Personalized weight loss strategies—the role of macronutrient distribution

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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.

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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/m^2) 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/m^{2}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, 6] 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.[7-9]

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.[10] 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).[11] 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.[12] In this context, the prevention and management of excessive weight gain or changes in body composition can be achieved through various approaches.[13] 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.[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,[17] and to determine whether calories derived from different macronutrients have equivalent fuel values for the body.[18, 19] 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.[19] 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.[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.[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.[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.[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.[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.[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.[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. [31] 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.[32]

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.[33] 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.[34]

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[36] 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.[36] 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.[36]

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.[37] The test diets consisted of 55% carbohydrates with either high or low glycaemic index, or 25% protein and either high or low glycaemic index.[37] 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.[38] 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.[39] 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.[39] 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.[39]

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).[40] 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,[40] which was in accordance with the results of previous short-term studies and critical reviews.[22, 41, 42] 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.[40]

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.[43] 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.[43] 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.[44]

Clinical trials

A total of 771 obese individuals in the NUGENOB study (mean BMI 35.6 kg/m^2) 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.[45] 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.[46] The three intervention groups received specific advice to adhere to their diet. Despite all diets being unrestricted in terms of calorific intake. and 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.[46]

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.[47] 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,[48] 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.[48] 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.[53] 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 2014[55] 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.[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.[55] Indeed, adherence to dietary recommendations, and improving success rates, are issues that also need attention in future studies.

Evidence from clinical trials

Short follow-up periods and substantial dropout rates are common problems observed in RCTs.[49, 56] For example, a 2-year nutritional intervention (DIRECT) was designed and developed to test the efficacy of three different diets.[57] 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.[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,[58] impaired flow-mediated dilatation,[59] and increased LDL-cholesterol levels,[50] although contradictory evidence exists on the latter point.[41] 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.[60]

Mixed dietary restrictions

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. [61,62] Several meta-analyses have studied the differential effects of diets with a low glycaemic index or low glycaemic load,[63] high fat content,[64] or high protein content[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.[63] These meta-analyses[64,65] as well as other systematic reviews[41, 66] 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/m^2) over a 10 week study period.[67] 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.[56] 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).[56] 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.[56]

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,[68] 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.[68] 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.[69, 70] Increased physical exercise was not unequivocally identified as an independent cause of weight loss except in highly active individuals, in an extensive review[69] and meta-analysis.[70] In the same analysis, no synergistic effects on body weight were detected between low-calorie diets and exercise.[70] Although the benefits of regular physical activity include improved cardiovascular health and maintenance of skeletal muscle mass,[71-73] 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.[69]

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.[74] 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.[74]

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.[24, 76] Indeed, approximately 50 candidate genes have been associated with the regulation of energy metabolism[77] 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,[78] leptin receptor,[79] or melanocortin 4 receptor.[80, 81] 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, 82] 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.[83] 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.[28]

Despite some ethical and methodological concerns over the use of genetic testing to support personalized nutrition,[84,85] direct-to-consumer tests for genetic predisposition to a range of diseases are already available,[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.[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.[87] These strategies have focused on genes related to appetite control, energy and lipid metabolism[25, 82], adipocyte function and inflammation[88, 89]. 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.[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[91] or high-fat (fried) food[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).[93] 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).[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),[95] who seem to achieve improved weight loss in response to a low-fat (20–25% of total calorie intake) diet after ≥2years. 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.[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.[94, 95]

Dietary fat[97] and fibre[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.[97] The TULIP study results[98] 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.[98] 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.[99]

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.[100] This weight loss was apparently exercise-dependent.[100]

In summary, these observations raise questions as to what kind of individualized dietary advice should be based on an individual's genetic make-up.[100] For example, in noncarriers of alleles associated with risk of obesity linked to sugar-sweetened beverages[91] or fried foods,[92] 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.[84, 101] 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.[102] 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.[103] 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,[104] and are predictive of weight loss.[102] 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.[102] Furthermore, practical, social and ethical considerations are essential in the design of future research studies**.** Evidence must be accumulated through extensive, well-designed RCTs,[27, 105] and the public perception, attitudes and trust towards personalized nutrition should be explored and consolidated.[84, 106]

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.[107, 108] 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.[109, 110] 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.[111, 112] However, whether personalized nutrition based on genomic data will have the dramatic impact on health that researchers once predicted remains unclear.[113]

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[114] 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.[115]

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.[116] 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.[117]

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.[118] 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.[84]

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.[14] Indeed, proteins seem to be fuel substrates that promote thermogenesis[35, 48]. Diets rich in protein and low glycaemic index carbohydrates also improve satiety and avoid or reduce excess weight gain[39, 48, 119]. Animal and human studies also show that fat intake is potentially linked to overeating and a positive energy balance[44, 120], although high fat diets do not necessarily cause weight gain[52, 53], 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[35, 37, 40, 54, 68] Furthermore, the advances in bioinformatics and 'omics' technologies may herald a new era in personalized medicine,[121] although applications of epigenetic and genome-wide profiling are some way from clinical implementation or global consensus.[122]

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.

