Personalized weight loss strategies—the role of macronutrient distribution

J. Alfredo Martinez, Santiago Navas–Carretero, Wim H. M. Saris and Arne Astrup

Abstract

A large number of different dietary approaches have been studied in the attempt to achieve healthy, sustainable weight loss among individuals with overweight and obesity. Restriction of energy intake is the primary method of producing a negative energy balance leading to weight loss. However, owing to the different metabolic roles of proteins, carbohydrates and lipids in energy homeostasis, diets of similar overall energy content but with different macronutrient distribution can differentially affect metabolism, appetite and thermogenesis. Evidence increasingly suggests that the fuel values of calories provided by distinct macronutrients should be considered separately, as metabolism of specific molecular components generates differences in energy yield and. The causes of variation in individual responses to various diets are currently under debate, and some evidence suggests that differences are associated with specific genotypes. This narrative Review discusses all available systematic reviews and meta-analyses, and summarizes the results of relevant randomized controlled intervention trials assessing the influence of macronutrient composition on weight management. The initial findings of research into personalized nutrition, based on the interactions of macronutrient intake and genetic background and its potential influence on dietary intervention strategies, are also discussed.

Centre for Nutrition Research, CIÉROBn (fisiopatología de la obesidad), University of Navarra, c/Irunlarrea, 1, 31008 Pamplona, Navarra, Spain (J.A.M & S.N.–C.). Nutrition and Toxicology Research Institute Maastricht (NUTRIM), Maastricht University Medical Centre, Maastricht, 616, 6200 MD, Netherlands (W.H.M.S.). Department of Nutrition, Exercise and Sports (NEXS), Faculty of Science, University of Copenhagen, Rolighedsvej 26 Frederiksberg C, DK-1958, Denmark (A.A.).

Correspondence to: J.A.M.
jalfmtz@unav.es

Competing interests

A.A. declares that he has acted as a consultant or member of the advisory boards for the following companies and organizations: Beer Knowledge Institute, McCain, Pathway Genomics, McDonalds and Global Dairy Platform, and he has received lecture fees from Arla Foods and Campina. W.H.S. declares that he has acted as a consultant for Nutrition and Santé, is a member of the advisory boards of Food for Health, and International Life Sciences Institute Research Foundation, is a member of review panels for MRC (Medical Research Council), INRA (French National Institute for Agricultural Research) and NordForsk, and that he is employed part-time as Corporate Scientist in Nutrition at DSM Corp. NL (Dutch States Mines). In addition, A.A. declares that his department at the University of Copenhagen has received research support from more than 100 food companies, and W.H.S. declares that his institution (Maastricht University Medical Centre) receives research support from the Dutch Dairy Foundation and Novo Nordisk. The other authors declare no competing interests.

Key points
• The relative contributions of different aetiological factors to obesity remains to be fully defined, although the importance of different dietary macronutrients, physical activity patterns and genetics is acknowledged

• Improved understanding of the mechanisms of weight gain and obesity might lead to comprehensive and efficient strategies to prevent and ameliorate this global epidemic

• Studies of the roles of individual macronutrients in weight management are needed to define whether diets of similar calorific content but different composition differentially effect energy yield and utilization

• Experts generally agree that weight-loss strategies should aim to not only reduce body fat in the short term, but also achieve long-term maintenance of healthy body weight

• The study of gene–nutrient interactions and the differential effects of genotype on macronutrient utilization might identify personalized strategies for effective weight loss and maintenance of healthy body weight

Introduction

The general consensus is that overweight (BMI 25–30 kg/m²) and excessive fat accumulation result from a higher calorific intake than energy expenditure.¹ Experts also concur on the applicability of the laws of thermodynamics within living organisms, in terms of body energy balance.² Less agreement is evident on the specific contributions of various aetiological factors, such as the proportions of dietary macronutrients (fats, proteins and carbohydrates), the quantitative importance of physical activity patterns and the influence of genetic factors, to the rising levels of obesity (BMI >30 kg/m² observed in many countries worldwide, with a global increase in obesity from 28.8% to 36.9% in men and from 29.8% to 38% in women during the last 33 years.³ The excessive accumulation of body fat is associated with various health risks, most of which are linked to increased all-cause mortality,⁴ despite some apparent controversies regarding this issue.⁵ However, to what extent individuals should be held accountable for the macronutrient composition of their diet, and the exact relevance of individual macronutrient intake to the energy equation are unclear.⁶⁷

Primary care strategies and public-health policies to combat obesity mainly focus on restriction of dietary carbohydrate and fat intake, together with promotion of physical activity.⁸ Various items have been suggested as risk factors for obesity: infectious or inflammatory agents, high maternal age, superior fertility in overweight women, selective mating among obese people, chronobiological and sleep disorders, endocrine dysfunction, drug adverse effects, uncontrolled environmental and climate circumstances, and epigenetic mechanisms (including intrauterine or transgenerational influences).⁹ Improved understanding of the mechanisms through which these risk factors lead to excess weight gain might lead to the development of personalized, comprehensive and effective strategies for prevention and treatment of this global epidemic.¹⁰ In this context, the prevention and management of excessive weight gain or changes in body composition can be achieved through various approaches.¹¹ Dietary approaches include calorie restriction, macronutrient distribution shifts within unlimited or restricted calorific intake patterns and the inclusion of satiating or thermogenic food components, such as fibre, proteins and curcumin. Lifestyle interventions combine dietary modifications (such as meal replacement
plans) and exercise or activity programs. Surgery is also an option, although it is not discussed in this Review.\textsuperscript{14–16}

The specific contribution of individual macronutrients to promotion of weight loss in obese individuals has received growing attention, to overcome the metabolic difficulties and poor compliance associated with strict energy-restricted diets,\textsuperscript{17} and to determine whether calories derived from different macronutrients have equivalent fuel values for the body.\textsuperscript{15-17} The roles of each macronutrient and their specific subtypes or components (that is, different protein sources, specific sugars, amino acids or fatty acids) beyond total energy intake are still under debate, as is the way each person metabolizes different macronutrients.\textsuperscript{18} A myriad of nutritional plans and dietary approaches have, therefore, been designed to reduce energy intake or metabolic efficiency, including intermittent fasting, low-carbohydrate or low-fat diets, low-glycaemic-index or whole-grain foods, high-fat and high-protein models, Mediterranean-type food patterns, or other feeding regimes based on increased consumption of antioxidants or other bioactive compounds.\textsuperscript{20–22} Many of the various commercially available dietary interventions are successful in the short term, but often fail to achieve long-term weight control, which has been explained by poor long-term compliance and resistance to weight loss attributed to a genetic predisposition to retain or maintain body weight under circumstances of energy deficit.\textsuperscript{23}

