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HOT TOPIC

# Obesity and Weight Control: Is There Light at the End of the Tunnel?

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**Abstract**
*Purpose of Review* Our global population recently arrived at the landmark figure of seven billion, and the nutrition problems we face are increasing as rapidly, with the longstanding crisis of undernutrition joined by the escalating problem of overconsumption and obesity. Over the past 30 years, it has become clear that control of body weight is as simple as matching energy intake to expenditure, yet how to achieve this in the current obesigenic environment is far from simple. A review of causative mechanisms shows controlling eating behaviour and food intake as central to regulation of body weight, but in an environment where the need to suppress intake is uppermost, there are few physiological mechanisms with which to tackle this.
*Recent Findings* Macronutrient composition, energy density, food format (beverages), palatability, portion size and hedonics all influence intake and readily promote overeating. Currently, the most successful obesity treatment is restrictive bariatric surgery, both invasive and expensive, achieving better outcomes than diet and exercise. Despite considerable advances, there remains a critical gap in translation of underpinning knowledge into successful public health outcomes, as recently outlined in the 2nd Lancet series in obesity with no country reporting decreased obesity prevalence in the last 30 years.
*Summary* Future contribution may come from better understanding of mechanisms including gut-brain axis and regulation of appetite, the gut microbiome and the genetic underpinning of bodyweight control. Clearly, prevention is the key, with nutrition education required to lead changes in behaviour, and possibly the only viable long-term approach. Whether the global obesity trend can be reversed without significant change in national food policies and/or the built environment however is under debate, and without doubt a major public health challenge for tomorrow if there is to be light at the end of the obesity tunnel.

**Keywords** Obesity · Appetite · Energy density · Portion size · Plate size · Prevention · Built environment

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## Introduction

The issue of weight gain and its accompanying disease profile of poor metabolic health, type 2 diabetes (T2D), cardiovascular disease (CVD) and some cancers [1] is a major health challenge [2]. A review of the greatest future challenges in nutrition-elected controlling obesity and its accompanying metabolic dysregulation as the primary challenge for the coming 30 years [3]. At the end of 2011, a population landmark of seven billion was reached [4], and clearly, the nutrition problems now faced are changing just as rapidly. A longstanding global crisis of undernutrition has been joined by the escalating problem of overconsumption, overweight and obesity, and this truly is a time of nutrition transition [5]. Over the past 30 years, it has become clear that control of body weight really is as simple as matching food intake to expenditure [6], yet how to achieve this in the current obesigenic environment [7, 8] is far from simple [9•, 10•, 11•].

This paper reviews the growing problem of obesity and recent public health and nutrition policies that have attempted to halt progression; overconsumption as a primary cause of weight gain including evidence that macronutrient composition, energy density, food format, portion and plate size may be contributory factors; and areas of future research including gut-brain axis, microbiome, viral exposure and genetic/epigenetic drivers.

## Global Obesity and the Nutrition Transition

Global numbers of obese adults and children have been steadily increasing for more than two decades. In 2003, predictions were for ~2 billion (~30% of the world's population) to be overweight or obese by 2015, a landmark which was very close to being achieved [12•]. The medical costs of obesity within the USA alone have been estimated at >US$150B per annum [13]. The World Health Organisation (WHO) have reported that up to 80% of heart disease, stroke and T2D could be prevented by eliminating risk factors resulting from an unhealthy lifestyle [14]. This is a monumental cliff to climb, with data from countries such as the USA showing that more than half of the population reports being on a weight-reducing diet at any time, almost all of whom fail to maintain weight loss long-term [15].

In 2010, the OECD countries report showed New Zealand, Mexico and the USA to be ranked as the top 3 worst affected with adult obesity rates ≥30% [16] (Fig. 1). High rates of overweight and obesity within the south Pacific nation of New Zealand are a surprise to many and due in large part to significant ethnic inequalities [17] and differences in socio-economic status [18]. Globally, approximately 1.5 billion people still live on <US$2 per day [19], yet the developing world's new burden is obesity [20], with under-nutrition and obesity found within the same country, community or even the same household [21]. WHO recently reported 65% of the global population to be overweight or obese with more fatal consequences than underweight [21]. Low-income families, particularly those within urbanised communities, have greater rates of obesity, likely due at least in part to ready availability of cheap high energy density (ED) and nutrient-poor foods. Asia in particular is facing a rising tide of obesity. China was once amongst the world's slimmest nations [22], but in the last 20 years, overweight and obesity has risen to 30% of adults [23, 24]. The sheer size of population means that >1/5 of those overweight globally come from China [25], mainly attributed to a rapid growth of the Asian economy and socio-economic, nutrition and lifestyle transition [22]. With Asian children and adolescents also getting fat, unprecedented numbers will develop metabolic health problems previously only seen in older adults, and with a greater susceptibility to adverse metabolic health than Caucasian counterparts, even modest weight gain may lead to more rapid metabolic dysregulation and development of T2D. Three hundred million Chinese adults have been identified with T2D [24], 500 million with pre-diabetes, with costs of obesity predicted to almost double to ~US$5 billion before 2024 [26].

