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Gene–diet interaction and weight loss

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Abstract

Purpose of review—The purpose of this review is to summarize recent advances in investigations of dietary factors, genetic factors, and their interactive effects on obesity and weight loss.

Recent findings—Even with a tremendous body of research conducted, controversy still abounds regarding the relative effectiveness of various weight-loss diets. Recent advances in genome-wide association studies have made great strides in unraveling the genetic basis of regulation of body weight. In prospective cohorts, reproducible evidence is emerging to show interactions between genetic factors and dietary factors such as sugar-sweetened beverage on obesity. In randomized clinical trials, individuals' genotypes have also been found to modify diet interventions on weight loss, weight maintenance, and changes in related metabolic traits such as lipids, insulin resistance, and blood pressure. However, replication, functional exploration, and translation of the findings into personalized diet interventions remain the chief challenges.

Summary—Preliminary but promising data have emerged to lend support to gene–diet interaction in determining weight loss and maintenance; and studies in the area hold great promise to inform future personalized diet interventions on the reduction of obesity and related health problems.

Keywords

diet; gene; interaction; weight loss

INTRODUCTION

Obesity has become an increasingly serious health issue throughout the world [1]. The escalating epidemic of obesity is believed to be largely due to noticeable transition from a 'traditional' to 'obesogenic' environmental patterns featured by increased access to highly palatable, calorie-dense foodstuffs and beverages, as well as sedentary lifestyle [2,3].

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Conflicts of interest

There are no conflicts of interest.

As one of the main stream efforts struggling against rapid rise of obesity and its comorbidities such as type 2 diabetes, cardiovascular disease, and certain cancers, various diet interventions have been proposed to improve weight loss and long-term weight maintenance [4,5]. Although these diets generally show no significant difference in effectiveness on weight loss, considerable interindividual heterogeneity has been noted in participants' response; and accumulating evidence suggests that genomic makeup may at least partly account for such variability [6–8]. In the past few years, genome-wide investigations have identified several dozens of variants associated with body weight and obesity [9,10]. Interestingly, these findings suggest that pathways of neurological regulation of appetite and food intakes are heavily involved, providing biological basis for the potential interactions between genetic factors and dietary factors in determining body weight [11]. In line with these findings, recently emerging data from both observational studies and randomized controlled trials (RCTs) have shown promising evidence to support the potential gene–diet interactions on obesity and weight loss [8,12[■],13[■]].

The purpose of the present review is to summarize the recent literature about gene–diet interactions in relation to obesity, weight loss, and maintenance. The review will also briefly address the potential challenges that lie in the area and future directions.

KEY POINTS

- Both dietary and genetic factors affect obesity and weight loss, through an interactive manner.
- Studying gene–diet interactions in large prospective cohorts and randomized clinical trials are essential and complementary approaches.
- Personalized diet intervention on weight loss and maintenance holds great promise for delivering more efficient prevention and treatment on obesity and related metabolic disorders.

DIET AND WEIGHT LOSS

Traditionally, energy-restricted diets are commonly prescribed for weight loss treatment [14]. In recent years, there has been substantial focus on the macronutrient profile of a diet in potentiating weight loss and maintenance [15–17]. In a meta-analysis of 33 RCTs and 10 cohort studies, Hooper *et al.* [18] reported that lower total fat intake led to moderate but significant weight loss in adults with baseline fat intakes of 28–43% of energy intake and durations from 6 months to over 8 years. In another meta-analysis including 1141 obese patients, it was found that the low carbohydrate diet was associated with approximately 7 kg reduction in body weight [19]. Recent evidence suggests that a high-protein (25–35% of energy) and low-fat diet may increase body fat mass loss, increase satiety, and improve cardiovascular risk factors. Wycherley *et al.* [20] conducted a systemic review on the carbohydrate-to-protein ratio of low-fat diets. Compared with an energy-restricted standard protein diet, an isocalorically prescribed high-protein diet provided modest benefits for reductions in body weight, fat mass.

