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Plenary Lecture

Clinical treatment of obesity: are drugs and surgery the answer?

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Obesity treatment remains a 'Cinderella' of all clinical management programmes, but generally without a happy ending. The great expectation for new therapeutic agents has not been fulfilled in clinical practice, whilst the restriction of eating through surgical division of the upper bowel seems strange in an age of advanced and sophisticated technology. The better understanding of the neuro-regulation of appetite, and its application as part of evidence-based clinical interventions, could lead to a more coherent approach to obesity treatment. Nevertheless, investigation of potential neuroendocrine targets for appetite suppression suggests redundancy in the systems, which make development of effective agents against single receptors impractical. Importantly, the progressive rise in the prevalence of obesity will inevitably mean that only a small proportion of afflicted patients will actually be treated by long-term drugs and surgery. Drugs and surgery are not currently the answer for the majority of obese individuals. What is required is a better way of identifying patients who may particularly benefit from such approaches. However, the major emphasis must be the development of effective population-wide interventions that halt the increase in fatness and ensure that future generations maintain and enjoy a healthy body weight.

Obesity: Anti-obesity drugs: Obesity surgery

Overweight and obesity are now so common among the world's population that they are becoming the most important contributors to ill health. Deaths linked to obesity shorten life expectancy by 9 years (Royal College of Physicians, Royal College of Paediatrics and Child Health and the Faculty of Public Health, 2004). The increasing prevalence of overweight and obesity has ensured that they are now considered as major medical problems; there is an increasing belief from patients, and some health professionals, that drugs and surgery are the only effective treatment options.

Increasing prevalence

The latest Health Survey for England (Department of Health, 2003) demonstrates that between 1993 and 2002 the percentage of overweight and obese adults rose from 62·2 to 70·4 among men, and from 55·7 to 62·6 among women. Importantly, there is no marked change in the proportion of adults who are overweight, but there is a marked increase in the proportion of adults who are obese. The percentage of men who were categorised as obese increased from 13·2 in 1993 to 22·1 in 2002, and that for women from 16·4 in 1993 to 22·8 in 2002. Obesity now affects over one in five adults in the UK.

Overweight young people have a 50% chance of being overweight adults, and children of overweight parents have twice the risk of being overweight compared with those with healthy-weight parents. Obese 10- to 14-year-olds with at least one obese parent have a 79% chance of becoming an obese adult. Furthermore, parental obesity more than doubles the risk of adult obesity in obese and non-obese children <10 years.

If current trends continue, at least one-third of adults, one-fifth of boys and one-third of girls will be obese by 2020 (Lobstein *et al.* 2003). These forward projections

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from existing data show conservative predictions. If the much faster increase in childhood obesity witnessed in the last decade is taken into account, the predicted prevalence in children for 2020 will be >50%.

Medical complications of obesity

Obesity causes or exacerbates a large number of health problems, both independently and in association with other diseases (Kopelman, 2000). In particular, it is associated with the development of type 2 diabetes mellitus, CHD, an increased incidence of certain forms of cancer, obstructive sleep apnoea and osteoarthritis of large and small joints. The Build and Blood Pressure Study (Lew, 1985) has shown that the adverse effects of excess weight tend to be delayed, sometimes for ≥10 years.

Analysis of prospective findings in the Framingham Heart Study (Peeters *et al*. 2003) has shown that 40-year-old women who are non-smokers lose 3·3 years of expected life because of overweight (BMI 25–29·9 kg/m^2) and men of similar age lose 3·1 years.

The 40 year-old non-smoking obese women (BMI ≥30 kg/m^2) lose 7·1 years of life because of obesity, and obese men of comparable status lose 6·7 years. However, in obese people who smoke, the years of life lost almost doubles; obese female smokers lose 13·3 years of expected life and obese male smokers lose 13·7 years of life, compared with life expectancy for normal-weight non-smoking women and men. BMI at ages 30–49 years predicts mortality after ages 50–69 years, even after adjustment for BMI at age 50–69 years (Peeters *et al*. 2003).

There is, therefore, an absolute requirement to develop effective therapeutic interventions for those individuals with established obesity and, most particularly, those individuals who are overweight or obese with established co-morbidities.

Successful therapeutic interventions for chronic and relapsing diseases

Advances in medical treatments during the past two decades have revolutionised the care of several chronic and/or relapsing conditions that previously had a major impact on health care and associated costs. As a medical student in the 1970s, the author recalls a number of senior consultants who spent time from practice, or underwent highly-selective vagotomies with pyeloplasties, as treatment for peptic ulcer disease. The advent of H_2 antagonists, the introduction of proton pump antagonists and the isolation of *Helicobacter pylori* have meant that this condition now rarely requires hospitalisation (Calam, 2003).