## Public Health and Nutrition Policies

Progress in prevention and treatment was recently reviewed in a 2nd Lancet series in obesity outlining the poor progress made in the public health arena. With more than two billion overweight globally [27], no country has reported a decrease

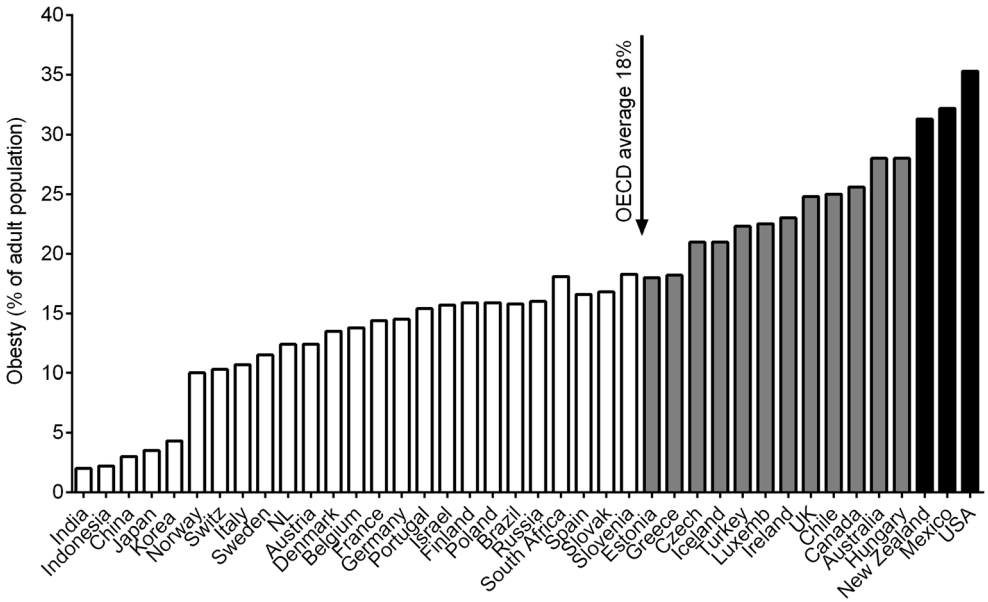


**Fig. 1** The Organisation for Economic Co-operation and Development (OECD) countries report from 2010 showed New Zealand, Mexico and the USA to be ranked as the top 3 worst affected, with adult obesity rates ≥30% [16]. The average OECD rate of obesity is 18%

in obesity prevalence in the last 30 years [9•, 10•]. Internationally, WHO's global action plan for the prevention and control of non-communicable diseases 2013–2020 was adopted at the world health assembly in Geneva in 2013 and has the ambitious target of halting the increase in obesity prevalence between 2010 and 2025 [2]. It has long been purported that implementation of national food policies may have an essential role to play in halting the obesity trajectory, although there is little international consensus as yet either on policy content or route to successful implementation, nor significant traction. Recent global initiatives include the International Network for Food and Obesity/non-communicable Diseases Research, Monitoring and Action Support (INFORMAS), the aims of which include monitoring, benchmarking and supporting public and private sector actions to create healthy food environments [28]. Also the NOURISHING framework the aim of which is to highlight where governments must take action to promote healthy diets and decrease overweight and obesity [29]. Hawkes and colleagues recently reviewed policy implementation [30], focusing on a range of topics including (i) economic strategies where 'unhealthy' food taxes and 'healthy' food subsidies have been imposed, (ii) nutrition labelling strategies such as mandatory labelling and ease of consumer understanding and (iii) strategies within population sectors such as the school environment. Their objective was to identify how such policies can be designed to be more effective and postulated that food tax systems have shown potential to reduce consumer purchasing of targeted dietary items [31, 32] and pointed to countries where taxation has resulted in positive findings. To date, these include the Danish saturated fat tax [33], public health product tax in Hungary [34] and sugary beverage tax in Mexico [35]. Mandatory nutrition labelling, whilst having been shown to have divergent effects across socio-economic/education status with less success in lower SES and associated groups, appears to push the food industry to reformulate products. Mandatory labelling of food items introduced into a handful of countries in Europe (Choices logo, NL [36]), USA, Canada and Asia (trans fat labelling [37, 38]) and New Zealand (Pick the Tick [39]), as well as menu labelling in parts of the USA [40] and Australia [41, 42] has led to a change in product composition and hence diet. Voluntary labelling such as Australia's health star rating system is also becoming more commonplace [43]. Proposing that well-designed food policies have a potential to improve diets, Hawkes et al. concluded that a step change towards smarter policies that make healthy choices the *preferred* choices not just the *easy* choices are required. They also propose that government policy should prioritise two areas, to create an environment for healthy preference learning amongst the young and ensure those who want to make healthy food choices have the opportunity to do so [30].