Body weight homeostasis is under the control of metabolic influences that are closely related to body composition, energy metabolism and obesity, such as appetite, adipocyte differentiation and adipogenesis, mitochondrial functions, lipid turnover, thermogenesis and cellular efficiency.\textsuperscript{24–26} Given that all of these processes are to some extent genetically regulated, a customized, genotype-driven prescription of dietary approaches might be an effective form of weight management.\textsuperscript{25} How, and to what extent, an individual’s phenotype might be influenced by genomic, genetic and epigenetic factors (single nucleotide polymorphisms, copy number variation, nucleotide repeats, insertions or deletions, alterations in telomere length and epigenetic changes) that directly affect the metabolism and utilization of foods and accompanying components remains to be determined.\textsuperscript{26} The integration of this new knowledge into nutritional research to achieve evidence-based personalization of nutritional advice is a major challenge in the prevention of obesity and related diseases.\textsuperscript{27, 28}

In this Review, we suggest that the global obesity epidemic could be addressed through a combination of public-health strategies focused on promoting sensible diets and lifestyles that can benefit the general population of healthy but obese individuals, together with personalized, genotype-based recommendations. We present a reappraisal and update of the available evidence in this area and assess the efficacy of dietary macronutrient composition on weight loss. We critically review the results of randomized controlled trials (RCTs) designed to accomplish weight loss by manipulating the distribution of energy-yielding macronutrients, and describe various examples of gene–nutrient interactions with differential effects on weight loss that depend on both genotype and macronutrient intake.

**Dietary macronutrient composition**

Research is currently focused on unravelling the optimal macronutrient distribution for achievement of sustainable weight loss using both energy-restricted and unrestricted diets. The specific roles of different metabolic processes involved in weight management (appetite, thermogenesis, adipogenesis) are being actively investigated, mainly through RCTs.\textsuperscript{29, 30} Systematic reviews of the literature and meta-analyses
are also being conducted to ascertain the singular role of different macronutrients (Table 1). For example, some dietary patterns might have specific benefits, not only for ameliorating features of the metabolic syndrome (such as insulin resistance, hypertension, lipid disturbances and central adiposity) but also for preservation of lean mass or treatment of some metabolic adverse features.22 Owing to the specificity of the research question or the nature of the hypothesis to be tested, some trials of weight-loss diets with altered macronutrient composition have not been included in meta-analyses or systematic reviews. However, some of the omitted trials provide unique information about the underlying mechanisms and metabolic aspects of weight loss that have potential nutritional applications in healthy weight management (Table 2).

Carbohydrates

Meta-analyses and systematic reviews

The link between sugar consumption and body weight in both children and adults has been investigated through an extensive meta-analysis of data from 30 RCTs and 38 cohort studies.11 Trials in adults with unrestricted food intake showed that reduced consumption of dietary sugars, achieved by limiting consumption of sugar-containing foods, or substituting high-sugar foods for low-sugar alternatives, led to a reduction body weight (of 0.80 kg) compared with controls. High dietary sugar intakes (which were predominantly linked to increased consumption of sweetened beverages) led to a comparable weight increase (0.75 kg) compared with controls. The researchers concluded that the changes in body weight due to variation in the consumption of sugars were related to differences in total energy intake, but not to the complexity or quality of carbohydrates, which was not in agreement with the conclusions of another similar meta-analysis.22

A Cochrane review evaluated the outcomes of 202 overweight or obese participants assigned to either a low-glycaemic-index diet or a control diet over a period of 5 weeks to 6 months. Following the low-glycaemic index diet resulted in a significant weight reduction of 1.1 kg versus following the control diet. The researchers concluded that reducing glycaemic load is advisable to facilitate weight loss.31 Canadian researchers who conducted a review of clinical evidence on the effects of low-glycaemic-index and low-glycaemic-load diets on weight loss found that the specific effects of these two approaches could not be ascertained from clinical trial outcomes alone.34 In addition, their results suggested that a reduced calorific intake was the basis of successful weight reduction, although glycaemic index (and other factors) could have a role. Nevertheless, the possible effect of dietary glycaemic index or glycaemic load has yet to be proven in RCTs with long-term follow-up.31

The safety, efficacy and optimum level of carbohydrate restriction in low-carbohydrate diet is hotly debated, and has been addressed in a systematic review.35 94 studies were identified, comprising 3,268 adult participants who received a dietary intervention lasting 4 days or more, and involving energy restriction of at least 500 kcal daily. Low carbohydrate consumption was associated with reduced calorific intake and a long intervention period. The researchers reported a trend towards increased weight loss for diets with reduced carbohydrate content: −3.6 kg for <60g daily versus −2.1 kg >60 g daily.35 It must be mentioned that the dietary interventions tested in this review were not isocaloric, thus the weight loss associated with lower carbohydrate intake might be to some extent caused by a lower energy intake generally.
Clinical trials

The CARMEN study investigated the role of different carbohydrate sources (simple versus complex sugars) in low-fat but calorie-unrestricted diets, compared to a control unrestricted diet, on the success of weight loss in overweight or obese adults. The study suggested that a reduction of 10% fat content in calorie-unrestricted diets led to an effective reduction in body weight and fat mass, regardless of the complexity of the carbohydrates. By contrast, exchanging dietary sugars for complex carbohydrates with a similar energy content did not result in a significant change in body weight, which confirmed the outcomes of earlier similar trials.

Although low-glycaemic-index and high-protein diets are quite popular, their effects on weight loss have not been thoroughly compared in appropriately controlled trials. In one trial, 129 overweight or obese young adults were randomly assigned to one of four different diets over 12 weeks. The test diets consisted of 55% carbohydrates with either high or low glycaemic index, or 25% protein and either high or low glycaemic index. All four intervention groups experienced similar weight loss (ranging from –6.2% to –4.8%). However, the high-protein, low-glycaemic-index diet specifically promoted body fat reduction, whereas the high-carbohydrate, low-glycaemic-index diet elicited a clinically relevant cardiovascular risk reduction.

Another intervention trial examined the effects of a high-glycaemic-load diet versus a low-glycaemic-load diet, both resulting in a 30% energy restriction, in 34 healthy but overweight adults. Weight loss in both groups was similar after 1 year (–8.0% and –7.8% in high-glycaemic-load and low-glycaemic-load groups, respectively). In another trial, low-glycaemic-index diets helped to maintain weight loss. After 8 weeks following either a low-glycaemic-index or a high-glycaemic-index diet, both representing a 30% energy restriction, participants from the low-glycaemic-index group lost significantly more weight (–5.3% versus –2.9%). Moreover, weight regain 1 year after the intervention was only significant in the group allocated to the high-glycaemic-index diet. Given these interesting and promising outcomes, the authors hypothesized that low-glycaemic-index diets might result in favourable physiological adaptations during energy restriction that facilitate weight loss as well as preventing long-term weight regain.

