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Personalized nutrition and obesity

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Abstract

The past few decades have witnessed a rapid rise in nutrition-related disorders such as obesity in the United States and over the world. Traditional nutrition research has associated various foods and nutrients with obesity. Recent advances in genomics have led to identification of the genetic variants determining body weight and related dietary factors such as intakes of energy and macronutrients. In addition, compelling evidence has lent support to interactions between genetic variations and dietary factors in relation to obesity and weight change. Moreover, recently emerging data from other 'omics' studies such as epigenomics and metabolomics suggest that more complex interplays between the global features of human body and dietary factors may exist at multiple tiers in affecting individuals' susceptibility to obesity; and a concept of 'personalized nutrition' has been proposed to integrate this novel knowledge with traditional nutrition research, with the hope ultimately to endorse person-centric diet intervention to mitigate obesity and related disorders.

Keywords

Genomics; nutrition; obesity; personalized

Introduction

Obesity is one of the major nutrition-related disorders, and its rapid rise in the United States and many other countries has been paralleled with a dramatic shift from traditional, more nutritionally dense dietary patterns toward more energy-rich, unhealthy patterns (1,2). The importance of nutrition in prevention and treatment of obesity has gained much attention from public health professionals (3,4).

The etiology of obesity is multifactorial and involves complex interplays between dietary factors and various 'internal' (e.g. genomic, epigenomic, and metabolic profiles) or 'external' (e.g. lifestyle) exposures. The past 10 years have witnessed speedy advances in research of genomics, which has made great strides in detection of genetic variants associated with body weight regulation and obesity (5). In addition, emerging data have shown that the genetic variants may interact with dietary factors in relation to obesity and

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weight change (6 – 9). Moreover, recent studies on other global characteristics of the human body, such as epigenomics and metabolomics, suggest more complex interplays may exist at multiple tiers in affecting individuals' susceptibility to obesity, and a concept of 'personalized nutrition' has been proposed to integrate these new advances with traditional nutrition research.

Key messages

- A group of dietary factors or eating habits have been related to obesity; however, the data for the majority of these factors are still inconsistent.
- Emerging evidence supports potential interaction between genetic factors and dietary factors in relation to obesity.
- Personalized nutrition holds great promise to understand interindividual variation in responses to specific foods and nutrients, and such knowledge would be translated into public health benefit.

This article summarizes recent advances in nutrition, genomics, gene – diet interaction, and other omics studies on obesity, and particularly addresses 'personalized nutrition' in integration of this knowledge and the potential application in person-centric diet intervention to mitigate obesity and related disorders. The article does not comprehensively review the publications in the related areas, but only presents sampled findings as examples.

Foods, nutrients, eating habits, and obesity

The root of obesity etiology is imbalance between dietary energy intake and energy expenditure. Human evolution has favored a preference for energy-dense and fatty foods, as a consequence of exposure to ancestral famine (10). This leaves humans susceptible to modern obesogenic environments regarding rise of energy intakes and subsequent elevation of obesity risk. Data from the National Health and Nutrition Examination Survey (NHANES) have shown a marked upward shift of energy intake, increasing by 7% in men and 22% in women from 1971 – 1974 to 1999 – 2000 (11), in parallel with a rapid increment of obesity in the same period of time.

Many foods may tip the balance of energy input and output. For example, fast foods or takeaway foods, typically high in fat and energy density, and low in fiber, have been related to escalation of total calories intake. Consumption of these foods increased from 20% of total calories in 1970 to 40% of total calories in 1995 in the United States (12). Positive associations between fast foods consumption and obesity risk have been reported in several epidemiology studies, though the data are not entirely consistent (13 – 15). It remains debatable whether the fast foods were driving the obesity, or vice versa. In the last half century, there has been a sudden upsurge in consumption of carbohydrates, especially those in a more refined form (16). Although population-based data directly linking carbohydrates and obesity are still sparse, several short-term intervention trials have shown that carbohydrate restriction might moderately promote weight loss (17,18). A group of studies have shown that diets rich in whole grains and fiber were inversely related to body mass

index (BMI) and weight gain (19,20), partly due to the incomplete digestion and absorption and increased satiety caused by delayed gastric emptying and subsequent gastric distention. Other foods and nutrients such as nuts, fruits and vegetables, and dairy products have also been associated with body weight; however, the data are similarly conflicting (21 – 25). The mid-1990s saw the surge in popularity of sugar-sweetened beverages (SSB), paralleled by the rise in obesity prevalence, in the United States (26). Compelling evidence supports a positive association of high SSB consumption with weight gain and obesity risk (27,28). Data from several recent randomized clinical trials added more solid evidence that the relation between SSB and body weight may be causal (29,30). Of note, there are very few with appropriate long follow-up which may give reliable data on the real health effects of long-term dietary and lifestyle changes on weight reduction. A recent study reported that after over 13 years of follow-up in the Finnish Diabetes Prevention Study (DPS), participants assigned to reduced intakes of total fat and saturated fat and increased intake of fiber, and moderate exercise for at least 30 minutes per day sustained lower absolute levels of body weight (31). Similarly, in The Look AHEAD, intervention combining increased physical activity and diet modification (total calorie of 1200 – 1800 kcal/day, with < 30% from fat and < 10% from saturated fat) resulted in long-term (4 years) weight loss (32).