## The Obesity Epidemic: What Caused It and How Can We Stop It?

Obesity is clearly a multifactorial and currently intractable issue, but the manner in which weight gain occurs is simple. Energy intake (EI) exceeding energy expenditure (EE) leads to a positive energy balance (EB), with excess energy stored in various fuel formats, the most efficient of which is triglyceride (TAG) lipid. TAG is energy dense (37 kJ/g) with capacity for extreme fat storage of 200 kg + within adipose tissue, equivalent to ~8000 MJ and theoretically sufficient to fuel >2 years of famine. More typically, a lean adult carries close to 10 kg body fat, half the weight of an equivalent energy source if stored as liver or muscle glycogen (16 kJ/g; 23 kg) [44]. TAG is an efficient storage fuel and a clear marker of a positive EB. The additional intake required each day to lead to obesity is relatively small [45], with a gradual gain of 10 kg in body weight over 10 years requiring a mismatch between EI and EE of only ~20 kJ (~5 kcal) at each meal. It seems paradoxical that obesity is so difficult to prevent or treat [6], not least because the basic causes of weight gain are so apparently simple—eating too much, exercising too little and consequent storage of excess lipid in adipose tissue. The key to these issues is better understanding of both sides of the energy equation. What drives overeating and what is known about the foods that we eat and the food-related environment in which we live; what is the effect of increasing expenditure through more rigorous or frequent daily activities; and how best to marry these two sides of the energy equation to stop weight gain and enhance weight loss?

### Appetite Regulation

Overeating or, more precisely, chronic consumption of more energy than is expended over a prolonged period is the key. Control of food intake is central to control of body weight, with appetite arguably the most important driver of eating behaviour. Regulation of appetite is complicated, with physiological components commonly assessed as subjective feelings of hunger, fullness, desire to eat and other similar ratings. Originally elegantly conceptualised as a satiety cascade by Blundell and colleagues [46], a process of satiation operates whilst eating is in progress which terminates a meal, whilst satiety arises after a meal and inhibits further eating. The three phases comprise sensory and cognitive, post-*ingestive* (e.g. gut hormones) and post-*absorptive* (e.g. metabolites including glucose, insulin, amino acids, fatty acids in peripheral blood; oxidation of macronutrients by metabolically active tissues) effects (see Fig. 2). Operating together satiation and satiety determine size and frequency of meals and snacks during the day. Of significance in today's environment is the strong drive to eat and weak drive to terminate eating. Critical in a situation of feast and famine, this becomes an adverse pressure against

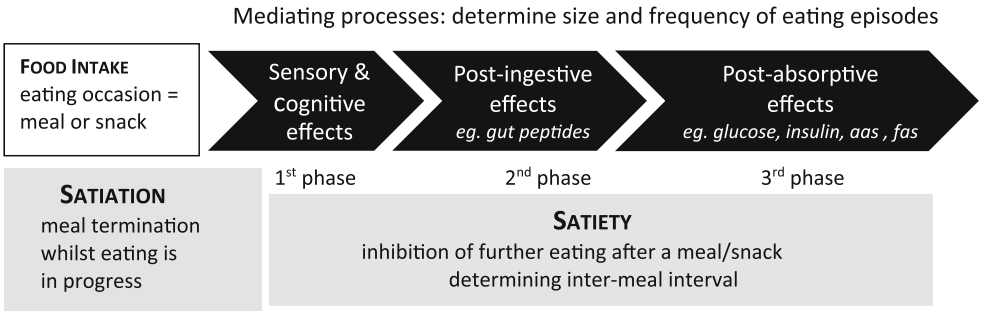


**Fig. 2** As originally proposed by Blundell and colleagues, satiation operates whilst eating is in progress and has the effect of terminating the meal whilst satiety arises after a meal and functions to inhibit further eating [46]. Sensory and cognitive effects occur early in the process, followed by post-ingestive (e.g. release of gut peptides: CCK, GLP-1, PYY) and finally post-absorptive (e.g. circulation of metabolites: glucose, insulin, amino acids, fatty acids) effects

a background of societal norms of inexpensive, readily available foods, wide and varied choices, 'fast' foods, snack foods; all you can eat buffets and considerable food advertising amongst other drivers. Yet, the characteristics of foods may still have a role in the regulation of intake, including macronutrient content and composition, ED, food form (beverages, solid foods), portion and plate size. Human physiology has a poor defence against overeating, and weight gain rather than loss is prevalent.