1. Martinez, J.A. Body-weight regulation: causes of obesity. *Proc. Nutr. Soc.* **59**, 337-345 (2000).

2. Galgani, J. & Ravussin, E. Energy metabolism, fuel selection and body weight regulation. *Int. J. Obes. (Lond)* **32** , S109-S119 (2008).

3. Ng, M. *et al.* Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* **384**, 766-781 (2014).

4. Berrington de Gonzalez, A. *et al.* Body-mass index and mortality among 1.46 million white adults. *N. Engl. J. Med.* **363**, 2211-2219 (2010).

5. Greenberg, J.A. The obesity paradox in the US population. *Am. J. Clin. Nutr.* **97**, 1195-1200 (2013).

6. Flegal, K.M., Kit, B.K. & Graubard, B.I. Overweight, obesity, and all-cause mortality--reply. *JAMA* **309**, 1681-1682 (2013).

7. Marti, A. *et al.* Methodological approaches to assess body-weight regulation and aetiology of obesity. *Proc. Nutr. Soc.* **59**, 405-411 (2000).

8. Ho, M. *et al.* Effectiveness of lifestyle interventions in child obesity: systematic review with meta-analysis. *Pediatrics* **130**, e1647-1671 (2012).

9. Astrup, A. & Brand-Miller, J. Obesity: Have new guidelines overlooked the role of diet composition? *Nat. Rev. Endocrinol.* **10**, 132-133 (2014).

10. Sparling, P.B., Franklin, B.A. & Hill, J.O. Energy balance: the key to a unified message on diet and physical activity. *J Cardiopulm Rehabil Prev* **33**, 12-15 (2013).

11. McAllister, E.J. *et al.* Ten putative contributors to the obesity epidemic. *Crit. Rev. Food Sci. Nutr.* **49**, 868-913 (2009).

12. Malik, V.S., Willett, W.C. & Hu, F.B. Global obesity: trends, risk factors and policy implications. *Nat. Rev. Endocrinol.* **9**, 13-27 (2013).

13. Galani, C. & Schneider, H. Prevention and treatment of obesity with lifestyle interventions: review and meta-analysis. *Int. J. Public Health* **52**, 348-359 (2007).

14. Abete, I., Goyenechea, E., Zulet, M.A. & Martinez, J.A. Obesity and metabolic syndrome: potential benefit from specific nutritional components. *Nutr. Metab. Cardiovasc. Dis.* **21**, B1-B15 (2011).

15. Lepor, N.E., Fouchia, D.D. & McCullough, P.A. New vistas for the treatment of obesity: turning the tide against the leading cause of morbidity and cardiovascular mortality in the developed world. *Rev. Cardiovasc. Med.* **14**, 20-39 (2013).

16. Heath, V. Obesity: Benefits of intensive lifestyle modification programs in the spotlight. *Nat. Rev. Endocrinol.* **7**, 1 (2011).

17. Purnell, J.Q. Obesity: Calories or content: what is the best weight-loss diet? *Nat. Rev. Endocrinol.* **5**, 419-420 (2009).

18. Buchholz, A.C. & Schoeller, D.A. Is a calorie a calorie? *Am. J. Clin. Nutr.* **79**, 899S-906S (2004).

19. Foreyt, J.P. *et al.* Weight-reducing diets: are there any differences? *Nutr. Rev.* **67** , S99-S101 (2009).

20. Zulet, M.A. *et al.* The reduction of the metabolyc syndrome in Navarra-Spain (RESMENA-S) study: a multidisciplinary strategy based on chrononutrition and nutritional education, together with dietetic and psychological control. *Nutr. Hosp.* **26**, 16-26 (2011).

21. Wilson, C. Obesity: finding weight loss strategies that work in primary care. *Nat. Rev. Endocrinol*. **9**, 126 (2013).

22. Abete, I., Astrup, A., Martinez, J.A., Thorsdottir, I. & Zulet, M.A. Obesity and the metabolic syndrome: role of different dietary macronutrient distribution patterns and specific nutritional components on weight loss and maintenance. *Nutr. Rev.* **68**, 214-231 (2010).

23. Turk, M.W. *et al.* Randomized clinical trials of weight loss maintenance: a review. *J. Cardiovasc. Nurs.* **24**, 58-80 (2009).

24. Martinez, J.A., Enriquez, L., Moreno-Aliaga, M.J. & Marti, A. Genetics of obesity. *Public Health Nutr.* **10**, 1138-1144 (2007).