In addition, there is growing interest in the relations between eating behaviors and obesity, because they may reflect the joint effect of several foods and nutrients. For example, Kaisari et al. found that higher eating frequency was associated with lower body weight in children and adolescents, mainly in boys (33). Similarly, in adults, it was found that participants who reported eating breakfast daily gained 1.9 kg less weight over 18 years, compared with those with infrequent breakfast consumption (0 – 3 days/week) (34).

Genomic determinants of obesity-related eating behaviors and dietary factors

Eating habits are thought to be a voluntary, conscious behavior, and a large body of evidence has shown that habitual diet intake is largely controlled by a powerful, unconscious biological system especially through balancing energy intake and expenditure (35,36). In addition, a variety of factors such as socio-economic environment, learned eating behaviors, physiological conditions such as stress, and depression can also influence appetite and food selection (37). In the meantime, compelling evidence has indicated that genetic factors may also play a role in eating habits (38 – 40).

Several studies have assessed heritability of eating behaviors or dietary intakes. Steinle et al. examined eating behaviors in 624 adults from 28 families participating in the Amish Family Diabetes Study (41). Heritability estimates were 28% for restraint, 40% for disinhibition, and 23% for hunger. In 575 Danish and 2009 Finnish adult twin pairs, Hasselbalch et al. found moderate heritability for bread intake frequency (23% – 40%). The genetic influence on intake of white bread was 24% – 31%, while the genetic influence on intake of rye bread was higher in men (41% – 45%) than in women (24% – 33%) (42). In family and twin studies, the range of heritability estimates for intake of the macronutrients carbohydrate, protein, and fat was 11% – 65% (38). However, population-based analyses showed relatively

a lower proportion of variance for these nutrients (6% – 8%) explained by genetic components (39).

The efforts to map genetic variants determining dietary intake have been focused on biologically relevant candidate genes. For example, *MC4R* is a key factor in the leptin-melanocortin signaling pathway, controlling food intake via both anorexigenic and orexigenic signals (43). There is a group of studies that have assessed the relation of variants in the *MC4R* gene with binge eating disorder, snacking, psychological factors, satiety responsiveness, and intake of energy and macro/micronutrients. Although several small-sized studies reported that the *MC4R* mutations might impair eating behaviors or motivation, the data are highly mixed (44,45). In 5724 women from the Nurses' Health Study (NHS), Qi et al. found that the *MC4R* variant rs17782313 was related to high intakes of total energy and macronutrients such as fat and protein (46). In the European Prospective Study into Cancer and Nutrition study ($n = 17,357$), it was found that common allelic variations in the leptin or leptin receptor gene (*LEP* or *LEPR*) associated with an increased risk to display extreme snacking behavior, while common allelic variations in the *CCK* gene associated with an increased risk of eating increased meal sizes (47).

Recently, Chu et al. (39) conducted the first genome-wide association study (GWAS) on dietary intakes of macronutrients (carbohydrate, protein, and fat) in 33,533 men and women from three large cohorts: the NHS, Health Professionals Follow-up Study (HPFS), and Women Genome Health Study (WGHS). A common variant rs838133 in the *FGF21* gene, which encodes fibroblast growth factor 21, was found to be related to protein intake at genome-wide significant level. FGF21 is a circulating hepatokine and adipokine involved in regulation of energy homeostasis (48). In another similarly-sized GWAS ($n = 38,360$) (49), it was found that a variant in the same gene (rs838145) was associated with higher carbohydrate intake. The variants in this locus were associated with circulating FGF21 protein concentrations. Interestingly, it was also found that variant rs142108 in the obesity-associated *FTO* gene was associated with higher protein intake.

Gene – diet interaction and obesity

A principal assumption underlying the traditional nutrition research is that disease risk conferred by dietary intakes is uniform for each individual. Such assumption, however, appears not to be accurate. Large-scale nutrition surveys have shown that a shift from principally more nutritionally dense diet to more energy-dense diet is among the driving forces responsible for the rapid increase in obesity (2,50,51), while several lines of evidence suggest that inherent variation may also play a role in shaping the epidemic of obesity. For example, the prevalence of obesity in the United States had been rising since 1970s but leveled off around year 2000. Afterward, the prevalence kept at a relatively stable level with approximately 60% of the population remaining non-obese or lean, regardless of continuing exposure to the same obesogenic environment (51). Such temporal pattern indicates that considerable diversity exists within the population in response to the obesogenic environment, as well as the changes in other factors such as socio-economic status and ethnic compositions. In line with these observations, a wide range of interindividual

heterogeneity has been noted in responses to diet interventions in clinical trials, at least partly due to genetic variations (8,9,18,52 – 54).