Sacks *et al.* [6] compared four popular weight-loss diets varying in fat, protein, or carbohydrates in a 2-year intervention trial of 811 overweight or obese participants. These diets appeared not significantly different in promoting weight loss. In diabetic patients, Ajala *et al.* [21] compared 20 RCTs that assessed a variety of diets with interventions at least 6 months; and found that low-carbohydrate and Mediterranean diets led to greater weight loss (−0.69 kg and −1.84 kg, respectively).

In addition, several dietary factors have been related to reduction of body weight. For example, high intakes of whole grains have been consistently associated with lower BMI and reduced risk of obesity, though data from clinical trials are still sparse and controversial [22]. Dairy products have also been found to facilitate weight loss in several short-term RCTs, though the effects were moderate [23]. In addition, two recent RCTs showed that reduced consumption of sugar sweetened beverages (SSBs) promoted weight loss in Children [24,25]. However, even with a tremendous body of research conducted, controversy still abounds regarding the relative effectiveness of various weight-loss diets.

GENETICS OF OBESITY AND WEIGHT LOSS

Accumulating evidence has strongly implicated a genetic component in determining body weight and susceptibility to obesity. Numerous twin, family, and adoption studies have yielded insight into the contribution of genetic factors to BMI, the most commonly used measure for obesity [26]. These studies have generated widely ranged estimates for the proportion of variance in BMI accounted for by the genetic factors (namely, heritability, h^2), with a general consensus being about 40–60%. In the past few years, the application of genome-wide association study (GWAS) has made significant advances in the identification of specific genetic variants; and thus far more than 30 genomic loci containing variants affecting BMI have been detected (Fig. 1). On average, these variants raise BMI by 0.17 (0.06–0.39) kg/m² per allele. The frequencies of the effective alleles lie between 4 and 87% (Fig. 1). Among the identified loci, FTO shows the strongest association. Interestingly, many obesity genes are highly expressed in the brain specially regions involved in the regulation of appetite and food intakes, highlighting a neuronal influence on body weight regulation. In addition to BMI, GWASs have also identified dozens of variants that are related to body fat distribution such as waist circumference or waist to hip ratio [27].

Two GWASs have been conducted on weight loss after gastric bypass surgery. In one study of 693 individuals undergoing Roux-en-Y gastric bypass (RYGB) surgery with replication in an independent population of 327 individuals undergoing RYGB, Hatoum *et al.* [28] identified a locus on chromosome 15 that was associated with weight loss after RYGB. In another even smaller study ($n=258$), several additional loci were identified [29]. However, the reported associations did not reach a widely accepted genome-wide significant level (e.g., P of 5×10^{-8}), raising concerns about potentially false-positive findings. Apparently, large-scale collaborations of multiple weight-loss trials are essential to improve study power to identify new genetic loci. To date, there is no GWAS on weight loss induced by diet intervention. In addition, little is known about the function of the genetic variants that have been identified.

GENE–DIET INTERACTIONS ON OBESITY IN OBSERVATIONAL STUDIES

It has been widely accepted that dietary factors and genetic factors may not independently affect body weight. Instead, these factors may interplay with each other [8,30,31]. However, in population studies, detection of gene–diet interactions has been perplexed. Statistical models for interaction test usually attempt to simplify complex biological events, and therefore may perform inadequately in capturing the diverse patterns of gene–diet interactions. In addition, the majority of the previous studies is flawed by relatively small sample size and cross-sectional design, and is subject to potential bias such as confounding and reverse causation. These limitations may partly account for most of the previously reported gene–diet interactions that are not reproducible [8,31,32].

In our recent analysis [12[■]], we for the first time tested gene–diet interactions in multiple prospective cohorts with replication design. The study assessed interactions between SSB intake and genetic susceptibility to obesity (evaluated on 32 BMI-associated loci) in relation to BMI and obesity among three cohorts – the Nurses' Health Study, the Health Professional Follow-up Study, and the Women Genome Health Study. We observed directionally consistent interactions between genetic susceptibility and SSB. In the three cohorts combined, the pooled relative risks (95% CI) for incident obesity per increment of 10 risk alleles were 1.34 (1.16–1.52), 1.58 (1.30–1.87), 1.52 (1.21–1.83), and 3.24 (1.90–4.58) across the four categories of SSB intake (P for interaction <0.001).

