The Obesity Epidemic

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Abstract

Hippocrates believed that the goal of "protecting and developing health must rank even above that of restoring it when it is impaired." This aspiration is particularly relevant at present as escalating obesity levels challenge our health service. Obesity, defined as a body mass index (BMI) higher than 30 kg/m^2, is the commonest nutritional disorder worldwide. Its medical, psychological, social and economic effects have major consequences for health, yet an effective treatment remains elusive. Genetic, environmental and behavioural factors have all been implicated in the pathophysiology of obesity, but the individual contribution of each factor is as yet unknown. This review aims to elucidate the underlying factors influencing the obesity pandemic.

Introduction

According to the World Health Organisation (WHO), there are at least 300 million obese individuals worldwide. This number is considerably higher than the 1995 estimate of 200 million, indicating that we are currently facing an acceleration of the problem.[1] Even in the developing world, obesity is escalating wildly, inflicting the paradoxical double burden of obesity and malnutrition on poorer nations. The obesity epidemic now merits pandemic status.[2] Eighteen percent of Irish adults are obese and 39% are overweight.[3] The crisis has also filtered down to paediatrics – 20% of five to twelve year old children are overweight or obese, and these figures are estimated to be rising by over 3% each year.[4,5] Obesity imposes a substantial burden on our health services. The lifetime medical costs of adults with a BMI of 32.5, is estimated to be 42% to 56% greater than those with a BMI of 22.5.[6] The cost of treating obesity and its complications is set to increase hugely as the obesity crisis comes of age.

Obesity is a chronic disease with important consequences on health, psychosocial well-being and quality of life. Extremes of BMI are related to mortality and can be illustrated by a J-shaped curve.[7]

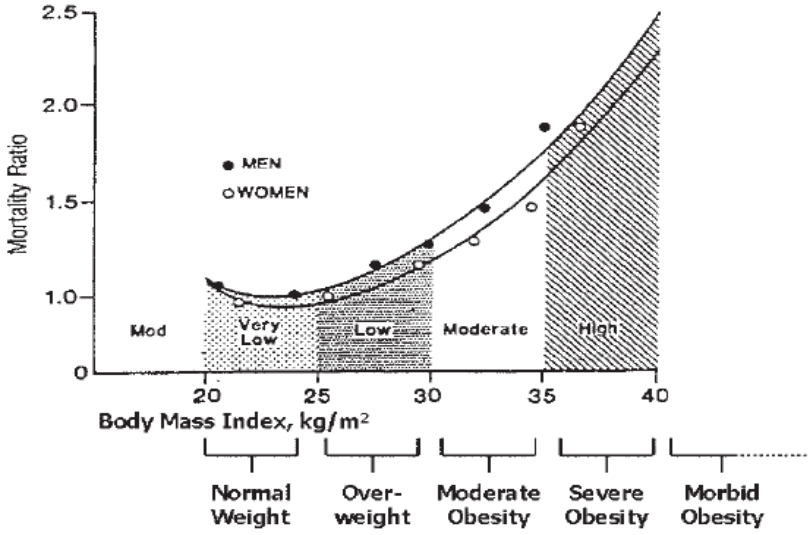

Figure 1: J-shaped curve[7]

Annually, at least 2000 people in Ireland die prematurely from obesity and related illnesses. In addition to having an increased risk of premature death, overweight and obese individuals are more likely to suffer from other adverse health effects.[9] While obesity affects almost every body system it most commonly and detrimentally affects the cardiovascular system. Obese individuals are at an increased risk of coronary heart disease, stroke, venous thromboembolism, cardiomyopathy and congestive heart failure. These effects are mediated partly by increasing cardiovascular risk factors including hypertension, dyslipidaemia, insulin resistance and inflammatory and thrombotic markers, and partly by an unknown mechanism independent of these factors. Additionally, there is a direct association between BMI and the development of type 2 diabetes mellitus.[10] The risk of developing diabetes mellitus increases as weight increases; the relative risk of diabetes increases by 25% for every extra unit of BMI greater than 22.[9] Cardiovascular and diabetes risks start to increase below the threshold of obesity. In the Nurses Health Study, each kilogram of weight gained from the age of 18 years was associated with a 3.1% increased risk of cardiovascular disease.[11]