In population studies, to detect gene – diet interactions seems intricate. Statistical models employed in testing interactions usually attempt to simplify complex biological phenomena. However, gene – diet interactions underlie the flexibility in affecting disease risk through miscellaneous ways, and may be not adequately captured by simplified statistical models (6,55,56). Statistical interaction is defined as departure from an additive effect of individual factors in a linear model on a chosen scale of the outcome measure (57). As compared with genetic discovery studies, analyses on gene – diet interactions are subject to much more potential bias, such as confounding and reverse causation. Therefore, prospective design and careful adjustment for confounding are essential in analyses of gene – diet interaction. In addition, large sample size and replication are also important to minimize false positive and false negative results. Moreover, the significance of data coming from different study designs may further help validation. For example, the most significant results from observational studies should be replicated in well controlled dietary intervention studies with an appropriate study designs, i.e. validated intervention and adequate follow-up.

In our recent analysis (7), we assessed interactions between habitual SSB intake and genetic obesity susceptibility, evaluated by a genetic risk score derived from 32 obesity-associated loci, in relation to BMI and obesity risk (Table I). We employed a two-stage design consisting of three prospective cohorts—the NHS and HPFS in the discovery stage, and the WGHS in the replication stage. We observed directionally consistent interaction between genetic susceptibility and SSB consumption in NHS and HPFS. In the combined samples of these cohorts, the increases in BMI (kg/m^2) per 10 risk alleles were 1.00 for participants with SSB intake of < 1 serving/month, 1.03 for 1–4 servings/month, 1.39 for 2 – 6 servings/week, and 1.77 for ≥ 1 servings/day (P for interaction < 0.001). The findings were successfully replicated in the WGHS (P for interaction = 0.001). As compared with the lowest intake group, the size of the genetic effect increased approximately 80%, and such difference is clinically relevant regarding risk of chronic diseases such as diabetes and cardiovascular disease (CVD). We also observed consistent gene – SSB interactions on obesity risk in all the three cohorts. Our study for the first time provides reproducible evidence for the interactions between genetic factors and dietary factors in relation to obesity risk. Several other studies have also examined the gene – diet interactions in obesity in multiple cohorts. For example, Corella et al. investigated whether fat and carbohydrate intake modified the association of FTO gene variation with BMI in two populations with different ethnicities, and found that the effects of saturated fatty acid intake significantly interacted with that of FTO genotype on BMI in both populations (58). However, most of the previous analyses on gene – diet interactions were conducted in a single cohort, and the results are highly inconsistent. In another study in the NHS and HPFS (59), we found that lifestyle factors closely related to energy expenditure, such as physical activity and television watching, also interacted with the genetic obesity risk score in relation to BMI, and stronger genetic effects were observed in those with low physical activity or more hours of television watching. Similar gene – physical activity interactions were also observed in other studies (Table I) (60). These data together emphasize the essentiality to consider genomic make-up in nutrition research. Of note, associations observed in the observational

studies cannot be translated into causality. Therefore, it is essential to validate further the findings in randomized clinical trials and functional experiments before application in practice.

Genetic modification on weight loss and maintenance by diet interventions

Evidence-based prevention and treatment rely mainly on evidence from randomized clinical trials, which are more relevant regarding future development of diet interventions to prevent obesity. We have investigated gene – diet interactions in the POUNDS LOST trial, a 2-year diet intervention study comparing four weight-loss diets varying in macronutrient contents among 811 overweight or obese adults (18). In one study, we found that a single-nucleotide polymorphism (SNP) rs2943641 near the insulin- and diabetes-related *IRS1* gene significantly interacted with carbohydrate intake in relation to weight loss (*P* for interaction < 0.03) (61). The participants with the risk-conferring CC genotype had greater weight loss when carbohydrate intake was high. In another study, we found that a variant rs1558902 in the obesity-associated *FTO* gene interacted with dietary protein on 2-year changes in measures of body composition and abdominal fat distribution, including fat-free mass, total percentage of fat mass, and total, visceral, and superficial adipose tissue mass (9). A high-protein diet appeared beneficial for weight loss and improvement of body composition and fat distribution in individuals carrying the risk allele A.

The Tübingen Lifestyle Intervention Program (TULIP) tested diet intervention with decreased intake of fat and increased intake of fibers (> 15 g fiber per 1,000 kcal). Heni et al. recently found that the CC genotype of the diabetes-associated *TCF7L2* SNP rs7903146 was associated with greater weight loss in participants with high fiber intake, but not in those with low fiber intake (Table I) (62). In another 2-year diet intervention trial, it was found that genetic variants in the leptin gene (*LEP;* SNPs rs4731426 and rs2071045) were significantly associated with weight regain after weight loss at 6 months. In addition, it was found that addition of the genotype significantly improved the predictive value of weight regain by 34% (Table I) (63).