25. Abete, I., Navas-Carretero, S., Marti, A. & Martinez, J.A. Nutrigenetics and nutrigenomics of caloric restriction. *Prog. Mol. Biol. Transl. Sci.* **108**, 323-346 (2012).

26. Fenech, M. *et al.* Nutrigenetics and nutrigenomics: viewpoints on the current status and applications in nutrition research and practice. *J. Nutrigenet. Nutrigenomics* **4**, 69-89 (2011).

27. de Roos, B. Personalised nutrition: ready for practice? *Proc. Nutr. Soc.* **72**, 48-52 (2013).

28. De Caterina, R. Opportunities and challenges in nutrigenetics/nutrigenomics and health. *World Rev. Nutr. Diet.* **101**, 1-7 (2010).

29. Westerterp-Plantenga, M.S., Nieuwenhuizen, A., Tome, D., Soenen, S. & Westerterp, K.R. Dietary protein, weight loss, and weight maintenance. *Annu. Rev. Nutr.* **29**, 21-41 (2009).

30. de Souza, R.J., Swain, J.F., Appel, L.J. & Sacks, F.M. Alternatives for macronutrient intake and chronic disease: a comparison of the OmniHeart diets with popular diets and with dietary recommendations. *Am. J. Clin. Nutr.* **88**, 1-11 (2008).

31. Te Morenga, L., Mallard, S. & Mann, J. Dietary sugars and body weight: systematic review and meta-analyses of randomised controlled trials and cohort studies. *BMJ* **346**, e7492 (2013).

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).

33. Thomas, D.E., Elliott, E.J. & Baur, L. Low glycaemic index or low glycaemic load diets for overweight and obesity. *Cochrane Database Syst. Rev.* 10.1002/14651858.CD005105.pub2, CD005105 (2007).

34. Esfahani, A., Wong, J.M., Mirrahimi, A., Villa, C.R. & Kendall, C.W. The application of the glycemic index and glycemic load in weight loss: A review of the clinical evidence. *IUBMB Life* **63**, 7-13 (2011).

35. Bravata, D.M. *et al.* Efficacy and safety of low-carbohydrate diets: a systematic review. *JAMA* **289**, 1837-1850 (2003).

36. Saris, W.H. *et al.* Randomized controlled trial of changes in dietary carbohydrate/fat ratio and simple vs complex carbohydrates on body weight and blood lipids: the CARMEN study. The Carbohydrate Ratio Management in European National diets. *Int. J. Obes. Relat. Metab. Disord.* **24**, 1310-1318 (2000).

37. McMillan-Price, J. *et al.* Comparison of 4 diets of varying glycemic load on weight loss and cardiovascular risk reduction in overweight and obese young adults: a randomized controlled trial. *Arch. Intern. Med.* **166**, 1466-1475 (2006).

38. Das, S.K. *et al.* Long-term effects of 2 energy-restricted diets differing in glycemic load on dietary adherence, body composition, and metabolism in CALERIE: a 1-y randomized controlled trial. *Am. J. Clin. Nutr.* **85**, 1023-1030 (2007).

39. Abete, I., Parra, D. & Martinez, J.A. Energy-restricted diets based on a distinct food selection affecting the glycemic index induce different weight loss and oxidative response. *Clin. Nutr.* **27**, 545-551 (2008).

40. Gardner, C.D. *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* **297**, 969-977 (2007).

41. Hu, T. *et al.* Effects of low-carbohydrate diets versus low-fat diets on metabolic risk factors: a meta-analysis of randomized controlled clinical trials. *Am J Epidemiol* **176** , S44-S54 (2012).

42. Yancy, W.S., Jr., Olsen, M.K., Guyton, J.R., Bakst, R.P. & Westman, E.C. A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: a randomized, controlled trial. *Ann. Intern. Med.* **140**, 769-777 (2004).

43. Hooper, L. *et al.* Effect of reducing total fat intake on body weight: systematic review and meta-analysis of randomised controlled trials and cohort studies. *BMJ* **345**, e7666 (2012).

44. Astrup, A., Grunwald, G.K., Melanson, E.L., Saris, W.H. & Hill, J.O. The role of low-fat diets in body weight control: a meta-analysis of ad libitum dietary intervention studies. *Int. J. Obes. Relat. Metab. Disord.* **24**, 1545-1552 (2000).

45. Handjieva-Darlenska, T. *et al.* Clinical correlates of weight loss and attrition during a 10-week dietary intervention study: results from the NUGENOB project. *Obes. Facts* **5**, 928-936 (2012).

46. Salas-Salvado, J. *et al.* Effect of a Mediterranean diet supplemented with nuts on metabolic syndrome status: one-year results of the PREDIMED randomized trial. *Arch. Intern. Med.* **168**, 2449-2458 (2008).