GENOTYPE AND WEIGHT LOSS IN RESPONSE TO DIET INTERVENTION

Testing gene–diet interactions in observational settings may be biased by confounding and reverse causation; and provides tortuous information about how genotype modifies dietary effect on weight loss. Evidence-based prevention and treatment rely mainly on the statistical interpretation of data from clinical trials. Therefore, to detect gene–diet interaction in diet intervention trials on weight loss would be essential.

We have performed a series of analyses on gene–diet interactions in randomized diet intervention trials. The Preventing Overweight Using Novel Dietary Strategies (Pounds Lost) is a clinical trial including a total of 811 overweight or obese adults assigned to one of four weight-loss diets varying in macronutrient contents for 2 years [6]. At 6 months, participants assigned to each diet had lost an average of 6 kg; but began to regain weight after 12 months. By 2 years, weight loss remained similar in those who were assigned to various diets. In the Pounds Lost trial, we recently found significant interactions between the *IRS1* SNP rs2943641 and carbohydrate intake in relation to changes in weight loss and insulin resistance [33]. At 6 months, participants with the risk-conferring CC genotype had greater decreases in weight loss ($P=0.018$) than those without this genotype in the highest-carbohydrate diet group; whereas the genetic effect was not significant in the lowest-carbohydrate diet group (P for interaction $=0.03$). The gene–diet interaction was attenuated at 2 years due to weight regain. We also found SNP rs1558902 in obesity gene *FTO* interacted with dietary protein on 2-year changes in fat-free mass, total percentage of fat mass, and total, visceral, and superficial adipose tissue mass [34[■]]. It appeared that a high-

protein diet were more beneficial in individuals with the risk allele A. These data indicate considerable genetic heterogeneity in weight loss in response to diet interventions.

Several other studies have also assessed gene–diet interactions in randomized intervention trials. Pan *et al.* genotyped 20 tagging SNPs for MC4R, a gene involved in the melanocortin system and energy homeostasis, in Diabetes Prevention Program (DPP) participants ($N=3819$), which were randomized into intensive lifestyle modification (eating less fat and calories, and exercising for a total of 150 min a week), metformin or placebo control. The minor allele of rs17066866 was associated with less short-term (baseline to 6 months; $P=0.006$) and long-term (baseline to 2 years, $P=0.004$) weight loss in the lifestyle intervention group, but not in placebo group [35]. However, it is difficult to tease out which lifestyle components (diet or exercise) interacted with the genotype. In another study, SNP rs7903146 in TCF7L2 gene was found to be related to weight loss in the Tübingen Lifestyle Intervention Program (TULIP), a trial consisted of exercise and diet intervention with decreased intake of fat and increased intake of fibers (>15 g fiber per 1000 kcal). However, the findings were not replicated in DPP. The authors speculated that this might be because increased fiber intake was not part of DPP. In a follow-up study of 304 participants from the TULIP, it was found that CC genotype of the TCF7L2 SNP was associated with significantly greater weight loss in participants with high fiber intake, but not in those with low fiber intake [36]. These data highlight the importance and challenges in replication of gene–diet interactions in RCTs.

GENOTYPE AND WEIGHT LOSS MAINTENANCE

It has been noted for a long time that weight maintenance after intentional weight loss is difficult to achieve. Although dietary restriction and/or increased physical activity may usually lead to weight loss shortly after intervention, a proportion of the participants regain body weight later during the course of intervention and the majority of them regain weight after intervention. Physiological adaptation to weight loss encouraging restoration of body weight, including alterations in energy expenditure, substrate metabolism, and hormone secretion in appetite regulation, is a major hindrance [37]. Weight loss maintenance is particularly challenging in the ‘obesogenic’ environment that prevails in many of the developed and rapidly developing countries.