Other potentially life-threatening complications associated with obesity include gallstones, cholecystitis and some cancers (including endometrial, prostate, breast and colon)[9]. A recent meta-analysis concluded that 3.4% of cancers in males and 6.4% cancers in females could be attributed to being overweight.[10] Furthermore, overweight people have an increased incidence of chronic incapacitating disorders such as osteoarthritis, obstructive sleep apnoea, gout, complications in pregnancy, poor female reproductive health, bladder control problems and skin conditions.[1]

While most of the medical and social burden of obesity is borne by the adult population, obese children also endure significant morbidity. Studies have shown that overweight children demonstrate cardiovascular risk factors such as dyslipidaemia, insulin resistance and hypertension. The incidence of type 2 diabetes in children has risen in recent years and this appears to be associated with the increasing levels of overweight and obesity in children.[9] They are also at risk of long term sequelae – obesity in childhood predicts risk factors and morbidity for coronary heart disease.[9] In addition, evidence suggests that childhood obesity tends to persist; overweight children grow into overweight adults. Reilly and colleagues reported that 70% of obese prepubescent children became obese adults, whereas 80% of obese adolescents remained obese in adulthood.[12]

Obesity is associated with a diminished quality of life. Obese people face discrimination in education, work, healthcare and social relationships and tend to earn lower incomes and have lower marriage rates.[13] Children as young as 3 years old display a negative attitude towards obese people, which intensifies with age.[14] A British study of 180 predominantly lean 4-11 year olds describes how professionally drawn pictures of overweight children, compared with those of normal or under-weight children, attracted many more negative attributes. Overweight children were thought of as ugly, lazy, stupid, and selfish.[9]

Pathophysiology

Obesity develops when energy intake exceeds energy output, leading to accumulation of adipose tissue. Energy balance is maintained through the control of appetite and metabolism. Appetite regulation is a complex process, influenced by peripheral and central signals. In the gastrointestinal tract, ghrelin and decreasing concentrations of nutrients such as glucose, fatty acids and amino acids stimulate hunger.[15] Ghrelin is an endogenous ligand of growth hormone secretagogue receptor (GHSR).[16] It is believed to stimulate food intake, carbohydrate utilisation and growth hormone secretion from the pituitary gland, and its administration has been shown to increase adiposity in rodents.[17] Following a meal, gastric and duodenal distension produce the feeling of satiety, aided by release of gastrointestinal peptides such as cholecystokinin, glucagon-like peptide 1 and peptide YY 3-36.[15] Cholecystokinin acts rapidly to increase satiety and decrease food intake. Peptide YY is released after the ingestion of food by endocrine L cells in the small and large intestines and it decreases food intake. Glucagon-like peptide is also secreted in response to nutrients in the intestines and increases satiety.[16] Signals regarding appetite regulation are received centrally by the brainstem and hypothalamus; these central control centres are linked by projections from brain stem neurons to the paraventricular nucleus and lateral hypothalamus. The brainstem receives information concerned with satiety via afferent vagal fibres shortly after meals, whereas the hypothalamus integrates short term and long term signals from the brain, gastrointestinal tract and peripheral circulation.[16]

The size of energy stores and the hormone leptin control appetite over a longer period of time.[15] Leptin is a hormone produced by adipose tissue which acts chiefly at the hypothalamus by binding to the leptin receptor[10]. Leptin is involved in regulating energy intake by mediating between adipose stores and the hypothalamus, and it regulates energy expenditure by stimulating the sympathetic nervous system.[18] Leptin inhibits pathways which stimulate food intake and promote weight gain by inhibiting orexins such as melanin-concentrating hormone (MCH) in the paraventricular nucleus, neuropeptide Y (NPY) and agouti-related protein (AgRP) in the arcuate nucleus.[15] It stimulates pathways which promote anorexia and weight loss, by stimulating anorexigenic signals, such as alpha melanocyte-stimulating hormone (αMSH), which affects the melanocortin-4 receptors (MC4R), corticotrophin-releasing factor in the paraventricular nucleus, preopiomelanocortin precursor polypeptide (POMC) and cocaine- and amphetamine-regulated transcript (CART) in the arcuate nucleus.[15]