Finally, another trial compared the efficacy of four popular weight-loss diets: Atkins (20–50 g daily carbohydrates); Ornish (high carbohydrate content, maximum 10% fat); Zone (30% protein, 30% fat, 40% carbohydrates) and Learn (55–60% carbohydrates). 311 overweight or obese premenopausal women were randomly assigned to follow one of these diets for 12 months. The Atkins diet group had more weight loss than the other three groups (–4.7 kg Atkins, versus –1.6 kg Zone, –2.6 kg Learn, and –2.6 kg Ornish), showing significant differences with the Zone diet groups. No adverse effects were observed after 12 months in patients following the Atkins diet, which was in accordance with the results of previous short-term studies and critical reviews. However, the authors could not establish whether the increased weight loss was due to the reduced carbohydrate content or the increased amount of protein in the Atkins diet.

Fats

Meta-analyses and systematic reviews
Associations between fat intake and body weight have been summarized in several critical reviews and analyses: 33 RCTs (73,589 participants) and 10 cohort studies were screened to establish the effects of low versus normal levels of dietary fat intake on body weight. These outcomes were assessed in studies of durations ranging from 6 months to more than 8 years, and in both children and adults; despite this heterogeneity, similar trends were reported. A meta-analysis of data from 57,735 participants in these trials revealed that a low total dietary fat intake is linked to a reduction in body weight (−1.6 kg) versus a normal fat intake. Baseline fat intakes ranged from 28% to 43% of total energy, and decreasing fat intake in participants with a low baseline fat intake was associated with additional weight loss relative to controls. These findings confirmed the results of a previous meta-analysis published in 2000, in which reducing dietary fat intake was clearly associated with an improvement in weight loss in participants receiving unrestricted diets.

Clinical trials

A total of 771 obese individuals in the NUGENOB study (mean BMI 35.6 kg/m²) from eight clinical centres in seven European countries underwent a 10-week dietary intervention to compare two low-energy diets (both involving a reduction in intake of 600 kcal daily) of different fat content. However, weight losses were similar in both groups (6.7 kg and 6.9 kg), despite the differences in fat content.

A Mediterranean diet is considered to protect against features of the metabolic syndrome, such as increased central adiposity. A pilot prospective dietary intervention study compared the effects of two Mediterranean dietary patterns, supplemented with either olive oil or nuts, to that of a low-fat Western diet on features of the metabolic syndrome in 1,224 participants from the PREDIMED multicentre trial. The three intervention groups received specific advice to adhere to their diet. Despite all diets being unrestricted in terms of calorific intake, the Mediterranean diets containing more fat than the control diet, no significant differences in body weight between the three groups was observed after 1 year.

The role of dietary fat in weight loss is hard to define. For example, diets involving either reduced carbohydrate intake or increased protein intake are likely to result in increased fat intake. The desired outcomes of a dietary intervention (weight loss and improved body composition) are expected to be accompanied by improvements in risk factors for metabolic diseases, particularly dyslipidaemia and impaired glucose metabolism. However, the available literature does not always agree on the additional benefits of dietary interventions beyond weight loss.

Proteins

High-protein diets have been widely studied in relation to the reduction of body weight and fat mass. In a meta-analysis, high-protein diets were associated with increased satiety. Furthermore, in eight of the 15 trials included in this meta-analysis, high-protein diets led to greater weight loss than low-protein diets. However, protein content had a neutral effect on weight loss in the remaining seven trials. The authors of this analysis concluded that high dietary protein intake was associated with increased thermogenesis and decreased appetite. These results indicate that the partial substitution of high-glycaemic-index carbohydrates with protein-rich foods that are low in saturated fat might be a feasible
dietary recommendation. A subsequent large, randomized trial showed that diets with moderate protein content and a modest reduction in glycaemic index were associated with improved compliance and were specifically useful in preventing weight regain.49

Low-carbohydrate, high-protein diets

Meta-analyses and systematic reviews

One meta-analysis compared energy-restricted, low-fat diets to very-low-carbohydrate ketogenic diets, which were prescribed to individuals with obesity for >1 year. Weight loss was significantly greater in participants receiving no more than 50 g carbohydrate daily (10% of total caloric intake) than in those on low-fat diets.50 However, the lack of an adequate description of the protein and fat content of the studied diets means that the observed weight loss cannot be attributed to the specific role of protein or fat. The researchers also reported an increase in LDL-cholesterol levels in the group following a very-low-carbohydrate regimen, and these results must be carefully examined, as they might represent an increase in cardiovascular risks.50 Although their long-term effects and safety (especially with regard to ketosis and rises in LDL levels) remains unresolved, diets low in carbohydrates and high in protein have been proposed as a possible alternative to the traditional dietary recommendations for weight loss in primary care health services.51

Another meta-analysis compared the changes in body weight associated with energy-unrestricted, low-carbohydrate diets and energy-restricted, low-fat diets in 447 participants from six trials selected using the Cochrane Collaboration search strategy.52 After 6 months, individuals on low-carbohydrate diets had more substantial weight loss than those on low-fat diets (weighted mean difference −3.3 kg in favour of the low-carbohydrate diets). After 1 year, however, the energy-unrestricted, low-carbohydrate diets were at least as effective for inducing weight loss as the energy-restricted, low-fat diets.

A combined systematic review and meta-analysis pooled data from RCTs of dietary interventions lasting ≥6 months in overweight or obese people with or without type 2 diabetes mellitus.53 The effects of diets with different macronutrient distributions (low-carbohydrate, high-protein or low-glycaemic-index) or specific nutritional requirements (vegetarian, vegan, high-fibre or Mediterranean) were compared, either to each other or to reference standard diets (low-fat, high-glycaemic-index, American Diabetes Association, European Association for the Study of Diabetes, or low-protein), with regard to effects on glucose regulation, lipid metabolism and weight management or weight loss.54 Interestingly, the Mediterranean and low-carbohydrate diets produced the greatest weight loss (−1.84 kg and −0.69 kg from baseline, respectively), and were also associated with the greatest improvements in cardiovascular risk markers. Another meta-analysis of 24 randomized trials involving 1,063 adult participants assessed the effect on weight loss of modifying the carbohydrate:protein ratio in energy-restricted, low-fat diets with similar energy and fat content.54 The average intervention duration was 12.1 ± 9.3 weeks. Diets with the highest protein content significantly produced the most favourable reductions from baseline in body weight (−0.79 kg) and resulted in an interesting mitigation of the loss in lean mass as compared to the reference standard diets.54

Finally, a systematic review and meta-analysis published in 201455 analysed the long-term effects of increased protein intake on body weight and fat mass. The 32 identified studies compared dietary advice
promoting high protein and low carbohydrate intake with control dietary patterns. The authors concluded that a minimum difference of 5% in daily intakes (higher protein and lower carbohydrate) promoted improved weight loss, and resulted in up to 1 kg less fat mass, even in the long term.\textsuperscript{55} However, these researchers also point out the high dropout rates in these trials, and stress the importance of thorough follow-up and correct implementation of the dietary change advice.\textsuperscript{55} Indeed, adherence to dietary recommendations, and improving success rates, are issues that also need attention in future studies.