Several studies have examined the gene–diet interactions in relation to weight loss maintenance. The Diet, Obesity and Genes (DIOGENES) is a randomized, controlled 6-month dietary intervention study that examines the effects of dietary protein and glycemic index on weight regain and metabolic risk factors in overweight and obese families, after an 8-week weight loss period on a low-calorie diet. In 742 participants from the DIOGENES, Larsen *et al.* [38] examined 768 tagging SNPs for nutrient-sensitive candidate genes for obesity and obesity-related diseases. The SNPs in genes GHRL, CCK, MLXIPL, and LEPR showed interactions with dietary protein on weight regain; and the SNPs in genes PPARG, FABP1, LPIN1, and PLAUR showed interactions with dietary protein on fat mass regain. In the 2-year Dietary Intervention Randomized Controlled Trial (DIRECT), Erez *et al.* [39] assessed potential predictors for weight changes during the ‘weight loss phase’ (0–6 months) and the ‘weight maintenance/regain phase’ (7–24 months). Mean weight reduction was 5.5%

after 6 months, with a mean weight regain of 1.2% of baseline weight during the subsequent 7–24 months. Genetic variants in leptin gene (LEP; SNPs rs4731426 and rs2071045) were found to be associated with weight regain; and addition of LEP genotype to the other variables in the prediction model increased its predictive value of weight regain by 34%.

The Look Action For Health in Diabetes is a randomized trial to determine the effects of diabetes support and education (DSE) and intensive lifestyle intervention (ILI), which combined diet modification and increased physical activity designed to produce an average of 7% weight loss and maintenance, on cardiovascular morbidity and mortality in 5145 ethnically diverse overweight and obese participants with type 2 diabetes. McCaffery *et al.* [40] examined the interaction between 13 obesity-predisposing polymorphisms in eight genes and randomized treatment arm in predicting weight change at year 1, and weight regain at year 4 among individuals who lost 3% or more of their baseline weight by year 1. It was found that FTO SNP rs3751812 showed significant prediction in DSE group ($P=0.005$), but not within ILI group.

GENOTYPE AND WEIGHT LOSS-RELATED METABOLIC TRAITS

Obesity is a major risk factor for various metabolic disorders; and weight loss has been associated with improvement of metabolic profiles in many intervention trials [4,41]. A recent study suggest that, the trajectory change of the metabolic markers showed distinct patterns, and might not be parallel with cycling of weight loss and regain [42].

In the Pounds Lost trial, we have reported interactions between diet intervention and genetic variants in relation to several metabolic traits (Table 1) [13[■],33–36,38–40,43[■],44[■], 45,46,47[■],48[■],49] In one study, we found the T allele of the *GIPR* SNP rs2287019 was associated with greater decreases in fasting glucose, fasting insulin, and HOMA-IR (all $P < 0.03$) in participants assigned to low-fat diets, whereas there was no significant genotype effect on changes in these traits in those assigned to the high-fat diet (P -interaction = 0.04, 0.10, and 0.07, respectively) [13[■]]. In another study [43[■]], we found that dietary fat modified genotype effects of APOA5 rs964184 on changes in total-cholesterol, LDL-cholesterol, and HDL-cholesterol (P -interaction = 0.007, 0.017, and 0.006, respectively). Using metabolomic profiling methods, Wang *et al.* [50] recently reported that blood levels of branched chained amino acids (BCAAs) and aromatic amino acids (AAAs) predicted type 2 diabetes. A SNP rs1440581 near *PPMIK* gene was associated with higher serum ratio of BCAAs to AAAs [51]. We found that dietary fat significantly modified genetic effects of *PPMIK* SNP rs1440581 on changes in fasting insulin and HOMA-IR. Individuals carrying C allele of *PPMIK* SNP rs1440581 benefited less in the improvement of insulin sensitivity than those without this allele when they undertook an energy restricted high-fat diet [44[■]].