Leptin levels are directly proportional to levels of adipose tissue.[16] In severely obese individuals, subcutaneous adipose tissue concentrations of leptin mRNA are 80% higher than in controls, and plasma levels are also high. Plasma concentrations of leptin are reduced when weight loss occurs due to diet restriction.[15] Insulin-induced alterations in adipocyte metabolism are thought to stimulate production of leptin.[19] A diminution of adipose tissue results in reduced leptin release which stimulates appetite and restores the energy deficit.[15] The central nervous system responds to a lack of leptin as it would to an absence of adipose tissue stores, by increasing food intake and decreasing energy expenditure. Conversely, an increase in adipose tissue stimulates leptin release, thus reducing appetite and promoting weight gain.[15] Physiologic responses to decreased leptin are more pronounced than responses to increased levels of leptin, leading to speculation that the primary role of leptin is to adapt to a negative energy balance rather than to prevent obesity.[19] The feedback mechanism is not

completely understood. Adipose tissue mass may not be the sole determinant of leptin release and it has been suggested that leptin resistance may occur.[10] Many other signals such as ghrelin and cholecystokinin may have a role in long term regulation of appetite and energy, thus increasing the complexity of the feedback mechanism.[16]

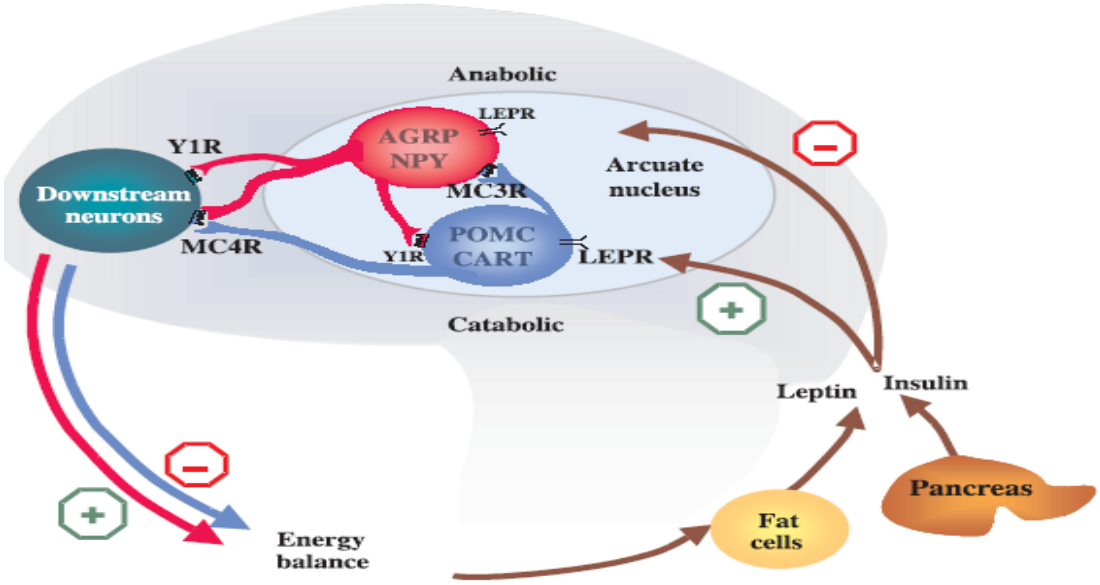

Figure 3: Central Pathways regulating Energy Balance[20]

The other side of the energy balance equation – total energy expenditure, is chiefly determined by the basal metabolic rate (BMR) thermogenesis and physical activity.[15] Metabolic rate contributes 60-70% of total energy expenditure and depends on lean body mass, energy intake, physical fitness and other factors such as age, height, stress and environmental temperature.[21] Fat-free mass is responsible for 60-80% of inter-individual variability in BMR.[21] Contrary to popular opinion, metabolic rate is generally higher in the obese than in lean individuals. This is because obese people have a correspondingly large lean body mass and tend to use a greater magnitude of energy than lean individuals when doing the same amount of activity.[13] Subject variability is also attributable to traits such as muscle fibre type, muscle tone and thyroid function.[21] Dietary thermogenesis is the energy required to digest and store food, and is greatest for protein rich meals, midway for carbohydrates and lowest for fat.[13] Physical activity is influenced by behavioural and environmental factors.

Aetiology of Obesity

Obesity is a multifaceted chronic disease with a complex aetiology, which has yet to be fully elucidated. It is an associated feature of many conditions including hypothyroidism, Cushings' syndrome, Stein-Leventhal syndrome, hypothalamic disease and drug-induced obesity, but these only account for a minority of cases.[15] Although the obesity crisis has been dominating headlines for many years, there is no consensus regarding its precise aetiology, much less the most appropriate treatment.