### *Macronutrient Composition*

Whilst it is change in EB that drives change in body weight and adiposity, macronutrient composition plays a role in determining EI through effects on hunger, fullness and other appetite-related responses. Under isoenergetic conditions, there is evidence for a hierarchy in satiety between macronutrients, data coming mainly from short postprandial studies where a fixed energy, variable macronutrient preload is given and eating behaviour at an ad libitum outcome meal measured. Per kilojoule of energy ingested, the hierarchy is protein > CHO > lipid [47–52] with energy dense fat inducing lower levels of satiety than other nutrients. The underpinning mechanisms are not yet clear, although ED plays an important role, as described later. Protein, with the greatest per kilojoule appetite-suppressing effect is at the top of the hierarchy and initially came to public attention as the popular Atkins very-low-CHO diet. Also a higher protein diet, the underpinning mechanisms include both appetite suppression and increased diet-induced energy expenditure [53]. Early clinical studies showed that an Atkins style diet may be successful for weight loss up to 12 months [54, 55], and now considerably refined into a moderate CHO/higher protein regime, there is a great interest in these diets [53, 56, 57]. The pan-European DioGenes trial was a successful large cohort intervention in ~1000 overweight adults where a higher protein/lower GI diet promoted long-term maintenance of weight loss [58], and currently being followed up by the 2500 participant PREVIEW (Prevention of diabetes through lifestyle Intervention in Europe and Worldwide) intervention [59], the largest study to date to investigate higher protein diets for long-term weight loss maintenance in addition to diabetes prevention. Alcohol, the 4th macronutrient, may engender lower satiety than the food macronutrients due in part to its liquid form and disinhibiting nature, neither of which is conducive to suppression of appetite [60, 61]. Many longer studies have now confirmed the hyperphagia that commonly accompanies a high-fat diet. One of the earliest studies conducted was in overweight women in our laboratory, using a 2 × 5 day cross-over design where dietary fat content of all food items was covertly manipulated (25 vs 50en% fat) [62]. Participants requested meals and snacks when hungry, ate ad libitum until full and were unable to discriminate between the two diets (Fig. 3a). EI on the low fat diet (25en%, ~8 MJ/d) was significantly lower than the high-fat diet (50en%, ~11 MJ/d). Long-term predictions show this positive EB to result in ~100 g/d increase in body weight, or 3 kg/month, a clinically important effect.

### *Energy Density*

The fat content of the diet per se, however, is not the primary driver of hyperphagia, rather the concurrent high ED [63–65] that promotes higher EI [65–68]. Primary determinants of ED are both macronutrient (increases) and water content (decreases ED) of foods [65]. Early well-controlled covert manipulations showed that the predicted increase in ad lib EI is abolished if ED is kept constant as fat content increases (see Fig. 3b, c) [63, 64]. A focus of interest has been on different structural forms of high-ED fats to ameliorate this hyperphagia, but only limited evidence [69–72] indicates that altering fat composition, structure and/or delivery method can alter hunger or food intake. Studies from our laboratory have been unable to identify characteristics of high-fat foods, other than ED, that may be modified to promote satiety [73–76]. Whilst CHO also contributes to this dietary ED seesaw, high-CHO foods (16 kJ/g) are typically of lower density than high-fat foods (37 kJ/g), although manipulation of diets to promote