Kostis *et al.* [45] examined the relationship of 21 SNPs associated with hypertension, diabetes, or obesity, with weight sensitivity in 722 patients from the Trial of Nonpharmacologic Interventions in the Elderly (TONE), in which participants with hypertension were randomized to receive intensive dietary intervention of sodium reduction, weight loss, both, or attention control. Three SNPs (rs4646994, rs2820037, and rs1800629) were related to weight sensitivity of systolic blood pressure and three SNPs (rs4646994,

rs2820037, and rs5744292) were related to diastolic blood pressure. In the DIOGENES, Brahe *et al.* [46] examined 240 SNPs tagging 24 nutrient-sensitive genes involved in lipid metabolism. A gene–protein interaction on triglyceride was observed for variant in LPIN1 gene (rs4315495), with opposite-directed genotype effects on triglyceride in low-protein and high-protein groups after the 6-month *ad libitum* weight maintenance diet.

PERSONALIZED INTERVENTIONS

Although obesity has become epidemic and associated with a plethora of comorbidities, its effective prevention and treatment have been difficult. One of the main objectives of nutrition research is to improve prevention and treatment of diseases through modification of diet. Currently, a one-size-fits-all strategy is adopted in nutrition recommendation. However, such approach requires substantial simplification and strong assumption that there is no interindividual variance in responses to diet interventions. Emerging evidence has shown that human genotypes may modify dietary effects on weight loss and maintenance, highlighting interindividual variance considering prevention or treatment of obesity through diet modification. Now more than ever, we have begun to appreciate that human genomic makeup should be emphasized in improving public health approaches to reduce obesity. However, translation of the discoveries from gene–diet interactions into preventive and therapeutic measures appears still appallingly puzzling.

In the postgenome era, empowering genotyping and sequencing technologies enables assessment of individual's genomic feature in unprecedented efficiency and detail. This leads to an expectation of switch from traditional, one-size-fits-all diet intervention toward personalized manner, by referring to 'individuality' of human genome. Genetic test, which aims to inform the customers of their lifetime risk of diseases and how they may respond to specific diets, has been already commercially available. Nevertheless, the validity of such direct-to-consumer genomic tests is largely unknown; and moreover, whether personalized genetic counseling may improve healthy diet habits or lifestyle has yet to be demonstrated. In a recent study, Grant *et al.* [52] conducted a randomized trial of diabetes genetic risk counseling among 108 overweight patients to examine whether diabetes genetic risk testing and counseling can improve diabetes prevention behaviors. Participants in the higher-genetic and lower-genetic risk received individual genetic counseling before being enrolled with untested control participants in a 12-week, validated, DPP. There were few statistically significant differences in self-reported motivation, program attendance, or mean weight loss when higher-risk recipients and lower-risk recipients were compared with controls ($P>0.05$ for all but one comparison), suggesting genetic counseling did not significantly alter self-reported motivation or prevention program adherence. However, it is notable that the study size is relatively small; and it remains unclear how genetic information would be translated to general patients regarding its interactive relation with diet/lifestyle modifications and implication on improvement of health. Similar studies considering genetic counseling on dietary interventions targeting weight loss are currently lacking, but urgently needed.

CONCLUSION

A collection of dietary factors has been related to obesity and weight loss. However, it remains ambiguous regarding effective diets for weight loss and maintenance. During the past few years, genetic research has made great strides in the identification of variants in human genome that affect body weight regulation; and emerging studies have shown evidence for interactions between genetic factors and dietary factors on obesity, weight loss, and maintenance. These findings have paved a new avenue for more extensive investigations on gene–diet interactions in the future. A usually very productive next step would be to perform genome-wide analysis in the well powered randomized diet intervention trials. Functional studies are also required to provide insights into the potential mechanisms underlying the interactions between genetic and dietary factors.

One of the ultimate goals of studying gene–diet interaction is to develop personalized diet interventions based on genetic profiles that are better tailored to meet the individuals' needs. Understanding gene–diet interactions in relation to weight loss holds great promise for delivering more efficient prevention and treatment on obesity and related metabolic disorders.

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FIGURE 1.
The effect sizes and frequencies of the risk alleles of the established SNPs associated with BMI and obesity.