Similarly, anti-hypertensive medication in the 1960s and 1970s was limited to thiazides, methyl dopa and α blockers, with many causing serious adverse drug reactions. The improved understanding of the patho-physiological mechanisms behind hypertension has led to a wide range of drugs that specifically target receptors involved in blood-pressure regulation. Importantly, the effectiveness of these drugs has been proven by long-term prospective studies that confirm very marked reductions in serious outcomes from hypertension such as premature death, myocardial infarction and stroke (Hansson *et al*. 1999).

Hypercholesterolaemia was a challenging condition to treat before the advent of statins. Dietary restriction of fat had limited benefit and the resins that interfered with the entero-hepatic biliary circulation were extremely unpalatable and, as a consequence, were often not taken by patients. The recognition of a defect within the receptor enzyme, hydroxymethylglutaryl-CoA reductase, and its blockade by statins has resulted in a very substantial fall in cholesterol. Prospective studies of the use of statins confirm long-term efficacy in reducing deaths from myocardial infarction and stroke (Sever, 2003).

In the context of these successful therapeutic interventions it is natural that many healthcare professionals anticipate similar advances in drug therapy for obesity.

Pathogenesis of human obesity

There is a relationship between low levels of physical activity and obesity. A longitudinal Finnish study (Rissanen *et al*. 1991) found that those participants reporting physical exercise three or more times each week had on average lost weight since a preceding survey. By contrast, those subjects who undertook little physical activity gained weight and had twice the risk of gaining ≥5 kg. Among children in the USA the relative risk of obesity is 5·3 times greater for children who watch television for ≥5 h each day compared with those children who watch for <2 h, even after correcting for a wide range of socio-economic variables (Gortmaker *et al*. 1996).

In the UK a study combining data on energy intake and physical activity in relation to the secular increase in adult obesity (Prentice & Jebb, 1995) has shown a close relationship between proxy measures of physical inactivity (television viewing and car ownership) and the prevalence of obesity. Nevertheless, food consumption and the appropriate regulation of eating are critical factors in the aetiology of overweight and obesity.

Regulation of eating

Food intake may be restricted either by a conscious decision to eat less (dietary treatment) or through pharmacologically-'imposed' alterations in the central regulation of appetite control. Alternatively, absorption of nutrients can be artificially reduced either by drug inhibition of digestive processes or by surgically-induced anatomical alterations to bowel anatomy.

Eating is dependent on a large number of factors that include the availability of food, an individual's mood and the physical attributes of the food, such as appearance, smell and palatability. The latter is now a complex science as a result of food technology. Food consumption in man is regulated through a number of complicated biological mechanisms designed to ensure that body weight remains relatively constant over long periods.

It is surprising that no direct correlation has been reported between increasing obesity prevalence and

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increased energy intake in developed nations, given the ready availability of highly-palatable foods. However, the lack of a direct correlation may be explained by under-reporting of food intake that confounds the understanding of the role of energy intake in the aetiology of obesity. Under-reporting is widely recognised as a feature of obesity. It is thus extremely difficult to obtain reliable data on the energy intake of obese subjects, and this factor makes it difficult to interpret eating surveys in the UK that suggest a decline in total energy ingestion. Proxy measures of energy intake do suggest altered intakes may have occurred since the 1970s; in the USA documented portion sizes have increased 2–5-fold (Young & Nestle, 2002).

From a clinical perspective, the most effective therapeutic intervention for weight reduction is energy restriction, which supports the clinical impression that overeating (disproportionate to energy expenditure) is the most important factor leading to overweight and obesity.

Neuroendocrine control of appetite

The identification of leptin and the discovery of its role in energy balance in animal models of obesity have resulted in considerable advances in the knowledge of the neuroendocrine regulation of eating. Leptin is synthesised mainly in adipose tissue, although low levels have been detected in skeletal muscle, the gastric fundus and the placenta. Leptin circulates as the free and bound hormone and reaches its targets in the brain via a saturable process. The importance of leptin to energy balance is evident in man, in whom rare mutations of leptin or leptin receptor genes result in increased appetite, morbid obesity and associated metabolic and endocrine abnormalities (Montague *et al*. 1997). However, in most obese subjects plasma leptin concentration increases in proportion to body fat such that the plasma levels are higher in obese individuals than in lean individuals (Considine *et al*. 1996).