Genetics

The genetic contribution to obesity is substantial, but in most cases its expression is influenced by other factors, although it is known that genetic factors predict the success rates of weight loss programmes.[22] The obesity gene map shows putative loci

on all chromosomes except the Y chromosome. There are more than six hundred genes, markers and chromosomal regions associated with obese phenotypes, either rare gene variants with a strong influence or common gene variants with a weak influence.[23] Key genes are located on chromosomes 2p, 3q, 5p, 6p, 7q, 10p, 11q, 17p and 20q.[20] Segregation analyses have suggested a role for a major recessive gene, but other studies have contradicted this research.[20,23] Whether the mode of inheritance is polygenic, oligogenic, or a mixture of the two is still under dispute.

Single gene defects comprise a less common cause of obesity (approximately 5%) but provide an insight into the pathophysiology of obesity. Disorders such as Prader-Willi syndrome, Albright Hereditary Osteodystrophy and Bardet-Biedl syndrome are inherited in Mendelian fashion and feature obesity as a clinical manifestation but not as the dominant characteristic.[20] Prader-Willi syndrome is the commonest form of syndromic obesity with a prevalence of 1/25,000. Causal genes have not yet been identified for Prader-Willi syndrome, but candidate genes are expressed in regions of the hypothalamus concerned with energy balance.[24] The genes affected in Albright Hereditary Osteodystrophy and Bardet-Biedl syndrome (BBS) are GNAS1 (Guanine nucleotide-binding protein, α-stimulating activity polypeptide 1) and BBS 1,2,4,6,8 respectively.[24] While these syndromes provide us with an important means of delineating the complex genetic and metabolic pathways involved in regulating appetite and energy balance, they are an infrequent cause of obesity.

Rare mutations in humans and model organisms where obesity is the dominant feature have also provided insights into these pathways. The putative obesity gene *ob* was first identified in the naturally occurring mutant *ob/ob* mouse in 1994. The *ob* gene is found on chromosome 7 and produces leptin. A mutation in the *ob* gene leads to production of a non-functioning protein. The *ob/ob* mouse demonstrated hyperphagia, hyperinsulinaemia and obesity. The leptin receptor deficient *db/db* mouse had a similar phenotype.[10] Administration of leptin to the *ob/ob* mouse resulted in a reduction in body weight, but did not alter body weight in the *db/db* mouse.[16] In humans, mutations in leptin or its receptor produce an obese phenotype that is not normalised by dietary restriction or exercise.[10] Treatment with recombinant leptin in leptin-deficient individuals results in a significant decrease in body weight.[16] However, most obese people produce structurally normal leptin, and due to their high adipose tissue mass, have high levels of circulating leptin. Other monogenic defects of interest include those affecting pro-opiomelanocortin, the melanocortin-4 receptor, adrenergic receptor, carboxypeptidase E, peroxyisome proliferator-activated receptor γ and prohormone convertase 1.[10]

Twin, adoption and family studies have shown that genetic factors play a significant role in the pathogenesis of obesity, although there is still doubt regarding the magnitude of the genetic contribution to obesity. Twin studies have shown that genetics are responsible for 50-90% of inter-individual variation in BMI, while family studies put this number at 20-80%.[20,25] The risk of obesity when a first-degree relative is obese is increased by a factor of five if the relative is extremely obese (BMI>40), but the risk is only elevated two-fold if the relative is moderately obese (BMI>30).[10] This data has led to the development of the 'major gene hypothesis', which asserts that the genetic mechanisms underlying extreme obesity differ from those leading to more common, moderate forms of obesity.[10]

In positive energy balance experiments, it has been shown that some individuals are more prone to weight gain than others. In one experiment, sets of monozygotic twins ate a surplus of calories, resulting in an average weight gain of 8.1kg. At the start of the experiment virtually all of the excess calories were converted to weight gain. After one hundred days only 60% of the surplus energy was being stored.[10] Among the participants, there were differences in the amount of weight gained and the distribution of the adipose tissue stored. This variance was greatest between pairs of monozygotic twins rather than within pairs, suggesting that the discrepancies in response to surplus calories were attributable to differences in genotypes. Similarly, in negative energy balance experiments where monozygotic twins were exposed to energy deficient environments, alterations in body mass and body fat were greater between twins than within twin pairs.[10]