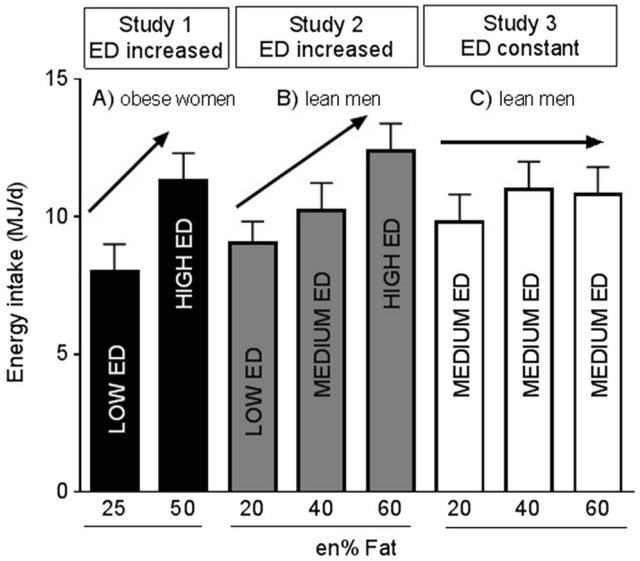


**Fig. 3** Ad libitum EI increased when low fat/low ED foods were covertly replaced **a**) by high-fat/high-ED foods (25 vs 50en% fat) over a 5-day period in overweight women; and **b**) medium fat/medium ED (20 vs 40en% fat) and high-fat/high-ED foods (20 vs 60en% fat) in lean men. The ED increased with % fat content. **c**) However, when ED was maintained constant and fat content differentially increased (20, 40 and 60en%), there was no subsequent increase in EI. Data compiled from Poppitt et al. [62] and Stubbs et al. [63, 64]. *EI* energy intake, *ED* energy density

high-ED, high-CHO foods is likely to also promote hyperphagia [77]. Under conditions of a constant weight of food consumed (typically ~2 kg/day), high-ED foods promote increased EI, as observed in the laboratory [65]. Covertly altering foods within a laboratory setting where food choice is removed, alters usual eating behaviours, however, and whether ED is a strong driver of intake in habitual environments of wide food choice is less well-understood.

*Food Format: Solid vs Beverage*

Within western countries, much of the energy consumed is in beverage format. Recent data from the USA showed that 15% of total EI is consumed in the form of liquid energy [78]. Dietary compensation for beverages may be weaker than for solid food [79], and instead of replacing a portion of the daily food energy with beverages, many individuals are *adding* beverages into their diet. Energy is important no matter the source, and liquids may be poor satiety agents. Whilst adverse effects of alcoholic beverages has been gaining gradual acceptance, due to both the addition of 'hidden' energy into the diet and the adverse health effects of alcohol per se, far more controversial are soft, sugar-sweetened beverages (SSBs). A recent editorial published in the New England Journal of Medicine [78] concluded that 'calories from soft drinks do matter' and that the time has now come to take action and implement recommendations from the US Institute of Medicine, American Heart Association, Obesity Society and others to reduce the consumption of SSBs.

*Portion Size*

Factors such as preference for high-fat, attraction to palatable foods, poor response to 'stop eating' satiety signals, disassociation between feelings of hunger and food intake may all vary between individuals, but a susceptibility to weight gain may be characterised by large (big meal sizes) and more frequent (meals plus snacks) eating episodes [80], plus a preferential selection of high-fat or high-ED foods. Portion size may exacerbate these effects, with evidence from ad lib studies that both weight of food consumed and EI increase in parallel with increasing portion size [81–83]. The 'supersize me' phenomenon of larger portion sizes has been growing [84, 85], foods are packaged in portion sizes that far exceed national recommendations [86] and many individuals may view the offer of larger portion sizes from food retailers as good economic sense. Rolls et al. [87, 88] conducted several studies to show that larger portion size increases EI proportionally; hyperphagic effects of ED and portion size are additive [89], and increasing either ED or portion size increases EI [90]. Serving size (SS) guidance is provided on many packaged foods, but whether this is understood or acted upon by consumers is debateable. Few studies have examined the direct impact of SS guidance on consumer behaviour, with mixed results. Eighty-seven worldwide SS guidance schemes were recently reviewed and found to communicate inconsistent and often conflicting messages about portion size selection [91]. Consumers had difficulty understanding the terms 'portion size' and 'serving size', commonly used interchangeably. Restricting portion sizes is clearly a useful strategy by which to suppress EI and may be a useful adjunct to weight loss [92–94]. Conversely, there are some positive outcomes from this strong effect of portion size on eating behaviour. For example, serving larger portions of vegetables to adults can increase their intake [95], with similar findings observed for fruits and vegetables in young children [96].

*Plate Size*

There is data to show the average size of a dining plate has been increasing [97], possibly leading to larger food portions [98]. Historically, recommendations propose a smaller plate as a strategy for portion size and EI regulation [99, 100]. There have been a number of studies investigating plate size effects, but with mixed findings with few studies showing a significant effect on eating behaviour [83, 101–103]. In a group of studies by Rolls et al., food was served onto dining plates of varying sizes in a number of ways including ad lib from a single main dish, ad lib from a buffet style meal,and in a fixed amount [102]. Under none of these conditions did a smaller dining plate decrease EI. Our laboratory has recently also assessed the effect

of plate size on EI in a group of overweight but unrestricted women, and also did not find significant effects [104]. In studies of snacking larger serving bowls did lead to a greater intake [83, 105], independent of whether or not portion size itself increased [106], but little data is available and making consensus based conclusions is at this stage premature.