47. Ades, P.A. & Savage, P.D. Potential benefits of weight loss in coronary heart disease. *Prog. Cardiovasc. Dis.* **56**, 448-456 (2014).

48. Halton, T.L. & Hu, F.B. The effects of high protein diets on thermogenesis, satiety and weight loss: a critical review. *J. Am. Coll. Nutr.* **23**, 373-385 (2004).

49. Larsen, T.M. *et al.* Diets with high or low protein content and glycemic index for weight-loss maintenance. *N. Engl. J. Med.* **363**, 2102-2113 (2010).

50. Bueno, N.B., de Melo, I.S., de Oliveira, S.L. & da Rocha Ataide, T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. *Br. J. Nutr.* **110**, 1178-1187 (2013).

51. Martinez, J.A. & Dolores Parra, M. Life-threatening complications of the Atkins diet? *Lancet* **368**, 23 (2006).

52. Nordmann, A.J. *et al.* Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. *Arch. Intern. Med.* **166**, 285-293 (2006).

53. Ajala, O., English, P. & Pinkney, J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. *Am. J. Clin. Nutr.* **97**, 505-516 (2013).

54. Wycherley, T.P., Moran, L.J., Clifton, P.M., Noakes, M. & Brinkworth, G.D. Effects of energy-restricted high-protein, low-fat compared with standard-protein, low-fat diets: a meta-analysis of randomized controlled trials. *Am. J. Clin. Nutr.* **96**, 1281-1298 (2012).

55. Clifton, P.M., Condo, D. & Keogh, J.B. Long term weight maintenance after advice to consume low carbohydrate, higher protein diets – A systematic review and meta analysis. *Nutr. Metab. Cardiovasc. Dis.* **24**, 224-235 (2014).

56. Sacks, F.M. *et al.* Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N. Engl. J. Med.* **360**, 859-873 (2009).

57. Shai, I. *et al.* Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N. Engl. J. Med.* **359**, 229-241 (2008).

58. Noto, H., Goto, A., Tsujimoto, T. & Noda, M. Low-carbohydrate diets and all-cause mortality: a systematic review and meta-analysis of observational studies. *PLoS One* **8**, e55030 (2013).

59. Schwingshackl, L. & Hoffmann, G. Low-carbohydrate diets impair flow-mediated dilatation: evidence from a systematic review and meta-analysis. *Br. J. Nutr.* **110**, 969-970 (2013).

60. Pagoto, S.L. & Appelhans, B.M. A call for an end to the diet debates. *JAMA* **310**, 687-688 (2013).

61. Martinez, J.A. Nutricion saludable frente a la Obesidad. Bases científicas y aspectos dietéticos (Ed. J. Alfredo Martínez) (Editorial médica Panamericana, Madrid, 2013).

62. Marti, A., Goyenechea, E. & Martinez, J.A. Nutrigenetics: a tool to provide personalized nutritional therapy to the obese. *J Nutrigenet. Nutrigenomics* **3**, 157-169 (2010).

63. Schwingshackl, L. & Hoffmann, G. Long-term effects of low glycemic index/load vs. high glycemic index/load diets on parameters of obesity and obesity-associated risks: a systematic review and meta-analysis. *Nutr. Metab. Cardiovasc. Dis.* **23**, 699-706 (2013).

64. Schwingshackl, L. & Hoffmann, G. Comparison of effects of long-term low-fat vs high-fat diets on blood lipid levels in overweight or obese patients: a systematic review and meta-analysis. *J. Acad. Nutr. Diet.* **113**, 1640-1661 (2013).

65. Schwingshackl, L. & Hoffmann, G. Long-term effects of low-fat diets either low or high in protein on cardiovascular and metabolic risk factors: a systematic review and meta-analysis. *Nutr. J.* **12**, 48 (2013).

66. Santos, F.L., Esteves, S.S., da Costa Pereira, A., Yancy, W.S., Jr. & Nunes, J.P. Systematic review and meta-analysis of clinical trials of the effects of low carbohydrate diets on cardiovascular risk factors. *Obes. Rev.* **13**, 1048-1066 (2012).

67. Labayen, I., Diez, N., Gonzalez, A., Parra, D. & Martinez, J.A. Effects of protein vs. carbohydrate-rich diets on fuel utilisation in obese women during weight loss. *Forum Nutr.* **56**, 168-170 (2003).

68. Meckling, K.A. & Sherfey, R. A randomized trial of a hypocaloric high-protein diet, with and without exercise, on weight loss, fitness, and markers of the Metabolic Syndrome in overweight and obese women. *Appl. Physiol. Nutr. Metab.* **32**, 743-752 (2007).