Other omics – diet interactions and obesity

In addition to genomics, other global features of the human body may also affect response to nutrition factors and risk of obesity, evidenced by emerging data in ‘omics’ studies such as epigenomics and metabolomics. Literally, epigenomics means ‘on top of genetics’, and is defined as the heritable changes that affect gene expression through mechanisms not associated with concomitant alterations in the DNA sequence, such as DNA methylation, histone modifications, and micro-RNA (miRNA) (64,65). Prenatal nutrition is believed to play pivotal roles in shaping persistent changes of epigenome, which links early developmental and adult disease risk. Prenatal exposures to nutritional challenge during famine have been related to later-life risk of obesity, hypertension, and diabetes (66 – 68). Several recent studies (69,70) found that exposure to famine *in utero* might affect methylation status in certain genes. In a recent study, Ortega et al. (71) reported that obesity was related to a marked increase in miR-140-5p, miR-142-3p, and miR-222 and a decrease in miR-532-5p, miR-125b, miR-130b, miR-221, miR-15a, miR-423-5p, and miR-520c-3p.

In addition, it was found that surgery-induced weight loss led to changes in miRNA profile; however, diet-induced weight loss did not significantly change miRNA levels.

Metabolomics characterizes the metabolic profile (metabotype), through the simultaneous measurement of a broad range of low-molecular-weight compounds (72,73). In a recent study (74), Wang et al. profiled plasma metabolites using an LC-MS platform in the Framingham Offspring Study, and identified three branched-chain amino acids (BCAAs), leucine, isoleucine, and valine, and two aromatic amino acids (AAAs), phenylalanine and tyrosine, predicting diabetes risk. Interestingly, these amino acids have been found to change in response to diet interventions, and related to obesity in a group of studies (75,76).

Personalized nutrition and obesity

One of the main objectives of nutrition research is to study the roles of foods and nutrients in causes and prevention of disease to ensure the highest quality of health recommendations. Currently, a one-size-fits-all strategy is adopted in nutrition recommendation; and such an approach requires substantial simplification and a strong assumption that there is no interindividual variance. However, accumulating evidences from genomics and other omics studies have suggested such simplification and assumption are likely misleading. Recently, a concept of ‘personalized medicine’, in which patients are treated based on their individual characteristics, has been proposed (77). Personalized medicine is expected to benefit from combining genomics information with monitoring of physiological states by multiple high-throughput omics methods. In line with this concept, ‘personalized nutrition’ specifically addresses nutrition-related health problems by connecting traditional nutrition research with various omics methods, with the hope to understand thoroughly the complex interactions between nutrition factors and various global features of the human body and help define nutrition recommendations that can be tailored to an individual with improved efficacy.

Currently, no study has investigated the relation between integrated omics profile and obesity in humans. However, recently emerging studies from multiple omics areas may help shape a picture of such systems efforts on personalized nutrition. A recent GWAS (78) found a SNP rs1440581 near the *PPM1K* gene (PP2C domain-containing protein phosphatase 1K) to be associated with serum BCAAs and AAAs, which have been related to obesity and diabetes risk (74,76). Interestingly, *PPM1K* was also identified as a susceptibility gene for type 2 diabetes by a systems genetic approach (79). We genotyped *PPM1K* SNP rs1440581 in participants from the POUNDS LOST trial (80), and found that dietary fat significantly modified genetic effects on changes in body weight, fasting insulin, and insulin resistance i.e. HOMA-IR. Individuals carrying the C allele of *PPM1K* SNP rs1440581 may benefit less in weight loss and improvement of insulin sensitivity than those without this allele when undertaking an energy-restricted high-fat diet. In addition, in the POUNDS LOST trial, we have assessed genetic-determined heterogeneity in response to weight loss diet interventions on various obesity-related metabolic changes including lipids, blood pressure, and metabolic syndrome (Table I) (9,52,53,61). These studies lend support to the potential application of personalized diet planning in prevention and treatment of obesity and related disorders.

Summary

Personalized nutrition has arisen from the marriage of traditional nutrition science with omics research, and simultaneously studies vast amounts of variations in genome, epigenome, metabolome, and their interactions with dietary factors at different tiers. In this instance, personalized nutrition aims to integrate multilevel information to characterize, comprehensively and precisely, the relation between nutrition and health disorders, such as obesity.

Personalized nutrition holds great promise to understand interindividual variation in responses to specific foods and nutrients, and such knowledge would be translated into public health benefit. There are examples reflecting some of the triumphs of the systems approach in deciphering the relation between nutrition and obesity. Yet many challenges exist, and the map of the nutrition – omics interface is far from complete. While whole population-based nutrition recommendations may continue to be effective in improvement of health, personalized intervention would be more efficient to reduce obesity-related disorders especially among high-risk populations determined by genetic makeup. Solid evidence should be achieved before the application of personalized diet intervention in practice.