Leptin affects several aspects of energy balance. In the laboratory a reduction in plasma leptin in rodents during fasting partly accounts for stimulation of appetite, activation of the hypothalamic–pituitary axis and suppression of thyroid and reproductive hormones. By contrast, a rise in leptin levels decreases meal size and modulates taste perception. Leptin mediates these actions through its action within hypothalamic nuclei (Ahima & Osei, 2002). Leptin inhibits the synthesis and release of neuropeptide Y and agouti-related peptide and increases pro-opiomelanocortin. Pro-opiomelanocortin is a precursor of α-melanocyte-stimulating hormone and cocaine- and amphetamine-regulated transcript through a direct action on synthesis in the arcuate nucleus. The anorexic action of α-melanocyte-stimulating hormone is regulated through melanocortin receptors 3 and 4. Neuropeptide Y/agouti-related peptide and α-melanocyte stimulating hormone/cocaine- and amphetamine-regulated transcript neurones project to the paraventricular hypothalamic nuclei and lateral hypothalamic area. Leptin also regulates feeding indirectly by suppressing the release of melanin-concentrating hormone and orexin in the lateral hypothalamic area. The ventromedial hypothalamus is regulated directly by leptin.

The initial hopes that leptin would provide a therapeutic breakthrough for the treatment of human obesity have not been realised. Leptin treatment in patients with the rare syndrome of congenital leptin deficiency does result in substantial weight reduction; the restoration of plasma leptin concentrations results in progressive weight loss over a 2-year period (Farooqi *et al*. 2002). By contrast, initial trials of leptin in obese patients (without leptin deficiency) have shown no benefit in terms of weight reduction unless substantial doses are given. Even high doses, which produce plasma concentrations approximately twenty times above the placebo-treatment baseline, result in variable weight loss, with any benefit being countered by the requirement to give the large volume of drug by subcutaneous injection (Heymsfield *et al*. 1999).

The fact that some obese individuals overeat despite high plasma leptin concentrations suggests leptin resistance. This resistance could be the result of a rate-limiting transport step for the entry of leptin into the brain or impaired receptor signalling. Attention is now being focused on developing compounds that target other neuronal receptors involved in appetite regulation such as neuropeptide Y, melanocortin receptors and cocaine- and amphetamine-regulated transcript.

The endocannabinoid system appears to play a role in maintaining energy balance through the regulation of food intake and energy expenditure. CB1 receptors are found in many areas of the brain, but most particularly the hypothalamus and brainstem. CB1 receptors are also found in the gastrointestinal system and adipocytes. In animals obesity appears to be associated with overactivity of the endocannabinoid system.

Nevertheless, the complexity of the neuronal control of eating suggests redundancy in the system, which may mean that the development of single agents against specific receptors is impractical.

Current pharmacological treatment of obesity

There are currently two categories of anti-obesity drugs, those that act on the gastrointestinal system (pancreatic lipase inhibitors) and those that act on the central nervous system to primarily suppress appetite (see Kopelman & Grace, 2004).

Drugs acting on the gastrointestinal system: pancreatic lipase inhibitors

Orlistat inhibits pancreatic and gastric lipase, thereby decreasing ingested triacylglycerol hydrolysis (see Kopelman & Grace, 2004). It produces a dose-dependent reduction in dietary fat absorption; weight loss in obese subjects largely results from reduction in fat intake to avoid gastrointestinal effects, including steatorrhoea. Vitamin supplementation (especially of vitamin D) may be considered if there is concern about a deficiency of fat-soluble vitamins. Orlistat is not licensed for use for >2 years because there is insufficient clinical experience beyond this period.

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Centrally-acting anti-obesity drugs

Sibutramine promotes a sense of satiety through its central action as a serotonin and noradrenaline re-uptake inhibitor (see Kopelman & Grace, 2004). In addition, it may mitigate against the fall in thermogenesis through stimulation of peripheral noradrenaline receptors. It is used in the adjunctive management of obesity in individuals with a BMI of $\geq 30\,kg/m^2$ (and no associated co-morbidity) or in individuals with a BMI of $\geq 27\,kg/m^2$ in the presence of other risk factors such as type 2 diabetes or hypercholesterolaemia. Sibutramine is not licensed for use for >1 year.

Rimonabant is a novel agent for the treatment of obesity. It is a selective antagonist of the CB1 receptor in the endocannabinoid system that is unlicensed at present (see Kopelman & Grace, 2004).

Efficacy of current pharmacological treatments for obesity

Randomised controlled trials of the use of orlistat and sibutramine suggest that approximately 60% of the treated patients will achieve and maintain a 5% loss from their starting weight after 12 months of treatment, and 40% of the patients will experience a 10% weight loss. Cessation of drug therapy is often associated with a gradual reversal of weight loss. The use of both drugs may also be limited by the side effects. Any deviation from a low-fat diet while taking orlistat results in unpleasant and often explosive diarrhoea. The use of sibutramine in clinical practice may be accompanied by an elevation in blood pressure that requires close monitoring. The National Institute for Clinical Excellence (2001, 2002*a*) has provided guidance for the use of orlistat and sibutramine.