69. Swift, D.L., Johannsen, N.M., Lavie, C.J., Earnest, C.P. & Church, T.S. The role of exercise and physical activity in weight loss and maintenance. *Prog. Cardiovasc. Dis.* **56**, 441-447 (2014).

70. Johansson, K., Neovius, M. & Hemmingsson, E. Effects of anti-obesity drugs, diet, and exercise on weight-loss maintenance after a very-low-calorie diet or low-calorie diet: a systematic review and meta-analysis of randomized controlled trials. *Am. J. Clin. Nutr.* **99**, 14-23 (2014).

71. Vanhees, L. *et al.* Importance of characteristics and modalities of physical activity and exercise in defining the benefits to cardiovascular health within the general population: recommendations from the EACPR (Part I). *Eur. J. Prev. Cardiol.* **19**, 670-686 (2012).

72. Vanhees, L. *et al.* Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular risk factors: recommendations from the EACPR. Part II. *Eur. J. Prev. Cardiol.* **19**, 1005-1033 (2012).

73. Vanhees, L. *et al.* Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular disease (Part III). *Eur. J. Prev. Cardiol.* **19**, 1333-1356 (2012).

74. Wing, R.R. *et al.* Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N. Engl. J. Med.* **369**, 145-154 (2013).

75. Hollis, J.F. *et al.* Weight loss during the intensive intervention phase of the weight-loss maintenance trial. *Am. J. Prev. Med.* **35**, 118-126 (2008).

76. Rankinen, T. *et al.* The human obesity gene map: the 2005 update. *Obesity (Silver Spring)* **14**, 529-644 (2006).

77. Bell, C.G., Walley, A.J. & Froguel, P. The genetics of human obesity. *Nat. Rev. Genet.* **6**, 221-234 (2005).

78. Montague, C.T. *et al.* Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature* **387**, 903-908 (1997).

79. Clement, K. *et al.* A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. *Nature* **392**, 398-401 (1998).

80. Vaisse, C., Clement, K., Guy-Grand, B. & Froguel, P. A frameshift mutation in human MC4R is associated with a dominant form of obesity. *Nat. Genet.* **20**, 113-114 (1998).

81. Yeo, G.S. *et al.* A frameshift mutation in MC4R associated with dominantly inherited human obesity. *Nat. Genet.* **20**, 111-112 (1998).

82. El-Sayed Moustafa, J.S. & Froguel, P. From obesity genetics to the future of personalized obesity therapy. *Nat. Rev. Endocrinol.* **9**, 402-413 (2013).

83. Subbiah, M.T. Nutrigenetics and nutraceuticals: the next wave riding on personalized medicine. *Transl. Res.* **149**, 55-61 (2007).

84. San-Cristobal, R., Milagro, F.I. & Martinez, J.A. Future challenges and present ethical considerations in the use of personalized nutrition based on genetic advice. *J. Acad. Nutr. Diet.* **113**, 1447-1454 (2013).

85. Kang, J.X. The coming of age of nutrigenetics and nutrigenomics. *J. Nutrigenet. Nutrigenomics* **5**, I-II (2012).

86. Imai, K., Kricka, L.J. & Fortina, P. Concordance study of 3 direct-to-consumer genetic-testing services. *Clin. Chem.* **57**, 518-521 (2011).

87. Campion, J., Milagro, F.I. & Martinez, J.A. Genetic manipulation in nutrition, metabolism, and obesity research. *Nutr. Rev.* **62**, 321-330 (2004).

88. Phillips, C.M. Nutrigenetics and metabolic disease: current status and implications for personalised nutrition. *Nutrients* **5**, 32-57 (2013).

89. Lovegrove, J.A. & Gitau, R. Nutrigenetics and CVD: what does the future hold? *Proc. Nutr. Soc.* **67**, 206-213 (2008).

90. Moreno-Aliaga, M.J., Santos, J.L., Marti, A. & Martinez, J.A. Does weight loss prognosis depend on genetic make-up? *Obes. Rev.* **6**, 155-168 (2005).

91. Qi, Q. *et al.* Sugar-sweetened beverages and genetic risk of obesity. *N. Engl. J. Med.* **367**, 1387-1396 (2012).

92. Qi, Q. *et al.* Fried food consumption, genetic risk, and body mass index: gene-diet interaction analysis in three US cohort studies. *BMJ* **348**, g1610 (2014).

93. Zhang, X. *et al.* FTO genotype and 2-year change in body composition and fat distribution in response to weight-loss diets: the POUNDS LOST Trial. *Diabetes* **61**, 3005-3011 (2012).

94. Qi, Q., Bray, G.A., Hu, F.B., Sacks, F.M. & 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.* **95**, 506-513 (2012).