\textit{Evidence from clinical trials}

Short follow-up periods and substantial dropout rates are common problems observed in RCTs.\textsuperscript{49, 50} For example, a 2-year nutritional intervention (DIRECT) was designed and developed to test the efficacy of three different diets.\textsuperscript{52} 322 adults with mild obesity were allocated to a low-fat energy-restricted diet, a Mediterranean energy-restricted diet, or to a low-carbohydrate, energy-unrestricted diet. The groups following the Mediterranean and low-carbohydrate diets lost similar amounts of weight (4.4 kg and 4.7 kg, respectively), whereas the low-fat diet group lost significantly less weight (2.9 kg). Dietary components other than macronutrients could be involved in these different outcomes, however, as could differences in genetic make-up and adherence to the intervention. Indeed, the authors suggested that personal preferences and metabolic status should be considered when selecting dietary interventions for individualized treatment of obesity, given that dropout rates in the three groups also showed statistically significant differences.\textsuperscript{57}

Overall, the consistent notion emerges that low-carbohydrate and high-protein diets result in improved weight management. These positive associations were detected despite the heterogeneity of the included studies in design, recruitment criteria and duration, as well as in the participants’ age, ethnic and genetic backgrounds. However, following a low-carbohydrate diet is also associated with increased all-cause mortality,\textsuperscript{58} impaired flow-mediated dilatation,\textsuperscript{59} and increased LDL-cholesterol levels,\textsuperscript{60} although contradictory evidence exists on the latter point.\textsuperscript{61} Some researchers have suggest that stressing the modest benefits observed for particular types of diet or macronutrient contents should be discouraged, given the lack of long-term evidence.\textsuperscript{60}

\textit{Mixed dietary restrictions}

\textit{Meta-analysis and systematic reviews}

Diets with different levels of energy restriction (total energy content <1,000–1,200 kcal, an energy deficit of ~600 kcal daily, or a 30% deficit in estimated daily energy requirements) have been prescribed with general success in the short term.\textsuperscript{63-62} Several meta-analyses have studied the differential effects of diets with a low glycaemic index or low glycaemic load,\textsuperscript{63} high fat content,\textsuperscript{64} or high protein content\textsuperscript{65} on obesity-associated health risks. Low-glycaemic-index and low-glycaemic-load diets reduce fasting insulin and C-reactive protein levels, which might (to some extent) prevent the development of type 2 diabetes or ameliorate the habitual low-grade inflammatory state associated with obesity.\textsuperscript{63} These meta-analyses\textsuperscript{63, 64} as well as other systematic reviews\textsuperscript{62, 64} could not prove additional beneficial or deleterious long-term effects associated with adherence to high-fat or high-protein diets.
**Clinical trials**

Two calorie-restricted diets high in either protein (30% of calorific intake) or carbohydrate (55% of calorific intake), both with moderate fat content (30% of total calorific intake) were compared in obese women (BMI >30 kg/m²) over a 10 week study period. Individuals in the high-protein group lost significantly more weight than those in the high-carbohydrate group (a difference of 4.4 kg), which was mainly due to increased loss of fat (3.7 kg of the total) since losses of lean mass were similar in both groups. Postabsorptive lipid oxidation remained constant in the high-protein group, but decreased by 48% in the high-carbohydrate group. These results suggest that the partial substitution of carbohydrate with protein is a feasible strategy for reducing fat mass while preserving lean mass.

Furthermore, the 2-year POUNDS LOST study, conducted in 811 overweight adults, was designed to distinguish the effects of individual dietary macronutrients on weight loss. The researchers compared four different diets, which were either low or high in fat (20% or 40% of total energy, respectively) and had either average or high protein content (15% and 25%, respectively). After 6 months, the mean weight loss in all four groups was 6 kg. Despite some weight regain after 12 months, the 80% of participants who completed the trial had an average weight loss of 4 kg, which again was similar in all groups. The authors concluded that energy restriction has a key role in successful weight loss, regardless of dietary composition.

**Exercise-related interventions**

The effects on body weight of diets with different ratios of carbohydrate to protein, with or without aerobic exercise, have also been investigated. In one study, 44 overweight or obese women were assigned to one of two energy-restricted dietary programs (carbohydrate:protein ratios of either 3:1 or 1:1), with or without regular exercise. After 12 weeks, women in the high-protein diet plus exercise group had lost an average of 7 kg, whereas the control (standard-protein diet, no exercise) group achieved an average weight loss of 2.1 kg. The high-protein, no-exercise group also achieved an average weight loss of 4.6 kg. Given these results, authors emphasized the potential for synergistic effects of altered macronutrient distribution in combination with exercise, as a weight-loss strategy. However, the effectiveness of exercise as a weight-loss strategy has not been fully established. Increased physical exercise was not unequivocally identified as an independent cause of weight loss except in highly active individuals, in an extensive review and meta-analysis. In the same analysis, no synergistic effects on body weight were detected between low-calorie diets and exercise. Although the benefits of regular physical activity include improved cardiovascular health and maintenance of skeletal muscle mass, the specific role of exercise in weight loss and maintenance of healthy body weight, and the effects of dietary macronutrient distribution on this association, remain to be elucidated.

As weight loss is strongly advised in overweight or obese patients with type 2 diabetes mellitus, an intensive lifestyle intervention including restricted energy intake could potentially decrease the excess cardiovascular risk and mortality in this group. In the LOOK AHEAD project, a total of 5,145 overweight or obese patients with type 2 diabetes from 16 study centres were randomly assigned to receive either an intensive lifestyle modification focused on weight loss through a combination of diet and exercise, or
a control intervention consisting of diabetes support and education. The intensive lifestyle intervention resulted in a marked reduction in body weight after 1 year (8.6% versus 0.7% in the control group), although weight regain substantially reduced this value to a nonsignificant 2.5% by the time the study had ended.24

Data from the previously discussed clinical trials seem conflicting in some aspects. For example, although energy restriction is always a key factor in reduction of body weight, in some studies the best outcomes were reported for diets with unrestricted calorific intake, which was attributed to their macronutrient distribution (moderately high protein levels and low glycaemic index). Other factors, such as age, sex ethnicity, physical activity level, personal phenotypic features and individuals’ specific dietary circumstances, as well as genetics, might explain some discrepancies in these trials. For example in the Weight Loss Maintenance trial, the mean weight loss after 6 months was 5.8 kg, but the investigators highlighted the existence of weight loss differences that were dependent on ethnicity and sex.75

In summary, caution is advised regarding the appropriate message for health professionals to deliver in primary and secondary prevention settings. Questions remain over whether high-protein diets should be promoted for weight loss, as the effectiveness of these diets is not unequivocal, and over what protein level is optimal. Furthermore, the role of specific sugars (simple versus complex), fatty acids with different saturation levels (eicosapentaenoic acid, docosahexaenoic acid, palmitoleic), specific amino acids (leucine, arginine, branched-chain amino acids), and bioactive compounds (curcumin, polyphenols) associated with weight loss remains to be investigated through specific RCTs, ideally with durations of at least 24 months and additional emphasis on personalized criteria (such as likes, dislikes, family history, and allergies). In the meantime, from a conservative and practical standpoint, moderately high protein diets deriving 35% of their total caloric value from proteins, mainly from vegetable sources and low-fat animal products are not disadvantageous, and adherence to such diets might be associated with improved health outcomes as well as additional weight loss compared to traditional high carbohydrate diets.