### Physical Activity—An aid to Weight Loss?

Equally important is the EE side of the balance equation. Sedentary behaviour, or physical inactivity, has steadily increased with more time spent on both work and leisure screen-related sedentary behaviours amongst others. Reporting data from 2008 WHO have stated that >30% of adults were insufficiently active (28% men, 34% women) with ~3.2 million deaths per year attributable to inactivity [107]. In turn, it would be reasonable to assume that increasing day-day physical activity would be an excellent strategy for weight management. However, the EB system is finely tuned and an increase in physical activity may result in an upregulation of appetite response such that EI is increased to balance or even exceed the exercise-induced expenditure. A Cochrane systematic review of 43 studies, comprising 3476 participants, showed that addition of exercise to a diet regime increased weight loss by only ~1.0 kg [108]. Compensation within the EB loop has been identified as a significant issue in weight control [109]. In a carefully supervised 3-month intervention where an exercise-induced 4 MJ/day deficit was achieved, almost 50% did not lose weight and a further 30% *gained* body weight and adipose mass [110]. An increased drive to eat offset increased the EE. Food reward following exercise is clearly a problem for those using exercise as a strategy for weight loss, although evidence shows insulin sensitivity [111], cardiorespiratory fitness (CRF) [110] and other aspects of health to improve even in those who fail to lose body weight. The phenomenon loosely termed 'fat but fit' has received considerable attention including meta-analyses which conclude that fit individuals who are overweight or obese are not automatically at a higher risk for all-cause mortality [112, 113], and quite controversially that risk of death is dependent upon level of CRF rather than BMI, with unfit individuals at twice the risk regardless of overweight or obesity [114].

## The Horizon for Obesity Research—Where Does It lie?

There are a number of promising areas likely to come to the fore in the coming 5–10 years, including gut-brain axis and regulation of appetite, the possible role of an obese microbiome, and the genetic and epigenetic underpinning of bodyweight control. Clearly, long-term body weight regulation is the light sought at the end of the tunnel.

### Long-Term Weight Management

Whilst short term weight loss is achievable and most people can lose some weight on most diets, almost none can maintain this loss long-term. Whilst there remains little consensus as to the optimum diet [115], and few are successful across the majority of the population, compliance to any dietary strategy is the key. As has been learnt over the years, the best diet is the one that you can actually maintain in the long-term. Researchers at the Harvard School of Public Health recently conducted a meta-analysis of 53 weight loss trials comprising more than 68,000 individuals and concluded that a wide of approaches lead to weight loss providing compliance is good, with the review failing to support low fat approaches [116•]. Following many years of research focus on low fat and/or low CHO diets, the role of higher protein diets has now taken centre stage. This came to public attention as the popular Atkins very-low-CHO diet but also a higher protein diet, the underpinning mechanisms for which include promotion of appetite suppression and increased diet-induced energy expenditure [53]. Early clinical studies showed that an Atkins style diet may be successful for weight loss over 12 months [54, 55]. Now, considerably refined over the ensuing 10 years into a moderate CHO and protein regime, there is a great interest in less extreme forms of these higher protein diets for long-term weight management.

### The Gut-Brain Axis

The gut-brain axis links the peripheral and central systems which feedback to continuously control energy homeostasis and ensure energy is available to fuel physiological needs [117]. Whilst the perception of hunger and satiety is modulated through this network, it is poorly set up to defend against overconsumption and weight gain and may in turn constrain weight loss. Improvements are needed in the understanding of mechanisms by which appetite signals, such as GI peptides [118, 119] which are transmitted centrally from gut to brain where choices as to eating behaviours are made, and in turn how the brain interprets these signals using interesting new functional MRI (fMRI) techniques [120, 121]. fMRI utilises adaptations of the MRI technique, extending structural information further into function of scanned tissues using a metric termed blood-oxygenation-level-dependent (BOLD) contrast based upon the different magnetic properties of oxygenated and deoxygenated blood. Early functional imaging studies identified the anatomical site for brain reward and showed modulation in activity even when foods were simply shown to participants and intake remained unchanged, whilst more recent studies have shown further activity during exogenous administration of satiety peptides, again in fasted individuals. Interestingly, differences in brain activity between lean and overweight individuals have also been identified opening a

gateway to investigation of physiological mechanisms underpinning overconsumption and the inability to regulate food intake, and recently reviewed in detail by de Silva and colleagues [121].