95. Mattei, J., Qi, Q., Hu, F.B., Sacks, F.M. & 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.* **96**, 1129-1136 (2012).

96. Stocks, T. *et al.* TFAP2B influences the effect of dietary fat on weight loss under energy restriction. *PLoS One* **7**, e43212 (2012).

97. Grau, K. *et al.* TCF7L2 rs7903146-macronutrient interaction in obese individuals' responses to a 10-wk randomized hypoenergetic diet. *Am J Clin Nutr* **91**, 472-479 (2010).

98. Haupt, A. *et al.* Gene variants of TCF7L2 influence weight loss and body composition during lifestyle intervention in a population at risk for type 2 diabetes. *Diabetes* **59**, 747-750 (2010).

99. Kim, J.Y. & Lee, S.S. The effects of uncoupling protein 1 and beta3-adrenergic receptor gene polymorphisms on weight loss and lipid profiles in obese women. *Int. J. Vitam. Nutr. Res.* **80**, 87-96 (2010).

100. Cameron, J.D. *et al.* The TaqIA RFLP is associated with attenuated intervention-induced body weight loss and increased carbohydrate intake in post-menopausal obese women. *Appetite* **60**, 111-116 (2013).

101. Vakili, S. & Caudill, M.A. Personalized nutrition: nutritional genomics as a potential tool for targeted medical nutrition therapy. *Nutr. Rev.* **65**, 301-315 (2007).

102. Milagro, F.I., Mansego, M.L., De Miguel, C. & Martinez, J.A. Dietary factors, epigenetic modifications and obesity outcomes: progresses and perspectives. *Mol. Aspects Med.* **34**, 782-812 (2013).

103. Campion, J., Milagro, F.I. & Martinez, J.A. Individuality and epigenetics in obesity. *Obes. Rev.* **10**, 383-392 (2009).

104. Burdge, G.C., Hoile, S.P. & Lillycrop, K.A. Epigenetics: are there implications for personalised nutrition? *Curr. Opin. Clin. Nutr. Metab. Care* **15**, 442-447 (2012).

105. Corella, D. & Ordovas, J.M. Can genotype be used to tailor treatment of obesity? State of the art and guidelines for future studies and applications. *Minerva Endocrinol.* **38**, 219-235 (2013).

106. Fallaize, R., Macready, A.L., Butler, L.T., Ellis, J.A. & Lovegrove, J.A. An insight into the public acceptance of nutrigenomic-based personalised nutrition. *Nutr. Res. Rev.* **26**, 39-48 (2013).

107. Castle, D. & DeBusk, R. The electronic health record, genetic information, and patient privacy. *J. Am. Diet. Assoc.* **108**, 1372-1374 (2008).

108. Goldsmith, L., Jackson, L., O'Connor, A. & Skirton, H. Direct-to-consumer genomic testing from the perspective of the health professional: a systematic review of the literature. *J. Community. Genet.* **4**, 169-180 (2013).

109. Bouwman, L., Te Molder, H. & Hiddink, G. Patients, evidence and genes: an exploration of GPs' perspectives on gene-based personalized nutrition advice. *Fam. Pract.* **25** i116-i122 (2008).

110. Jackson, L., Goldsmith, L. & Skirton, H. Guidance for patients considering direct-to-consumer genetic testing and health professionals involved in their care: development of a practical decision tool. *Fam. Pract.* **31**, 341-348 (2014).

111. Rubio-Aliaga, I., Kochhar, S. & Silva-Zolezzi, I. Biomarkers of nutrient bioactivity and efficacy: a route toward personalized nutrition. *J. Clin. Gastroenterol.* **46**, 545-554 (2012).

112. Hendriks, H.F. Use of nutrigenomics endpoints in dietary interventions. *Proc. Nutr. Soc.* **72**, 348-351 (2013).

113. Hesketh, J. Personalised nutrition: how far has nutrigenomics progressed? *Eur. J. Clin. Nutr.* **67**, 430-435 (2013).

114. Jensen, M.D. *et al.* 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *J. Am. Coll. Cardiol.* **63**, 2985-3023 (2014).

115. Pagoto, S. & Appelhans, B.M. Adherence to diets for weight loss--reply. *JAMA* **310**, 2676-2677 (2013).

116. Hernell, O. & West, C. Do we need personalized recommendations for infants at risk of developing disease? *Nestle Nutr. Workshop Ser. Pediatr. Program* **62**, 239-249 (2008).

117. McCabe-Sellers, B. *et al.* Personalizing nutrigenomics research through community based participatory research and omics technologies. *OMICS* **12**, 263-272 (2008).

118. Stover, P.J. & Caudill, M.A. Genetic and epigenetic contributions to human nutrition and health: managing genome-diet interactions. *J. Am. Diet. Assoc.* **108**, 1480-1487 (2008).