Personalized nutrition

Genetics

Approximately 25–70% of body weight variability is influenced by genetics, and more than 600 chromosomal regions could be implicated in the heritability of obesity.25 26 Indeed, approximately 50 candidate genes have been associated with the regulation of energy metabolism27 including some rare variants associated with monogenic forms of obesity that have variable penetrance, as it may be the case of mutations in the genes encoding for leptin,28 leptin receptor,29 or melanocortin 4 receptor.30 31 In addition, a wide range of common genetic variants each with small individual contributions to the heritability of obesity have been identified, predominantly through linkage analysis, candidate-gene studies and genome-wide association studies.2 12 From a systems biology perspective, this endogenous variability in responses to nutrition can be partly explained by gene-regulated mechanisms of absorption, biotransformation, metabolism, distribution or excretion of nutrients and food components.31 Studies of gene–environment relationships have shown that variations in genes involved in nutrient metabolism and transport affect requirements of specific nutrients.27 Indeed, studies on the
influence of genetic variants on dietary response patterns are paving the way for personalized management of obesity.\textsuperscript{29}

Despite some ethical and methodological concerns over the use of genetic testing to support personalized nutrition,\textsuperscript{84,85} direct-to-consumer tests for genetic predisposition to a range of diseases are already available,\textsuperscript{86} which suggests that similar tests might eventually be developed to identify polymorphisms associated with obesity. Advances in nutritional research and the development of ‘omics’ technologies have greatly improved our ability to identify new candidate genes and genetic variants putatively involved in gene–nutrient interactions. Given the nature and pace of this development, there is enormous potential for the development of personalized diets based on genotype.\textsuperscript{62}

**Gene–nutrient interactions**

Gene-nutrient interactions have been assessed through cross-sectional or retrospective case–control studies, controlled intervention trials applying linkage analysis approaches, candidate-gene screening or genome-wide association studies.\textsuperscript{81} These strategies have focused on genes related to appetite control, energy and lipid metabolism,\textsuperscript{15,82} adipocyte function and inflammation\textsuperscript{85,86}. For example, weight loss in response to a given dietary intervention has been assessed in carriers of different alleles of a gene associated with energy homeostasis.\textsuperscript{90}

The ability to give evidence-based dietary advice based upon an individual’s genetic make-up might improve their long-term weight regulation. For example, the influence of genotype has already been demonstrated in the context of responses to sugar-sweetened beverages\textsuperscript{21} or high-fat (fried) food\textsuperscript{92} in persons with a high genetic risk of obesity.

Researchers have investigated the way in which a specific diet or its macronutrient content might differentially affect weight loss (Table 3), depending on the presence of certain single nucleotide polymorphisms (SNPs). Within the POUNDS LOST study, diets with a high protein content (30% of total calorific intake) were associated with greater weight loss in obese individuals carrying the A allele of SNP rs1558902 in FTO (encoding α-ketoglutarate-dependent dioxygenase).\textsuperscript{83} Also in the POUNDS LOST study, a significantly greater decrease in fasting glucose and insulin resistance was detected in response to a low-fat diet, in obese individuals homozygous for the T allele of the SNP rs2287019, in GIPR (which encodes gastric inhibitory polypeptide receptor).\textsuperscript{94} A trend has also been identified in obese individuals homozygous for the T allele of rs12255372 in TCF7L2 (encoding transcription factor 7-like 2),\textsuperscript{95} who seem to achieve improved weight loss in response to a low-fat (20–25% of total calorie intake) diet after ≥2 years. Individuals homozygous for the A allele of SNP rs987237 of TFAP2B, encoding transcription factor AP-2β, lost more weight with a low-calorie, low-fat diet, while individuals homozygous for the G alleles responded in an opposite manner.\textsuperscript{96} However, in spite of some encouraging findings, no statistically significant associations have been found between genotype and improved weight loss in response to low-fat diets.\textsuperscript{94,95}

Dietary fat\textsuperscript{97} and fibre\textsuperscript{98} intakes are also associated with the efficacy of weight loss in individuals carrying the T allele of SNP rs7903146 in TCF7L2. Obese adults homozygous for the T allele of rs7903146 lost significantly more weight in response to low-fat, energy restricted diets than did noncarriers of this allele.
after 10 weeks of intervention. The TULIP study results also demonstrated an association between increased weight loss and high dietary fibre intake (>25g daily) in individuals homozygous for the C allele of SNP rs7903146. This association was not detected in T allele carriers. In another trial, individuals homozygous for the A allele of the -3826 A/G SNP (rs1800592) in UCP1 (encoding mitochondrial brown fat uncoupling protein 1) experienced increased weight loss in response to low-calorie meal replacements containing mixed rice, but not those containing white rice.

The interactions of diet with lifestyle modifications such as increasing exercise and physical activity levels are also of relevance to genotype-based dietary strategies, although the interactions between diet, genetics and exercise are not well studied. However, a study published in 2013 found that individuals homozygous for the C allele of SNP rs1800497 in ANKK1 (encoding ankyrin repeat and protein kinase domain containing protein 1) had increased weight loss in response to a calorie-restricted diet in conjunction with resistance training. This weight loss was apparently exercise-dependent.

In summary, these observations raise questions as to what kind of individualized dietary advice should be based on an individual’s genetic make-up. For example, in noncarriers of alleles associated with risk of obesity linked to sugar-sweetened beverages or fried foods, perhaps consumption of these foods need not be discouraged. Of course, sensible, evidence-based general recommendations should prevail, albeit without disregarding the development of personalized dietary advice. At this stage, the data from current studies on the interaction between genes and nutrition cannot be immediately translated into clinical practice. Prospective intervention studies, in which specific differences in genotype are studied in relation to the efficacy of a given dietary intervention must first be carried out, to confirm the observed associations.

