPR* rs2287019 variant, which is associated with obesity risk and glucose metabolism [64, 71, 72], tended to have greater weight loss than non-carriers by choosing a high-carbohydrate, low-fat diet [63]. However, it should be noted that the observed potential gene–diet

interactions were more evident with short-term (6-month) weight loss than with long-term (2-year) weight loss.

Conclusions

In summary, there are many dietary strategies focused on macronutrient composition or quality, and food-enriched manipulation for weight loss. Data from meta-analyses of dietary intervention trials suggest that some weight-loss diets, such as low-carbohydrate diets, low-GI/GL diets, and the Mediterranean diet, might be alternatives to conventional low-fat diets, especially for short-term weight loss, but have great variability of long-term effects. Moreover, the difference

in weight loss among these diets is only 1–2 kg or less, which appears to be of little clinical significance. Thus, overweight and obese people can choose many different weight-loss diets on the basis of their personal preferences. However, the greater challenge is to find appropriate dietary strategies to prevent weight regain and achieve long-term weight stability, since current evidence is still limited.

Weight loss and long-term weight maintenance are complex, multifactorial processes that depend on many environmental, behavioral and genetic factors. Although recent published studies of gene–diet interactions provided evidence supporting the notion of personalized dietary interventions for weight loss, it is premature to tailor obesity therapy based on individuals' genetic information at the current stage. More efforts are needed to identify factors, such as genetics, behaviors, biological information, and psychopathological conditions, which may influence response to weight-loss dietary interventions. Eventually, all these factors should be taken into account in future personalized dietary interventions to achieve effective weight loss and successful long-term weight stability.

Compliance with Ethics Guidelines

Conflict of Interest Hongyu Wu declares that he has no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance,
- Of major importance

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