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References

1. Malik VS, Willett WC, Hu FB. Global obesity: trends, risk factors and policy implications. Nat Rev Endocrinol. 2013; 9:13–27. [PubMed: 23165161]
2. Popkin BM, Adair LS, Ng SW. Global nutrition transition and the pandemic of obesity in developing countries. Nutr Rev. 2012; 70:3–21. [PubMed: 22221213]
3. Hu FB, Liu Y, Willett WC. Preventing chronic diseases by promoting healthy diet and lifestyle: public policy implications for China. Obes Rev. 2011; 12:552– 9. [PubMed: 21366840]
4. Willett WC. Overview and perspective in human nutrition. Asia Pac J Clin Nutr. 2008; 17(Suppl 1): 1–4.
5. Xia Q, Grant SF. The genetics of human obesity. Ann N Y Acad Sci. 2013; 1281:178– 90. [PubMed: 23360386]
6. Qi L, Cho YA. Gene-environment interaction and obesity. Nutr Rev. 2008; 66:684– 94. [PubMed: 19019037]
7. Qi Q, Chu AY, Kang JH, Jensen MK, Curhan GC, Pasquale LR, et al. Sugar-sweetened beverages and genetic risk of obesity. N Engl J Med. 2012; 367:1387– 96. [PubMed: 22998338]
8. Qi Q, Bray GA, Hu FB, Sacks FM, Qi L. Weight-loss diets modify glucose- dependent insulinotropic polypeptide receptor rs2287019 genotype effects on changes in body weight, fasting glucose, and insulin resistance: the Preventing Overweight Using Novel Dietary Strategies trial. Am J Clin Nutr. 2012; 95:506–13. [PubMed: 22237064]
9. Zhang X, Qi Q, Zhang C, Smith SR, Hu FB, Sacks FM, et al. F TO genotype and 2-year change in body composition and fat distribution in response to weight-loss diets: the POUNDS LOST Trial. Diabetes. 2012; 61:3005– 11. [PubMed: 22891219]

10. Prentice AM. Starvation in humans: evolutionary background and contemporary implications. Mech Ageing Dev. 2005; 126:976–81. [PubMed: 15907972]
11. Centers for Disease Control and Prevention (CDC). Trends in intake of energy and macronutrients--United States, 1971–2000. MMWR Morb Mortal Wkly Rep. 2004; 53:80– 2. [PubMed: 14762332]
12. Canoy D, Buchan I. Challenges in obesity epidemiology. Obes Rev. 2007; 8(Suppl 1):1– 11.
13. Bahadoran Z, Mirmiran P, Hosseini-Esfahani F, Azizi F. Fast food consumption and the risk of metabolic syndrome after 3-years of follow-up: Tehran Lipid and Glucose Study. Eur J Clin Nutr. 2013; 67:1303–9. [PubMed: 24193228]
14. Duffey KJ, Gordon-Larsen P, Jacobs DR Jr, Williams OD, Popkin BM. Differential associations of fast food and restaurant food consumption with 3-y change in body mass index: the Coronary Artery Risk Development in Young Adults Study. Am J Clin Nutr. 2007; 85:201–8. [PubMed: 17209197]
15. Jaworowska A, Blackham T, Davies IG, Stevenson L. Nutritional challenges and health implications of takeaway and fast food. Nutr Rev. 2013; 71:310– 18. [PubMed: 23590707]
16. Gross LS, Li L, Ford ES, Liu S. Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: an ecologic assessment. Am J Clin Nutr. 2004; 79:774–9. [PubMed: 15113714]
17. 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– 77. [PubMed: 17341711]
18. 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; 360:859–73. [PubMed: 19246357]
19. Pol K, Christensen R, Bartels EM, Raben A, Tetens I, Kristensen M. Whole grain and body weight changes in apparently healthy adults: a systematic review and meta-analysis of randomized controlled studies. Am J Clin Nutr. 2013; 98:872–84. [PubMed: 23945718]
20. Cho SS, Qi L, Fahey GC Jr, Klurfeld DM. Consumption of cereal fiber, mixtures of whole grains and bran, and whole grains and risk reduction in type 2 diabetes, obesity, and cardiovascular disease. Am J Clin Nutr. 2013; 98:594–619. [PubMed: 23803885]
21. Flores-Mateo G, Rojas-Rueda D, Basora J, Ros E, Salas-Salvado J. Nut intake and adiposity: meta-analysis of clinical trials. Am J Clin Nutr. 2013; 97:1346– 55. [PubMed: 23595878]
22. Martinez-Gonzalez MA, Bes-Rastrollo M. Nut consumption, weight gain and obesity: epidemiological evidence. Nutr Metab Cardiovasc Dis. 2011; 21(Suppl 1):S40– 5. [PubMed: 21216574]
23. He K, Hu FB, Colditz GA, Manson JE, Willett WC, Liu S. Changes in intake of fruits and vegetables in relation to risk of obesity and weight gain among middle-aged women. Int J Obes Relat Metab Disord. 2004; 28:1569– 74. [PubMed: 15467774]
24. Boeing H, Bechthold A, Bub A, Ellinger S, Haller D, Kroke A, et al. Critical review: vegetables and fruit in the prevention of chronic diseases. Eur J Nutr. 2012; 51:637– 63. [PubMed: 22684631]
25. Chen M, Pan A, Malik VS, Hu FB. Effects of dairy intake on body weight and fat: a meta-analysis of randomized controlled trials. Am J Clin Nutr. 2012; 96:735– 47. [PubMed: 22932282]
26. Malik VS, Popkin BM, Bray GA, Despres JP, Hu FB. Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. Circulation. 2010; 121:1356– 64. [PubMed: 20308626]
27. Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC, et al. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. JAMA. 2004; 292:927– 34. [PubMed: 15328324]
28. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med. 2011; 364:2392–404. [PubMed: 21696306]
29. Ebbeling CB, Feldman HA, Chomitz VR, Antonelli TA, Gortmaker SL, Osganian SK, et al. Arandomized trial of sugar-sweetened beverages and adolescent body weight. N Engl J Med. 2012; 367:1407–16. [PubMed: 22998339]