**Future directions**

Attention must be drawn to the role of epigenetic modifications, such as promoter methylation, in response to dietary macronutrients. There is increasing evidence that various dietary components, both macronutrients (i.e. protein) and micronutrient (mainly vitamins, aminoacids and some minerals) modulate gene expression through epigenomic phenomena. This science is, of course, in its early stages, although it is well established that epigenetic marks can be modified through diet and lifestyle interventions, and are predictive of weight loss. Research must, therefore, focus on identifying epigenetic biomarkers for prediction of disease risk, characterizing the mechanisms of epigenetic modification, and developing approaches for reversing the epigenetic modifications associated with increased risks of disease. Furthermore, practical, social and ethical considerations are essential in the design of future research studies. Evidence must be accumulated through extensive, well-designed RCTs, and the public perception, attitudes and trust towards personalized nutrition should be explored and consolidated.

Genetic tests, if handled by specialists, could facilitate the translation of scientific knowledge to the general public. However, testing alone is not enough; patients who are left to draw their own conclusions from the results are at risk of suboptimal self-administration of dietary advice. Thus, it is advisable to involve health professionals in the development of individualized medicine, specifically personalized nutrition, to establish new perspectives, identify barriers and ensure the optimum level of patient benefit. In this context, genetic biomarkers derived from genomic studies could potentially
be used for diagnosis, prediction of prognosis, treatment decision-making, and follow-up of patients receiving nutritional interventions. However, whether personalized nutrition based on genomic data will have the dramatic impact on health that researchers once predicted remains unclear.

Conclusions

Generally, most trials investigating dietary macronutrient content, distribution and restriction emphasize the beneficial role of protein and the type as well as proportion of carbohydrates over that of lipids as important factors in weight management. However, the conflicting data from RCTs and meta-analyses regarding the effects of different long-term dietary approaches on overall health need to be resolved. This situation is not helped by the preponderance of short-term (<6 months) studies. Indeed, consensus guidelines published by the American College of Cardiology, American Heart Association and The Obesity Society for management of overweight and obesity in adults stress the importance of conducting further studies to confirm the optimal dietary and lifestyle intervention for achieving sustained weight loss in adults. These guidelines also suggest that adherence to treatments is a key factor for a successful weight-loss strategy, and highlight the need for intervention trials of at least 2 years duration.

Despite the expenditure of much time and effort on nutritional research, important unresolved questions (and opposing conclusions) remain. Although trends in the evidence suggest that moderately high protein diets (less than 35% of total calories) and fibre-rich foods should be promoted, the long term metabolic effects of low-carbohydrate diets require thorough investigation. The utility of other important and often disregarded factors that affect weight loss, such as dietary adherence, physical activity levels and behavioural changes are also largely waiting to be addressed.

Public-health dietary recommendations currently emphasise the broad nutritional requirements for preventing and reducing obesity in the general population and specific at-risk groups, such as children and adolescents, pregnant women, elderly individuals, and those with relevant diseases (such as type 2 diabetes mellitus). However, it is becoming evident that in addition to universal recommendations promoting healthy eating habits, personalized dietary advice will need to focus on each individual’s unique circumstances, including phenotypic traits, food allergies and intolerances, likes and dislikes, environmental constraints, and genetic background.

In this context, it is obvious that addressing the global obesity epidemic is likely to require a combined approach: reduced consumption of high-energy-yielding foods, avoidance of sedentary lifestyles, and personalized dietary advice based upon the individual’s phenotype and genotype. Opportunities for providing personalized nutritional advice are increasing along with the availability of low-cost, high-throughput analysis of genomic information. This situation is opening the door for development of commercial, direct-to-consumer genetic testing, but uncertainties in the processing and interpretation of genetic data, as well as concerns about the ethical implications, await the development of suitable policies.

The importance of quality, as well as quantity of dietary macronutrients is beginning to be understood. Specifically, the types of fatty acids, amino acids and sugars present may have important effects on energy yield. Indeed, proteins seem to be fuel substrates that promote thermogenesis. Diets rich in protein and low glycaemic index carbohydrates also improve satiety and avoid or reduce excess weight
Animal and human studies also show that fat intake is potentially linked to overeating and a positive energy balance, although high fat diets do not necessarily cause weight gain, and low-carbohydrate diets (high-protein or high fat) have shown to be as effective as control or low-fat diets in weight loss treatments. Furthermore, the advances in bioinformatics and ‘omics’ technologies may herald a new era in personalized medicine, although applications of epigenetic and genome-wide profiling are some way from clinical implementation or global consensus.

**Review criteria**

A search for original articles focusing on the roles of macronutrients and interactions between genetics and dietary interventions in weight-loss studies, published between January 2003 and July 2014, was performed in the MEDLINE and PubMed databases. The search terms used were “weight loss”, “obesity” and “macronutrient”, “protein”, “sugar”, “fat”, “carbohydrates”, “fatty acids” and “diet”, alone and in combinations. All articles except for reference 61 were English-language, full-text papers. The reference lists of identified articles were also searched for relevant papers.


32. Hu, F.B. Resolved: there is sufficient scientific evidence that decreasing sugar-sweetened beverage consumption will reduce the prevalence of obesity and obesity-related diseases. *Obes. Rev.* 14, 606-619 (2013).


**Acknowledgements**
The authors acknowledge the editorial assistance from Peter Sidaway (Nature Clinical Reviews) through the publication process.

J.A.M. and S.N.-C. are also grateful to CIBERobn (CIBER of Physiopathology of Obesity, Instituto de Salud Carlos III, 28029 Madrid, Spain) for the financial support in their research.