## Gut Microbiome

The role of the gut in obesity also extends further to the interactions of the colonic bacteria and questions of a characteristic 'fat' microbiome [122]. This is gradually being unravelled [123, 124] particularly as metagenomic sequencing of the gastrointestinal microbiota becomes a common technology [125], but a proposal which undoubtedly remains controversial [126•, 127]. The composition of the gut microbioata is hypothesised to drive efficacy of energy harvest from the diet and has been shown to alter in response to weight loss therapies such as gastric bypass [128] and also following dietary restriction [129], although not necessarily always in a direction considered to be favourable. Whilst evidence has been presented at the phylum level with lower ratios of Bacteroidetes to Firmicutes as well as lower bacterial community diversity in obesity, much of this has come from rodent studies [130] and remains to be substantiated in large-scale clinical analyses [127]. A recent review commented that the lack of consensus suggests that there is no simple relationship between taxonomic composition and BMI at the phylum level nor convincing evidence that variance in genus-level profiles is significantly associated with BMI [99]. Between-study variability being significantly greater than within-study differences between lean and obese phenotypes. Nevertheless, faecal transplantation for treatment of obesity has been considered [131] following positive experimental data in animal studies, a procedure deemed virtually preposterous as little as 10 years ago. Since the microbiome's effect on body weight may not be mediated through its taxonomic composition but rather its function, metagenomic sequencing analysis has been employed to determine microbial function independent of taxanomic relationship. Through this technique, a human gut microbial gene catalogue has been established, identifying more than three million non-redundant microbial genes, approximately 150 times larger than that of the human gene complement [132]. Reliable estimates of the percentage of human obesity that can be attributed to differences in the colonic microbiome remain to be established.

## Viruses

Highly controversial yet worthy of some consideration is the question 'can you catch obesity?' The first report of an obesity syndrome in mice induced through viral exposure was published more than 30 years ago [133]. Mice infected with canine distemper virus (CDV) have been reported to increase body weight, fat cell size and fat cell number, proposed to be virus-induced hypothalamic damage [134] and a number of viruses including a range of human adenoviruses (Ad-2, Ad-5, Ad-31, Ad-36 and Ad-37) have been shown to cause obesity in chicken, rodents and non-human primates [135]. Ad-36 is the only human adenovirus correlated with obesity in humans but, since intervention requiring viral inoculation is not possible, cause and effect data cannot be assessed. Interestingly, however, serum antibodies to Ad-36 measured in obese and lean individuals have been shown to be higher in obesity, with antibody-positive individuals 9 BMI units heavier than those antibody negative [136]. Proposed mechanisms include upregulation of enzymes that direct fat accumulation leading to increased adipocyte size, or stimulation of rapid differentiation of adipocytes leading to increase adipoctye numbers [137]. Interest has again peaked following a recent meta-analysis, comprising data from 15 published studies, which reported an overall odds ratio of 2.0, with all but 3 of the trials showing a positive association between AD-36 and obesity [138•].

## Genetic Drivers

The rise of personalised medicine and the role that the genome may play in targeting obesity prevention and treatment of a number of disease states, such as specific cancers, has been growing steadily [139]. Technology advances for whole of genome sequencing has driven this field forward rapidly. The overlay of a personal genome onto personal body weight, lifestyle and medical history has brought to the fore opportunity to improve our predictive and preventative power; however, in the forum of obesity, significant practical gains from these rapidly developing technologies remain yet to be determined. The genetic underpinning of weight gain and obesity was investigated in early studies which described factors involved in rare monogenic and syndromic forms of extreme obesity [140], and which in turn directed attention towards dysfunction within leptin-melanocortin-related pathways in regulation of food intake as a potential contributor. Monogenic forms which promote this unregulated eating however are estimated to explain only ~6% of children with extreme obesity syndromes [141]. Polygenic single nucleotide polymorphisms (SNPs) associated with overweight and obesity have more recently been well-characterised [142]. In 2007, genome-wide association studies (GWAS) originally identified the fat mass and obesity (FTO)-associated SNP as a strong contributor to both childhood and adult obesity [143], again acting through dysfunction in eating behaviour. The effect of FTO SNPs on BMI has however since been shown to be modest, with the phenotype for those homozygous for the risk allele being estimated as only 1–3 kg heavier than those homozygous for the protective allele [144, 145•] The minor allele increases BMI by ~0.4 kg/m$^2$ and risk of obesity 1.2-fold. This association has been confirmed across the age groups, with the largest effect seen in younger adults, and within many global populations of diverse

ancestry although less prevalent in non-European ethnicities [145•]. Notably of course, this remains an association and not a causative relationship. Of great recent interest now are reports that obesity-associated SNPs appear functionally connected not with FTO but with two neighbouring genes IRX3 and RPGRIP1L [146]. Evidence has come from a variety of studies including quantitative trait loci (eQTL) mapping in human brain cerebellum where both FTO and IRX3 are highly expressed, which show that obesity-linked SNPs such as rs9930506 were associated with IRX3 but not FTO expression, and directly to IRX3 regulation [146]. Individuals with obesity risk A allele at rs8050136 also have reductions in both RPGRIP1L and FTO expression which are reported to cause diminished leptin signalling, increased food intake, and in turn body weight and adiposity [147].