In their review of the genetic causes of obesity, Loos and Bouchard divided genetic susceptibility into four main categories: genetically obese, strong predisposition to obesity, slight predisposition to obesity and genetically resistant. According to this classification, individuals in the genetically obese and genetically resistant groups are resistant to changes in their environments. Those who are genetically obese maintain their obese phenotype in a wide range of environments, while genetically resistant people remain lean, even in obesogenic circumstances. Those who are susceptible to obesity may be slightly overweight in a restrictive environment, but are at a high risk of developing extreme obesity in an obesogenic environment. Those who are slightly predisposed to obesity may maintain a normal weight with a healthy lifestyle, but a significant proportion will become obese in an obesogenic environment. This susceptibility stems from alleles at a number of loci, and accounts for the common forms of obesity.[20]

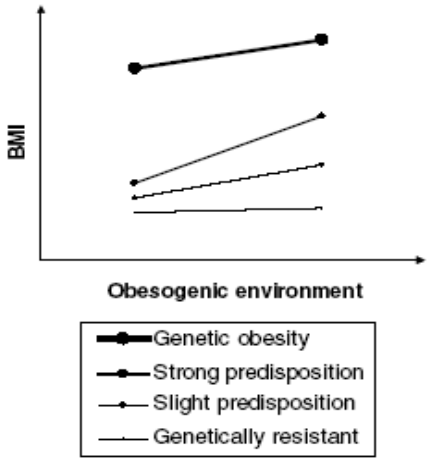

Figure 4: Genetic predisposition to obesity[20]

The "Thrifty Genotype" hypothesis first put forward by James Neel in 1962 suggests that the evolution of Homo Sapiens selected for genes that predispose to obesity.[26] Following the last glaciation, hunting decreased, while the culture of cereals rose. Protein intake, as well as that of other essential meat nutrients (iron and vitamins), decreased, producing dietary deficiencies mirrored by the reduction of body size and induction of important adaptations in the molecular processes regulating nutrient metabolism. This enabled humans to maintain glucose homeostasis and to guard

against food restrictions and deprivations. As a consequence of surviving in times of food scarcity, genes that predisposed to metabolic efficiency and increased energy stores conferred a survival advantage to the possessor. The advent of agriculture and breeding (10,000 years ago) marked a fundamental step in the human nutritional system, introducing new foods and transforming this selective metabolic advantage into a susceptibility to obesity. Humans have had little evolutional contact with diets high in fat and carbohydrate, so no mechanisms to mitigate against their over-consumption have developed.[9,20,28] Feedback regulation of fat and carbohydrate is not as efficient as for protein.[27,28] Our limited experience of energy dense, fatty foods has resulted in these foods being perceived as more palatable. Compared to animals, we store a large proportion of excess energy – rodents metabolize and eliminate 90% of their excess energy, while humans store 75% of their energy surplus.[27] In addition, the systems that regulate the body's energy balance evolved at a time of high energy expenditure. In today's obesogenic environment these conditions no longer apply and this has led to a decrease in our energy intake requirements.[29] These regulatory systems respond to increased energy expenditure by increasing intake accordingly; however, they are less efficient at lowering our energy intake in response to less physical activity.[27] Ample supplies of heavily marketed, palatable, energy-dense foods, along with labour-saving machinery and reliance on cars have combined to create an obesogenic environment to which our 'thrifty genotype' is ill-suited.

Even though genetic factors are important in the pathogenesis of obesity, the fact remains that obesity levels have escalated far too quickly to be a purely genetic phenomenon. Rather, these trends implicate environmental and behavioural changes capable of affecting large populations. The current obesity epidemic is thought to be the result of the interaction between individual genetic susceptibility and a toxic, obesogenic environment.

Nutrition

Philip James, chairman of the International Obesity Task Force, claimed that *"it's a miracle that anybody stays even moderately thin"* when meals such as a cheeseburger, a large portion of fries, and a 450 ml fizzy drink can add up to 1166 kcal (4900 kJ).[30] Surprisingly however, the National Nutrition Surveillance Centre's annual report revealed that on average, Irish people in 2002 ate less than their counterparts in 1948.[5] While energy intake may be decreasing, the energy density of the foods we eat is rising. The proportion of dietary fat consumed has increased in recent years. Recommendations from the Eurodiet Core report state that no more than 30% of the total energy intake should comprise fats, while figures show that 37% of Irish energy intake consists of fat and most people consume too much saturated fat.[3,31] Studies show an association between obesity and high fat diets, while low fat diets are a successful means of achieving weight loss (although some studies have shown that simultaneous reduction in total energy intake is necessary).[9,32] Given that fat is less satiating and more energy dense, (fat provides 9 kilocalories per gram, compared to 4 kilocalories for carbohydrates and for protein), it follows that a high fat diet predisposes to passive over-consumption of energy.[9,29]