Author contributions

J.A.M and S.N.—C researched data for the article and wrote the manuscript; J.A.M, S.N.—C, W.H.M.S. and AA provided substantial contributions to discussions of the content, and reviewed or editing of the manuscript before submission.
Table 1 Key trials* investigating the role of macronutrients in weight management.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Participants</th>
<th>Comparison</th>
<th>Duration</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bravata et al. (2003)</td>
<td>3,268 overweight or obese adults</td>
<td>Systematic review of low-carbohydrate diet (&lt;60g daily) versus control</td>
<td>Average 50–73 days</td>
<td>3.6 kg (95%CI, 1.2-6.0 kg) weight loss in low-carbohydrate group versus 2.1 kg (95%CI, 1.6-2.7 kg) in control group</td>
</tr>
<tr>
<td>Halton and Hu (2004)</td>
<td>720 overweight or obese adults</td>
<td>Critical review of high dietary protein intake versus control</td>
<td>7 days–6 months</td>
<td>Significant improvement in weight loss with high-protein diets in 7 of 15 trials. Other trials reported no significant differences</td>
</tr>
<tr>
<td>Nordman et al. (2006)</td>
<td>447 obese adults</td>
<td>Meta-analysis of low-fat (&lt;30% of total energy intake) versus low carbohydrate (&lt;60g daily) diets</td>
<td>6–12 months</td>
<td>Low-carbohydrate diets resulted in a weight loss of 3.3 kg (95%CI, -5.3- -1.4 kg) relative to low-fat diets at 6 months</td>
</tr>
<tr>
<td>Thomas et al. (2007)</td>
<td>202 overweight or obese adults</td>
<td>Cochrane review of low-glycaemic-index versus high-glycaemic-index diets</td>
<td>5 weeks–6 months</td>
<td>Low-glycaemic-index diets produced on average 1.1 kg more weight loss (95%CI, -2.0 - -0.2 kg, p&lt;0.05)</td>
</tr>
<tr>
<td>Hooper et al. (2012)</td>
<td>73,589 normal, overweight or obese adults</td>
<td>Systematic review and meta-analysis of reduced fat intake (&gt;30% total energy intake) versus normal fat intake</td>
<td>6 months–7.5 years</td>
<td>Diets with reduced fat intake produced an additional 1.57 kg (95%CI, -2.0 - -1.2 kg) weight loss relative to normal fat intake</td>
</tr>
<tr>
<td>Wycherley et al. (2012)</td>
<td>1,063 adults, BMI status not specified</td>
<td>Systematic review and meta-analysis of high (27–35% total energy intake) versus standard protein (16–21% total energy intake) low-fat diets</td>
<td>&gt;12 weeks</td>
<td>High-protein diets result in 0.79 (95%CI, -1.5- -0.08kg) kg more weight loss after 12 or more weeks</td>
</tr>
<tr>
<td>Ajala et al.</td>
<td>3,073 normal weight, overweight</td>
<td>Systematic review and meta-analysis</td>
<td>&gt;6</td>
<td>Low-carbohydrate diets (-0.69 kg, p=0.21) and</td>
</tr>
<tr>
<td>Study (Reference)</td>
<td>Participants</td>
<td>Intervention</td>
<td>Duration</td>
<td>Results</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------</td>
<td>--------------</td>
<td>----------</td>
<td>---------</td>
</tr>
<tr>
<td>Te Morenga et al. (2013)</td>
<td>1,286 adults</td>
<td>Meta-analysis of reduced dietary free sugars intake</td>
<td>10 weeks–8 months</td>
<td>Reduced sugar intake led to 0.80 kg (95%CI, 0.39-1.21 kg, p&lt;0.001) of weight loss</td>
</tr>
<tr>
<td>Te Morenga et al. (2013)</td>
<td>138 normal weight, overweight and obese adults</td>
<td>Meta-analysis of isocaloric diets high and low in free sugars</td>
<td>2 weeks–6 months</td>
<td>No significant changes in body weight after iso-energetic exchanges of free sugars with other macronutrients</td>
</tr>
<tr>
<td>Clifton et al. (2014)</td>
<td>3,492 overweight and obese adults</td>
<td>Systematic review and meta-analysis of high protein (&gt;25% total energy intake) versus control</td>
<td>&gt;1 year</td>
<td>Differences of 5% in protein intake led to nearly 1 kg reduction in fat mass compared to normal protein intake (p=0.038)</td>
</tr>
</tbody>
</table>

*Systematic reviews, meta-analyses of randomized controlled trials, and cohort studies.*
Table 2 Key randomized controlled trials investigating the effects of dietary macronutrient intake on body weight

<table>
<thead>
<tr>
<th>Reference</th>
<th>Participants</th>
<th>Comparisons</th>
<th>Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labayen et al. (2003)</td>
<td>11 obese adults</td>
<td>2 hypocaloric diets with different carbohydrate: protein ratios (1.3 versus 3.7)</td>
<td>10 weeks</td>
<td>Replacement of carbohydrate with protein resulted in weight loss by 4.4 kg (p&lt;0.05).</td>
</tr>
<tr>
<td>McMillan-Price et al. (2006)</td>
<td>129 young overweight and obese individuals</td>
<td>4 diets with different macronutrient distributions and glycaemic loads</td>
<td>12 weeks</td>
<td>Both high-protein and low-glycaemic-index diets resulted in increased fat loss (80% more fat loss, p=0.007).</td>
</tr>
<tr>
<td>Gardner et al. (2007)</td>
<td>311 overweight premenopausal women</td>
<td>4 diets representing a spectrum of low to high carbohydrate content</td>
<td>1 year</td>
<td>Greatest weight loss with the lowest carbohydrate diets (Atkins 4.7 kg, Zone 1.6 kg; Ornish 2.2 kg and LEARN 2.6 kg). Differences Atkins vs Zone were significant (p&lt;0.05)</td>
</tr>
<tr>
<td>Das et al. (2007)</td>
<td>34 obese adults</td>
<td>2 calorie-restricted diets with different glycaemic loads</td>
<td>1 year</td>
<td>Weight loss was similar in both diets: low glycaemic load, 8.0 kg; and high glycaemic load 7.8 kg</td>
</tr>
<tr>
<td>Meckling and Sherfey (2007)</td>
<td>44 overweight and obese women</td>
<td>4 energy-restricted diets with 3:1 to 1:1 carbohydrate:protein ratios</td>
<td>12 weeks</td>
<td>High-protein diet resulted in superior weight loss (4.6 kg) versus the low-fat high carbohydrate diet (2.1 kg)</td>
</tr>
<tr>
<td>Abete et al. (2008)</td>
<td>32 obese individuals</td>
<td>2 diets with different glycaemic index</td>
<td>8 weeks</td>
<td>Low-glycaemic-index diet led to improved weight loss (-7.5 kg versus -5.3 kg, p=0.032)</td>
</tr>
<tr>
<td>Salas-Salvado et al. (2008)</td>
<td>1,224 individuals at increased cardiovascular risk</td>
<td>Low-fat diet versus a Mediterranean diet</td>
<td>12 months</td>
<td>weight did not change after one year. Metabolic Syndrome reversion was higher in Mediterranean diet +nuts group (OR 1.7; 95%; CI 1.1-2.7)</td>
</tr>
<tr>
<td>Shai et al. (2008)</td>
<td>322 moderately obese individuals</td>
<td>Low-fat diet, with caloric restriction. Mediterranean diet with caloric restriction</td>
<td>2 years</td>
<td>All diets resulted in weight loss: low-fat, 3.3 kg; Mediterranean, 4.6 kg; and low carbohydrate,</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Interventions</td>
<td>Duration</td>
<td>Results</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>----------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hollis et al. (2008)</td>
<td>1,685 individuals at increased cardiovascular risk</td>
<td>Calorie restriction and lifestyle modification, including the DASH plan</td>
<td>6 months</td>
<td>Average weight loss 5.8 kg</td>
</tr>
<tr>
<td>Sacks et al. (2009)</td>
<td>811 overweight adults</td>
<td>4 diets with different macronutrient distributions (low versus high fat and low versus high protein)</td>
<td>6–24 months</td>
<td>Weight losses ranged from 2.9 kg to 3.6 kg, regardless of macronutrient distribution</td>
</tr>
<tr>
<td>Handjeva-Darlenska et al. (2012)</td>
<td>711 obese individuals</td>
<td>Low fat (20–25% total energy intake) versus moderately high (40–45% total energy intake) hypocaloric diets</td>
<td>10 weeks</td>
<td>Similar weight losses (6.9 kg versus 6.7 kg)</td>
</tr>
<tr>
<td>Wing et al. (2013)</td>
<td>5,145 overweight patients with diabetes</td>
<td>Energy-restricted diet plus exercise versus diabetes care</td>
<td>9.6 years</td>
<td>Increased weight loss in the dietary intervention (6.0%) versus. control group (3.5 %, p&lt;0.001)</td>
</tr>
</tbody>
</table>