119. Yancy, W.S., Vernon, M.C. & Westman, E.C. A pilot trial of a low-carbohydrate, ketogenic diet in patients with type 2 diabetes. *Metab. Syndr. Relat. Disord.* **1**, 239-243 (2003).

120. Astrup, A., Buemann, B., Flint, A. & Raben, A. Low-fat diets and energy balance: how does the evidence stand in 2002? *Proc. Nutr. Soc.* **61**, 299-309 (2002).

121. Bouchard, C. & Ordovas, J.M. Fundamentals of nutrigenetics and nutrigenomics. *Prog. Mol. Biol. Transl. Sci.* **108**, 1-15 (2012).

122. Bloss, C.S., Schork, N.J. & Topol, E.J. Effect of direct-to-consumer genomewide profiling to assess disease risk. *N. Engl. J. Med.* **364**, 524-534 (2011).

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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.				
Reference	**Participants**	**Comparison**	**Duration**	**Outcomes**
Bravata *et al*. (2003)[35]	3,268 overweight or obese adults	Systematic review of low-carbohydrate diet (<60g daily) versus control	Average 50–73 days	3.6 kg (95%CI, 1.2-6.0kg) weight loss in low-carbohydrate group versus 2.1 kg (95%CI, 1.6-2.7 kg) in control group
Halton and Hu (2004)[48]	720 overweight or obese adults	Critical review of high dietary protein intake versus control	7 days–6 months	Significant improvement in weight loss with high-protein diets in 7 of 15 trials. Other trials reported no significant differences
Nordman *et al*. (2006)[52]	447 obese adults	Meta-analysis of low-fat (<30% of total energy intake) versus low carbohydrate (<60g daily) diets	6–12 months	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
Thomas *et al*. (2007)[33]	202 overweight or obese adults	Cochrane review of low-glycaemic-index versus high-glycaemic-index diets	5 weeks–6 months	Low-glycaemic-index diets produced on average 1.1 kg more weight loss (95%CI, -2.0 - -0.2 kg, p<0.05)
Hooper *et al.* (2012)[43]	73,589 normal, overweight or obese adults	Systematic review and meta-analysis of reduced fat intake (>30% total energy intake) versus normal fat intake	6 months–7.5 years	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
Wycherley *et al.* (2012)[54]	1,063 adults, BMI status not specified	Systematic review and meta-analysis of high (27–35% total energy intake) versus standard protein (16–21% total energy intake) low-fat diets	>12 weeks	High-protein diets result in 0.79 (95%CI, -1.5- -0.08kg) kg more weight loss after 12 or more weeks
Ajala *et al.*	3,073 normal weight, overweight	Systematic review and meta-analysis	>6	Low-carbohydrate diets (-0.69 kg, p=0.21) and

(2013)[53]	or obese adults with or without diabetes	comparing low-carbohydrate, low-glycaemic index, Mediterranean and high-protein diets	months	Mediterranean diets (-1.84 kg, p<0.00001) gave greater weight loss relative to high-protein diets
Te Morenga *et al*. (2013)[31]	1,286 adults	Meta-analysis of reduced dietary free sugars intake	10 weeks–8 months	Reduced sugar intake led to 0.80 kg (95%CI, 0.39-1.21 kg, p<0.001) of weight loss
Te Morenga *et al*. (2013)[31]	138 normal weight, overweight and obese adults	Meta-analysis of isocaloric diets high and low in free sugars	2 weeks–6 months	No significant changes in body weight after iso-energetic exchanges of free sugars with other macronutrients
Clifton *et al*. (2014)[55]	3,492 overweight and obese adults	Systematic review and meta-analysis of high protein (>25% total energy intake) versus control	>1 year	Differences of 5% in protein intake led to nearly 1 kg reduction in fat mass compared to normal protein intake (p=0.038)
*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				
Reference	**Participants**	**Comparisons**	**Duration**	**Outcome**
Labayen *et al*. (2003)[67]	11 obese adults	2 hypocaloric diets with different carbohydrate: protein ratios (1.3 versus 3.7)	10 weeks	Replacement of carbohydrate with protein resulted in weight loss by 4.4 kg (p<0.05).
McMillan-Price *et al*. (2006)[37]	129 young overweight and obese individuals	4 diets with different macronutrient distributions and glycaemic loads	12 weeks	Both high-protein and low-glycaemic-index diets resulted in increased fat loss (80% more fat loss, p=0.007).
Gardner *et al*. (2007)[40]	311 overweight premenopausal women	4 diets representing a spectrum of low to high carbohydrate content	1 year	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<0.05)
Das *et al*. (2007)[38]	34 obese adults	2 calorie-restricted diets with different glycaemic loads	1 year	Weight loss was similar in both diets: low glycaemic load, 8.0 kg; and high glycaemic load 7.8 kg
Meckling and Sherfey (2007)[68]	44 overweight and obese women	4 energy-restricted diets with 3:1 to 1:1 carbohydrate:protein ratios	12 weeks	High-protein diet resulted in superior weight loss (4.6 kg) versus the low-fat high carbohydrate diet (2.1 kg)
Abete *et al*. (2008)[39]	32 obese individuals	2 diets with different glycaemic index	8 weeks	Low-glycaemic-index diet led to improved weight loss (-7.5 kg versus -5.3 kg, p=0.032)
Salas-Salvado *et al*. (2008)[46]	1,224 individuals at increased cardiovascular risk	Low-fat diet versus a Mediterranean diet	12 months	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)
Shai *et al*. (2008)[57]	322 moderately obese individuals	Low-fat diet, with caloric restriction. Mediterranean diet with caloric restriction	2 years	All diets resulted in weight loss: low-fat, 3.3 kg; Mediterranean, 4.6 kg; and low carbohydrate,