30. de Ruyter JC, Olthof MR, Seidell JC, Katan MB. A trial of sugar-free or sugar-sweetened beverages and body weight in children. N Engl J Med. 2012; 367:1397– 406. [PubMed: 22998340]
31. Lindstrom J, Peltonen M, Eriksson JG, Ilanne-Parikka P, Aunola S, Keinanen-Kiukaanniemi S, et al. Improved lifestyle and decreased diabetes risk over 13 years: long-term follow-up of the randomised Finnish Diabetes Prevention Study (DPS). Diabetologia. 2013; 56:284–93. [PubMed: 23093136]
32. Unick JL, Beavers D, Bond DS, Clark JM, Jakicic JM, Kitabchi AE, et al. The long-term effectiveness of a lifestyle intervention in severely obese individuals. Am J Med. 2013; 126:236–42. 42 e1–2. [PubMed: 23410564]
33. Kaisari P, Yannakoulia M, Panagiotakos DB. Eating frequency and overweight and obesity in children and adolescents: a meta-analysis. Pediatrics. 2013; 131:958– 67. [PubMed: 23569087]
34. Odegaard AO, Jacobs DR Jr, Steffen LM, Van Horn L, Ludwig DS, Pereira MA. Breakfast frequency and development of metabolic risk. Diabetes Care. 2013; 36:3100– 6. [PubMed: 23775814]
35. Lee M, Kim A, Chua SC Jr, Obici S, Wardlaw SL. Transgenic MSH over-expression attenuates the metabolic effects of a high-fat diet. Am J Physiol Endocrinol Metab. 2007; 293:E121–31. [PubMed: 17374695]
36. Zheng H, Lenard NR, Shin AC, Berthoud HR. Appetite control and energy balance regulation in the modern world: reward-driven brain overrides repletion signals. Int J Obes (Lond). 2009; 33(Suppl 2):S8–13. [PubMed: 19528982]
37. Cohen DA, Babey SH. Contextual influences on eating behaviours: heuristic processing and dietary choices. Obes Rev. 2012; 13:766–79. [PubMed: 22551473]
38. Rankinen T, Bouchard C. Genetics of food intake and eating behavior phenotypes in humans. Annu Rev Nutr. 2006; 26:413–34. [PubMed: 16848714]
39. Chu AY, Workalemahu T, Paynter NP, Rose LM, Giulianini F, Tanaka T, et al. Novel locus including FGF21 is associated with dietary macronutrient intake. Hum Mol Genet. 2013; 22:1895–902. [PubMed: 23372041]
40. Leturque A, Brot-Laroche E, Le Gall M. Carbohydrate intake. Prog Mol Biol Transl Sci. 2012; 108:113–27. [PubMed: 22656375]
41. Steinle NI, Hsueh WC, Snitker S, Pollin TI, Sakul H, St Jean PL, et al. Eating behavior in the Old Order Amish: heritability analysis and a genome-wide linkage analysis. Am J Clin Nutr. 2002; 75:1098–106. [PubMed: 12036819]
42. Hasselbalch AL, Silventoinen K, Keskitalo K, Pietilainen KH, Rissanen A, Heitmann BL, et al. Twin study of heritability of eating bread in Danish and Finnish men and women. Twin Res Hum Genet. 2010; 13:163–7. [PubMed: 20397746]
43. Greenfield JR. Melanocortin signalling and the regulation of blood pressure in human obesity. J Neuroendocrinol. 2011; 23:186–93. [PubMed: 21062377]
44. Valette M, Bellisle F, Carette C, Poitou C, Dubern B, Paradis G, et al. Eating behaviour in obese patients with melanocortin-4 receptor mutations: a literature review. Int J Obes (Lond). 2013; 37:1027–35. [PubMed: 23147118]
45. Branson R, Potoczna N, Kral JG, Lentes KU, Hoehe MR, Horber FF. Binge eating as a major phenotype of melanocortin 4 receptor gene mutations. N Engl J Med. 2003; 348:1096–103. [PubMed: 12646666]
46. Qi L, Kraft P, Hunter DJ, Hu FB. The common obesity variant near MC4R gene is associated with higher intakes of total energy and dietary fat, weight change and diabetes risk in women. Hum Mol Genet. 2008; 17:3502– 8. [PubMed: 18697794]
47. de Krom M, van der Schouw YT, Hendriks J, Ophoff RA, van Gils CH, Stolk RP, et al. Common genetic variations in CCK, leptin, and leptin receptor genes are associated with specific human eating patterns. Diabetes. 2007; 56:276–80. [PubMed: 17192493]
48. Lancha A, Fruhbeck G, Gomez-Ambrosi J. Peripheral signalling involved in energy homeostasis control. Nutr Res Rev. 2012; 25:223–48. [PubMed: 23174510]
49. Tanaka T, Ngwa JS, van Rooij FJ, Zillikens MC, Wojczynski MK, Frazier-Wood AC, et al. Genome-wide meta-analysis of observational studies shows common genetic variants associated with macronutrient intake. Am J Clin Nutr. 2013; 97:1395–402. [PubMed: 23636237]