Epigenetic effects and the modifiable role that diet may play in altering epigenetic marks are also of great interest. The key to this is the pre-natal environment where maternal nutritional is proposed to alter metabolism of the offspring through epigenetic regulation of specific genes, which in turn may be passed through to subsequent generations [148]. Epigenetic regulation of transcription, specifically DNA methylation and covalent modification of histones, may alter a large number of metabolic and developmental pathways, and there is now a well-developed literature describing the multifaceted induction of an altered foetal phenotype during pregnancy as a result of changes in maternal nutrition driving these mechanisms. In turn, components of the maternal diet that may generate positive modulations in DNA methylation or histone tail modifications and hence potentially influence body weight management of the offspring have been identified and include methyl donors such as folate, choline, methionine and vitamin B12 [149]. Also of interest are pharmaceutical DNA methylation and histone deacethylase inhibitors, both of which have had some success in treatment of cancers and now approved as clinical therapies [150]. Whether drugs targeting epigenetic enzymes for obesity may have potential is yet to be determined, but of considerable interest. Despite the considerable advances in both genetics and epigenetics, it appears unlikely however that a personalised obesity susceptibility or obesity resilience profile, whilst incorporating knowledge of the genome, can be truly informative without equally essential personalised environment information.

## Conclusions—Is There Light at the End of the Tunnel?

Over the past 30 years, it has become clear that control of body weight really is as simple as matching food intake to expenditure, yet how to achieve this in the westernised global environment is far from simple. Controlling eating behaviour and food intake is central to the control of body weight and adiposity, but it is a complex psychological as well as physiological drive which is influenced in large part by the environment. Hunger and a strong desire to eat have developed over years of human evolution with an unpredictable food supply. In an environment where the need to suppress intake is uppermost, there are few physiological mechanisms with which to tackle this. Despite the considerable global research efforts to combat obesity, the 'runaway weight gain train' [6] continues to roll forwards, and bright lights at the end of the tunnel are still sought. There is, as yet, no light at the end of the tunnel.

Prevention is essential, and possibly, the only viable long-term approach alongside of course better treatment strategies. Currently, the most successful treatment for obesity is bariatric surgery [151•, 152], both highly invasive and expensive, which achieves better outcomes than current diet and exercise strategies. Long-term bariatric surgery outcomes are yet to be determined, and irrespective of outcome should not become the only tool in the battle against obesity. Clearly, it is important that the public is well-informed around the problem of obesity, and educated in the message that weight gain is preventable and also in provision of tools to help them achieve the challenging goal of long-term maintenance of a healthy body weight.

One of the key areas of focus should be children, from young pre-schoolers through to adolescents and young adults. Evidence is gradually building that nutrition education may change lifestyle behaviours, and in turn that national standards for nutrition education may be required within the teaching curriculum [153], another policy challenge for many countries. The last 30 years has unravelled pieces of physiology underpinning weight gain and obesity, yet much remains to be done through basic and clinical sciences and public health. The recent Lancet series outlined poor outcomes in population health, with >2 billion overweight [27], and no country reporting significant improvements over 30 years [9•, 10•]. Lancet emphasises issues with the modern environment with an excess of nutrient-poor, energy-dense foods which are both highly appetising and have high reward value, where the reward (motivational, reinforcing) and hedonic (palatability, pleasure) value of foods influence energy intake and adiposity. It is proposed that the dichotomy of 'blame' for weight gain, which falls either upon the individual or the social/physical environment within which they live, may be impeding progress [10•]. Other authors argue that we are forestalled by an inability to convert knowledge that we have reliably obtained into behaviours that we routinely follow [115]. Nonetheless, action is required, with the need for a comprehensive management approach to obesity, the cornerstone of which should remain intensive lifestyle intervention (diet restriction, increased physical activity and behavioural management), and which it is still argued continues to be supported by a growing body of evidence [154]. Whether the obesity trend can be reversed without significantly changing the environment

however is debatable, may require considerable government input globally [11•, 155] and is the major challenge for tomorrow if progress is to be made.

**Compliance with Ethical Standards**

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