Abbreviation: DASH, Dietary Approaches to Stop Hypertension
Table 3. Selected randomized controlled trials that investigated interactions between SNPs and weight-loss dietary interventions

<table>
<thead>
<tr>
<th>Reference</th>
<th>Gene</th>
<th>Polymorphism</th>
<th>Study design</th>
<th>Participants</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grau et al. (2010)</td>
<td>TCF7L2</td>
<td>rs7903146</td>
<td>10 weeks energy restriction (low-fat versus high-fat)</td>
<td>771 obese adults</td>
<td>Individuals homozygous for the T allele are more responsive to low-fat diets (-2.6 additional kg lost, p=0.009)</td>
</tr>
<tr>
<td>Kim and Lee (2010)</td>
<td>UCP1 and ADRB3</td>
<td>-3826A/G and Trp64Arg</td>
<td>2 low-calorie rice-based diets with different fibre compositions</td>
<td>40 obese women</td>
<td>The AA UCP1 genotype produced significant weight loss (p=0.041) in the high-fibre group but ADRB3 genotype had no effect</td>
</tr>
<tr>
<td>Haupt et al. (2010)</td>
<td>TCF7L2</td>
<td>rs7903146</td>
<td>9 month lifestyle intervention with fat reduction and fibre increase</td>
<td>304 obese adults</td>
<td>Dietary fibre modulated the association between TCF7L2 variance and weight loss (p=0.0034)</td>
</tr>
<tr>
<td>Mattei et al. (2012)</td>
<td>TCF7L2</td>
<td>rs12255372</td>
<td>Dietary intervention with 4 diets (low or high fat and low or high protein) for 2 years</td>
<td>591 overweight adults</td>
<td>Individuals with the TT genotype lost more fat mass while consuming a diet lower in lipids (p&lt;0.05)</td>
</tr>
<tr>
<td>Qi et al. (2012)</td>
<td>GiPR</td>
<td>rs2287019</td>
<td>Intervention with 4 diets (low or high fat and low or high protein) for 3 years</td>
<td>757 overweight adults</td>
<td>The T allele was associated with increased weight loss when consuming a low fat diet (β±SE; -1.05±0.56%; p=0.06)</td>
</tr>
<tr>
<td>Stocks et al. (2012)</td>
<td>TFAP2B</td>
<td>rs987237</td>
<td>8 weeks energy-restricted diet</td>
<td>771 obese adults</td>
<td>Individuals with the AA genotype had improved weight loss</td>
</tr>
<tr>
<td>Study</td>
<td>SNP</td>
<td>Intervention Description</td>
<td>Participants</td>
<td>Intervention Outcome</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>----------</td>
<td>------------------------------------------------------------------------------------------</td>
<td>--------------</td>
<td>----------------------</td>
<td></td>
</tr>
<tr>
<td>Zhang et al. (2012)</td>
<td>FTO rs1558902</td>
<td>Intervention with 4 diets (low or high-fat &amp; low or high-protein) for 2 years</td>
<td>742 obese adults</td>
<td>High-protein diet may have specific benefits for weight loss (p&lt;0.05 for all interactions) in individuals with the risk allele (A)</td>
<td></td>
</tr>
<tr>
<td>Cameron et al. (2013)</td>
<td>DRD2 TAqARFLP</td>
<td>Caloric restriction and resistance training for 6 months</td>
<td>127 obese postmenopausal women</td>
<td>Carriers of the A1 allele lost significantly less body weight (p&lt;0.05), but this effect seemed to be exercise-dependent</td>
<td></td>
</tr>
</tbody>
</table>
J. Alfredo Martinez is BPharm (1979) and PhD in Nutrition (1982), both at the University of Navarra, and both granted with the University Award. He also holds a MD from the University of Zaragoza (2012). Since 1992 he is Professor of Nutrition and Scientific director of the Centre for Nutrition Research of the University of Navarra. He is former President of the Spanish Nutrition Society (1999-2001) and advisor for nutritional issues at the EU. He is President of the International Society of Nutrigenetics and Nutrigenomics (ISNN, 2014-) and president-elect of the International Union of Nutritional Sciences (IUNS, 2013-). He has published over 450 research articles in human nutrition and obesity. He has been involved in various EU Projects (Disparities, SEAFOODplus, NUGENOB, DIOGENES, Food4Me, PREVIEW).

Santiago Navas-Carretero gained his degree in Pharmacy in 2002 and PhD in Nutrition in 2007 (European Doctor) at the Complutense University of Madrid. He is researcher at the University of Navarra since 2008 and has participated so far in 21 National and European funded research projects. He is member of the Spanish Nutrition Society and external member of GENUTREN group of Madrid. He has published 50 research articles (38 indexed in Web of Science), all in the Human Nutrition research field, focusing on iron deficiency and prevention of iron deficiency anemia, and in Obesity and type 2 diabetes nutritional interventions.

Wim H.M. Saris (1949) earned his degree in Human Nutrition at Wageningen University (WUR) and MD and PhD degree at Nijmegen Catholic University, both in The Netherlands. He holds a chair in Human Nutrition at the Faculty of Health, Medicine and Life Sciences at Maastricht University since 1988. In 2005 he part-time joined DSM Corp. as Corporate Scientist Human Nutrition at DSM Food Specialties (DFS) The Netherlands. He published over 450 papers in the field of human nutrition and energy and intermediaries metabolism in health and disease such as type 2 diabetes and obesity.

Professor Arne Astrup is Head of Department of Nutrition, Exercise & Sports and Director of the Nordea Foundation OPUS Research Centre at the Faculty of Science, University of Copenhagen, and Consultant Physician at Herlev Hospital, Denmark. He has over 30 years’ experience in clinical research in the physiology and pathophysiology of energy and substrate metabolism, with particular focus on the etiology and treatment of obesity. Major research collaborations include participation in the EU multicenter studies EUROSTARCH, CARMEN, NUGENOB, DIABESITY, DIOGENES, EMOB, HEALTHGRAIN and MyNewGut. Thompson Reuters Science Index 2010: 5th for obesity publications / citations-H-index: 67.