		and low-carbohydrate diet without caloric restriction		5.5 kg
Hollis *et al.* (2008)[75]	1,685 individuals at increased cardiovascular risk	Calorie restriction and lifestyle modification, including the DASH plan	6 months	Average weight loss 5.8 kg
Sacks *et al.* (2009)[56]	811 overweight adults	4 diets with different macronutrient distributions (low versus high fat and low versus high protein)	6–24 months	Weight losses ranged from 2.9 kg to 3.6 kg, regardless of macronutrient distribution
Handjeva-Darlenska *et al.* (2012)[45]	711 obese individuals	Low fat (20–25% total energy intake) versus moderately high (40–45% total energy intake) hypocaloric diets	10 weeks	Similar weight losses (6.9 kg versus 6.7 kg)
Wing *et al.* (2013)[74]	5,145 overweight patients with diabetes	Energy-restricted diet plus exercise versus diabetes care	9.6 years	Increased weight loss in the dietary intervention (6.0%) versus. control group (3.5 %, p<0.001)
Abbreviation: DASH, Dietary Approaches to Stop Hypertension				

Table 3. Selected randomized controlled trials that investigated interactions between SNPs and weight-loss dietary interventions					
Reference	**Gene**	**Polymorphism**	**Study design**	**Participants**	**Outcome**
Grau *et al.* (2010)[97]	*TCF7L2*	rs7903146	10 weeks energy restriction (low-fat versus high-fat)	771 obese adults	Individuals homozygous for the T allele are more responsive to low-fat diets (-2.6 additional kg lost, p=0.009)
Kim and Lee[99] (2010)	*UCP1* and *ADRB3*	-3826A/G and Trp64Arg	2 low-calorie rice-based diets with different fibre compositions	40 obese women	The AA *UCP1* genotype produced significant weight loss (p=0.041) in the high-fibre group but *ADRB3* genotype had no effect
Haupt *et al.* (2010)[98]	*TCF7L2*	rs7903146	9 month lifestyle intervention with fat reduction and fibre increase	304 obese adults	Dietary fibre modulated the association between *TCF7L2* variance and weight loss (p=0.0034)
Mattei *et al.* (2012)[95]	*TCF7L2*	rs12255372	Dietary intervention with 4 diets (low or high fat and low or high protein) for 2 years	591 overweight adults	Individuals with the TT genotype lost more fat mass while consuming a diet lower in lipids (p<0.05)
Qi *et al.* (2012)[94]	*GIPR*	rs2287019	Intervention with 4 diets (low or high fat and low or high protein) for 3 years	757 overweight adults	The T allele was associated with increased weight loss when consuming a low fat diet (β±SE; -1.05±0.56%; p=0.06)
Stocks *et al.* (2012)[96]	*TFAP2B*	rs987237	8 weeks energy-restricted diet	771 obese adults	Individuals with the AA genotype had improved weight loss

			(low-fat versus high-fat)		in response to low-fat diets (1.0kg, 95%CI:0.4-1.6kg), whereas individuals with the GG genotype had improved weight loss in response to high-fat diets (2.6kg, 95%CI: 1.1-4.1kg)
Zhang *et al*. (2012)[93]	*FTO*	rs1558902	Intervention with 4 diets (low or high-fat & low or high-protein) for 2 years	742 obese adults	High-protein diet may have specific benefits for weight loss (p<0.05 for all interactions) in individuals with the risk allele (A)
Cameron *et al*. (2013)[100]	*DRD2*	TAqIARFLP	Caloric restriction and resistance training for 6 months	127 obese postmenopausal women	Carriers of the A1 allele lost significantly less body weight (p<0.05), but this effect seemed to be exercise-dependent

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