Dietary patterns

Dietary patterns have changed enormously. Globally, the availability of calories per capita has risen by 450 kilocalories per day.[28] A SLAN survey revealed that in Ireland, 22% of 18-34 year olds consume food prepared outside the home every day.[5]

Children who dine at home with their families eat more fruit and vegetables, consume fewer fizzy drinks and eat less fat overall.[33] The 2002 HSBC survey revealed that 51% of Irish children consume sweets and 27% consume crisps. Increased consumption of sweetened drinks has been linked to the obesity epidemic and in Ireland, 37% of children drink at least one such sugary beverage every day.[34] It has been shown that each additional can per day increases the risk of obesity by 60%.[9] The recent surge in the consumption of sweetened drinks and fast food may be due to their aggressive promotion in the media, especially on television. On average, children watch 100,000 television advertisements a year, the vast majority of these promoting fast food, sweets and sweetened drinks. Hastings and colleagues have demonstrated a link between the number and content of ads and being overweight, while Gortmander and others found a dose-response relationship between TV watching and weight gain.[2,35]

Physical Activity

Physical activity is defined as 'bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above the basal level.'[9] Reductions in physical activity contribute to the positive energy balance associated with weight gain.[37] A low level of physical activity is linked with a low daily energy requirement as well as changes in metabolic activity, and will cause obesity unless energy intake is restricted accordingly.[2,36] The metabolic activity of muscle has a key role in maintaining fat balance. Reduced muscle activity leads to reduced fat oxidation favouring fat imbalance.[37] On the other hand, high levels of physical activity, especially regular exercise, stimulate fat oxidation.[43] A high fat oxidation rate plays a protective role in the risk of weight gain.[37]

The largest available prospective study, which followed 12,000 Finnish adults over five years verified that low levels of physical activity are as important as dietary factors in the aetiology of obesity.[29] A large proportion of the Western population lives a sedentary life, facilitated by advances in technology and transport. While it is recommended that adults spend a total of one hour per day on most days of the week doing moderate-intensity activity, the average Irish adult spends less than one hour per week on physical exercise, and up to 46% of Irish adults report that they engage in no physical exercise at all.[3,9] Physical activity levels decrease with age and there is normally a significant decline after adolescence. Nevertheless, Irish adolescents already exhibit nominal levels of physical exercise. The Mid-Western Region Heart Rate Monitoring Study found that none of the adolescents studied were active for 30 minutes of moderate intensity cumulative exercise on all four days.[9] Socioeconomic factors, availability of amenities and facilities, peer influence, and activity level of parents all impact on the amount of exercise children receive.[37] Obesity itself can be a deterrent to physical activity due to the physical discomfort experienced, and while overweight people expend more energy when they partake in exercise, they tend to do less vigorous physical activity.[38,39] These reductions in levels of physical activity are most apparent in people who are substantially overweight.[40] Obesity also predisposes to conditions such as arthritis, which limit the capacity for physical activity.[41] Reducing levels of physical activity then promotes further weight gain, thereby perpetuating a vicious cycle of weight gain and debilitating sequelae.[40]

Conclusion
Current modern lifestyles are creating a generation of overweight children and adults. Childhood obesity is the most prevalent paediatric disease in Europe and some experts forecast that this generation of children may have a lower life expectancy than their parents because of diseases resulting from obesity. In economic terms, the cost of treating obesity in Ireland exceeds €0.4 billion annually.[9] Clearly, the problem of obesity is very costly to society in both human and financial terms, prompting governments, health professionals and non-governmental organizations around the world to search for approaches to its control. There is compelling evidence to support the effectiveness of low calorie (1,000-1,500 kcal/day) and low fat (where 30% or less of total daily energy is derived from fat) diets combined with energy restriction, or even low-fat diets alone.[9] Unfortunately, weight loss is usually temporary, with 90% to 95% of people regaining the weight following a clinical management programme. This suggests that while traditional weight control measures are necessary, they are insufficient to reverse the incidence of obesity.[43]

The National Taskforce on Obesity recommended that policies must be introduced at a national level which support individuals in their efforts to lose weight and prevent weight gain by addressing the underlying environmental, social and cultural factors acting as barriers to change. It is obvious that society would benefit by modifying diet and fat intake, as well as increasing activity levels in accordance with literature recommendations.

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