50. Yang Q, Cogswell ME, Flanders WD, Hong Y, Zhang Z, Loustalot F, et al. Trends in cardiovascular health metrics and associations with all-cause and CVD mortality among US adults. JAMA. 2012; 307:1273– 83. [PubMed: 22427615]
51. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. JAMA. 2012; 307:491– 7. [PubMed: 22253363]
52. Zhang X, Qi Q, Bray GA, Hu FB, Sacks FM, Qi L. A POA5 genotype modulates 2-y changes in lipid profile in response to weight-loss diet intervention: the Pounds Lost Trial. Am J Clin Nutr. 2012; 96:917–22. [PubMed: 22914552]
53. Mattei J, Qi Q, Hu FB, Sacks FM, Qi L. TCF7L2 genetic variants modulate the effect of dietary fat intake on changes in body composition during a weight-loss intervention. Am J Clin Nutr. 2012; 96:1129–36. [PubMed: 23034957]
54. 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; 359:229–41. [PubMed: 18635428]
55. Qi L, Liang J. Interactions between genetic factors that predict diabetes and dietary factors that ultimately impact on risk of diabetes. Curr Opin Lipidol. 2010; 21:31–7. [PubMed: 19915463]
56. Qi L, Hu FB, Hu G. Genes, environment, and interactions in prevention of type 2 diabetes: a focus on physical activity and lifestyle changes. Curr Mol Med. 2008; 8:519–32. [PubMed: 18781959]
57. Chen JJ. Not getting lost in the gene-environment interaction exploration. J Urol. 2012; 188:2361. [PubMed: 23141042]
58. Corella D, Arnett DK, Tucker KL, Kabagambe EK, Tsai M, Parnell LD, et al. A high intake of saturated fatty acids strengthens the association between the fat mass and obesity-associated gene and BMI. J Nutr. 2011; 141:2219– 25. [PubMed: 22049296]
59. Qi Q, Li Y, Chomistek AK, Kang JH, Curhan GC, Pasquale LR, et al. Television watching, leisure time physical activity, and the genetic predisposition in relation to body mass index in women and men. Circulation. 2012; 126:1821– 7. [PubMed: 22949498]
60. Ahmad S, Rukh G, Varga TV, Ali A, Kurbasic A, Shungin D, et al. Gene x physical activity interactions in obesity: combined analysis of 111,421 individuals of European ancestry. PLoS Genet. 2013; 9:e1003607. [PubMed: 23935507]
61. 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– 71. [PubMed: 21747052]
62. Heni M, Herzberg-Schafer S, Machicao F, Haring HU, Fritsche A. Dietary fiber intake modulates the association between variants in TCF7L2 and weight loss during a lifestyle intervention. Diabetes Care. 2012; 35:e24. [PubMed: 22355027]
63. Erez G, Tirosh A, Rudich A, Meiner V, Schwarzfuchs D, Sharon N, et al. Phenotypic and genetic variation in leptin as determinants of weight regain. Int J Obes (Lond). 2011; 35:785– 92. [PubMed: 21042325]
64. Waki H, Yamauchi T, Kadowaki T. The epigenome and its role in diabetes. Curr Diab Rep. 2012; 12:673–85. [PubMed: 23070559]
65. Sandoval J, Esteller M. Cancer epigenomics: beyond genomics. Curr Opin Genet Dev. 2012; 22:50– 5. [PubMed: 22402447]
66. van Abeelen AF, Elias SG, Bossuyt PM, Grobbee DE, van der Schouw YT, Roseboom TJ, et al. Famine exposure in the young and the risk of type 2 diabetes in adulthood. Diabetes. 2012; 61:2255– 60. [PubMed: 22648386]
67. Li Y, Jaddoe VW, Qi L, He Y, Lai J, Wang J, et al. Exposure to the Chinese famine in early life and the risk of hypertension in adulthood. J Hypertens. 2011; 29:1085–92. [PubMed: 21546877]
68. Li Y, He Y, Qi L, Jaddoe VW, Feskens EJ, Yang X, et al. Exposure to the Chinese famine in early life and the risk of hyperglycemia and type 2 diabetes in adulthood. Diabetes. 2010; 59:2400–6. [PubMed: 20622161]
69. Tobi EW, Heijmans BT, Kremer D, Putter H, Delemarre-van de Waal HA, Finken MJ, et al. DNA methylation of IGF2, GNASAS, INSIGF and LEP and being born small for gestational age. Epigenetics. 2011; 6:171– 6. [PubMed: 20930547]

70. Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci U S A. 2008; 105:17046–9. [PubMed: 18955703]

71. Ortega FJ, Mercader JM, Catalan V, Moreno-Navarrete JM, Pueyo N, Sabater M, et al. Targeting the circulating microRNA signature of obesity. Clin Chem. 2013; 59:781–92. [PubMed: 23396142]

72. Friedrich N. Metabolomics in diabetes research. J Endocrinol. 2012; 215:29– 42. [PubMed: 22718433]

73. Rasmiena AA, Ng TW, Meikle PJ. Metabolomics and ischaemic heart disease. Clin Sci (Lond). 2013; 124:289–306. [PubMed: 23157406]

74. Wang TJ, Larson MG, Vasan RS, Cheng S, Rhee EP, McCabe E, et al. Metabolite profiles and the risk of developing diabetes. Nat Med. 2011; 17:448– 53. [PubMed: 21423183]

75. Gu Y, Zhao A, Huang F, Zhang Y, Liu J, Wang C, et al. Very low carbohydrate diet significantly alters the serum metabolic profiles in obese subjects. J Proteome Res. 2013; 12:5801–11. [PubMed: 24224694]

76. McCormack SE, Shaham O, McCarthy MA, Deik AA, Wang TJ, Gerszten RE, et al. Circulating branched-chain amino acid concentrations are associated with obesity and future insulin resistance in children and adolescents. Pediatr Obes. 2013; 8:52–61. [PubMed: 22961720]

77. Goldberger JJ, Buxton AE. Personalized medicine vs guideline-based medicine. JAMA. 2013; 309:2559–60. [PubMed: 23712449]

78. Kettunen J, Tukiainen T, Sarin AP, Ortega-Alonso A, Tikkanen E, Lyytikainen LP, et al. Genome-wide association study identifies multiple loci influencing human serum metabolite levels. Nat Genet. 2012; 44:269–76. [PubMed: 22286219]

79. Taneera J, Lang S, Sharma A, Fadista J, Zhou Y, Ahlqvist E, et al. A systems genetics approach identifies genes and pathways for type 2 diabetes in human islets. Cell Metab. 2012; 16:122–34. [PubMed: 22768844]

80. Xu M, Qi Q, Liang J, Bray GA, Hu FB, Sacks FM, et al. Genetic determinant for amino acid metabolites and changes in body weight and insulin resistance in response to weight-loss diets: the Preventing Overweight Using Novel Dietary Strategies (POUNDS LOST) trial. Circulation. 2013; 127:1283– 9. [PubMed: 23446828]

Table I

Selected studies on gene – diet/lifestyle interactions in observational studies and randomized clinical trials.

Studies	Study design	Diet/lifestyle factors	Genetic factors	Major findings
Cohort studies				
Qi Q, et al. 2012 (7)	Three cohorts; *n* = 6,934, 4,423, and 21,740	Sugar-sweetened beverages	32 BMI- and obesity-related variants	The genetic associations with adiposity were modified by intake of sugar-sweetened beverages
Qi Q, et al. 2012 (59)	Two cohorts; *n* = 7,740 and 4,564	Physical activity and television watching	32 BMI- and obesity-related variants	The genetic effects on BMI were stronger in those with low physical activity or longer hours of television watching
Ahmad S, et al. 2013 (60)	*n* = 111,421	Physical activity	12 BMI- and obesity-related variants	The genetic effects on BMI and obesity risk were stronger in those with low physical activity
Randomized clinical trials				
Xu M, et al. 2013 (80)	2-year intervention; *n* = 734	Weight loss diets	BCAA-associated *PPM1K* SNP rs1440581	Dietary fat significantly modified genetic effects on changes in weight, fasting insulin, and insulin resistance
Mattei J, et al. 2012 (53)	2-year intervention; *n* = 591	Weight loss diets	Diabetes-associated *TCF7L2* SNP rs7903146	Dietary fat intake interacted with TCF7L2 genotype in relation to changes in BMI, total fat mass, and trunk fat mass
Heni M, et al. 2012 (62)	9-month intervention; *n* = 304	Decreased fat and increased fiber intakes	Diabetes-associated TCF7L2 SNP rs7903146	Fiber intake significantly modified the genetic effects on weight loss
Zhang X, et al. 2012 (9)	2-year intervention; *n* = 742	Weight loss diets	Obesity-related *FTO* SNP rs1558902	High-protein diet interacted with *FTO* genotype in relation to weight loss and improvement of body composition and fat distribution
Erez G, et al. 2011 (63)	2-year diet intervention; *n* = 322	Weight loss diets	*LEP* SNPs	*LEP* SNP significantly improved prediction of weight regain after weight loss

BCAA = branched chain amino acid; BMI = body mass index; CVD = cardiovascular disease; SNP = single nucleotide polymorphism.

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