Table 1

Selected studies on gene–diet interactions on weight loss, maintenance, and related metabolic traits

Studies	Study design	Genetic factors	Major findings
Qi <i>et al.</i> [33]	<i>N</i> =738; 2-y diet intervention	Diabetes associated <i>IRS1</i> rs2943641	<i>IRS1</i> genetic variants modified effects of dietary carbohydrate on weight loss and insulin resistance
Erez <i>et al.</i> [39]	<i>N</i> =322; 2-y diet intervention	Obesity related <i>LEP</i> SNPs	<i>LEP</i> genotype was related to weight regain from 7 to 24 months
Mattei <i>et al.</i> [47 [†]]	<i>N</i> =591; 2-y diet intervention	Diabetes associated <i>TCF7L2</i> SNP rs7903146	Dietary fat intake interacted with <i>TCF7L2</i> genotype in relation to changes in BMI, total fat mass, and trunk fat mass
Zhang <i>et al.</i> [34 [†]]	<i>N</i> =742; 2-y diet intervention	Obesity related <i>FTO</i> SNP rs1558902	High-protein diet interacted with <i>FTO</i> genotype in relation to weight loss and improvement of body composition and fat distribution
Heni <i>et al.</i> [36]	<i>N</i> =304; 9-m diet intervention	Diabetes associated <i>TCF7L2</i> SNP rs7903146	CC genotype was associated with greater weight loss in participants with high fiber intake, but not those with low fiber intake Heni, Herzberg-Schäfer
Zhang <i>et al.</i> [43 [†]]	<i>N</i> =734; 2-y diet intervention	Lipid metabolism related <i>APOA5</i> SNP rs964184	Dietary fat interacted with <i>APOA5</i> genotype in relation to 2-y changes in lipid profile
Zhang <i>et al.</i> [48 [†]]	<i>N</i> =723; 2-y diet intervention	Hypertension associated <i>NPY</i> SNP rs16147	<i>NPY</i> genotype modifies effects of dietary fat on 2-year changes of blood pressure
Larsen <i>et al.</i> [38]	<i>N</i> =742; 6-m diet intervention on weight loss maintenance	768 tagSNPs for nutrient-sensitive genes	Multiple interactions with GI or dietary protein on waist and fat mass regain
Qi <i>et al.</i> 2012 [13 [†]]	<i>N</i> =737; 2-y diet intervention	Diabetes related <i>GIPR</i> SNP rs2287019	Dietary carbohydrate modified <i>GIPR</i> genotype effects on changes in body weight, fasting glucose, and insulin resistance
Xu <i>et al.</i> [44 ^{††}]	<i>N</i> =734; 2-y diet intervention	BCAA associated <i>PPM1K</i> SNP rs1440581	Dietary fat significantly modified genetic effects on changes in weight, fasting insulin
Qi <i>et al.</i> 2013 [49]	<i>N</i> =738; 2-y diet intervention	Diabetes associated <i>IRS1</i> SNP rs1522813	<i>IRS1</i> genetic variants modified the effects of diets varying in fat content on the MetS status
Brahe <i>et al.</i> [46]	<i>N</i> =841 (baseline); 6-m diet intervention on weight loss maintenance	240 tagSNPs for candidate genes	<i>LPIN1</i> SNP rs4315495 genotype interacted with dietary protein on change of TG concentration
McCaffery <i>et al.</i> [40]	<i>N</i> =3899; 4-y lifestyle intervention in diabetic patients	Obesity related SNPs	Variations in the <i>FTO</i> and <i>BDNF</i> loci were related to weight regain after weight loss
Pan <i>et al.</i> [35]	<i>N</i> =3819; 2-y intervention; lifestyle modification and metformin	Obesity related <i>MC4R</i> SNPs	rs17066866 was associated with less short-term (baseline to 6 months) and less long-term (baseline to 2 years) weight loss in the lifestyle intervention group, but not in placebo group
Kostis <i>et al.</i> [45]	<i>N</i> =722; 4-m intervention; diet and medication	21 SNPs related to hypertension, diabetes, or obesity	Multiple genotypes were related to change in blood pressures in response to diet intervention.

BCAA, branched chain amino acid; CVD, cardiovascular disease; GI, glycemic index; MetS, metabolic syndrome; SNP, single nucleotide polymorphism; TG, triglyceride.