The results from 2-year studies that have compared different doses of Rimonabant and placebo in overweight and obese subjects with untreated dyslipidaemia and/or diabetes (Sjostrom *et al*. 2004) are encouraging. Of the subjects treated with 5 mg Rimonabant 42% were reported to have achieved and maintained a 5% weight loss at 2 years, with 16% achieving and maintaining a 10% reduction. For obese subjects treated with 10 mg Rimonabant 73% were reported to have achieved a 5% weight loss at 2 years, with 44% achieving a 10% weight reduction. Of the obese subjects treated with 10 mg Rimonabant >50% were reported to have experienced both a physical and a biochemical improvement in measures indicative of the metabolic syndrome at 1 year.

Surgical treatment of obesity

There are three operative procedures currently used for the surgical treatment of obesity: gastric restriction; gastric bypass operations; bilio-pancreatic diversion.

Gastric restriction involves the creation of a small capacity compartment (<20 ml) by either a combination of vertical stapling and a constrictive band opening, or a circum-gastric band pinching off a small proximal pouch. A modification of the latter procedure is an inflatable circum-gastric band attached to a subcutaneous reservoir that allows access by a hypodermic syringe to inject or withdraw fluid, thereby tightening or enlarging the band width.

Gastric bypass is performed by stapling shut a <20 ml vertically-oriented pouch and connecting this pouch to the jejunum transected 500 mm from the ligament of Treitz (Roux-en-Y gastric bypass). Published evidence confirms that this procedure produces greater weight loss but is accompanied by more frequent adverse effects including 'dumping' (Kral, 1996).

Bilio-pancreatic diversion includes a gastric resection and diversion of the bilio-pancreatic juice to the terminal ileum to reduce the absorption of nutrients. In this operation an entero–entero anastomosis is performed between the proximal limb of the transacted jejunum and ileum, 500–1000 mm proximal to the ileo-caecal valve. A more recent modification maintains the pylorus and a portion of the duodenum ('duodenal switch'), which improves protein absorption and results in fewer side effects.

Many anti-obesity surgical procedures are now routinely performed laparoscopically, which reduces the requirement for analgesia and facilitates prompt post-operative mobilisation.

Efficacy of surgical treatment

Surgery is usually successful in inducing substantial weight loss in the majority of obese patients, and is achieved primarily by an inevitable reduction in energy intake.

Gastric restriction. Gastric restriction operations require strict dietary compliance, because an intake of high-energy liquids or soft foods is not inhibited by the narrow outlet and may explain a failure to lose weight. The advantage of these techniques is their relative simplicity, with no anastomoses or bypass of any part of the bowel. As a consequence, operative mortality is very low and longer-term nutritional deficiencies unlikely. The reported excess weight loss after 3–5 years is between 40 and 60%, but there is a slow regain thereafter. Some patients lose no weight at all.

Gastric bypass. Gastric bypass operations generally achieve an excess weight loss of between 49 and 62% maintained over a 5–14 year period. The nature of the operation is more complicated and the operative mortality approximately 1%. This operative procedure can be associated with nutritional deficiency, although this outcome is unusual when detailed dietary advice is reinforced with dietary follow-up.

Bilio-pancreatic division. Bilio-pancreatic division achieves ≤78% excess weight loss at 18 years. Once again the operative mortality is 1% but nutritional deficiencies are relatively common (between 5 and 40% of the patients for the longer term). In addition, alterations in bowel movements are frequent with three to five motions, commonly offensive, occurring each day.

Long-term outcome following obesity surgery

The Swedish Obese Subjects study is a prospective intervention study that has evaluated the medical outcomes from obesity surgery over a 10-year period. The reported outcome to date after 8 years has shown a weight loss of

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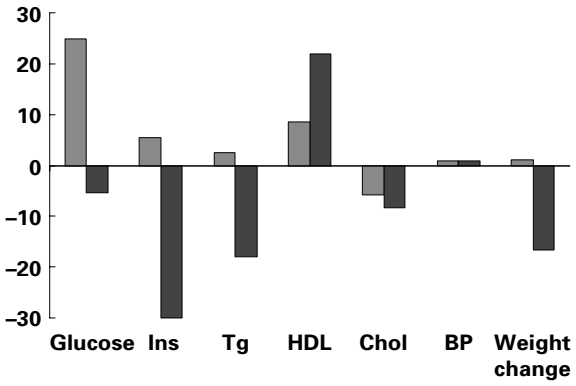

Fig. 1. Effect of surgically-induced weight loss on blood pressure and metabolic variables in Swedish obese subjects 10 years after anti-obesity surgery (▩) and in subjects treated by conventional medical methods (control; ■). Glucose, fasting blood glucose; Ins, fasting plasma insulin; Tg, serum triacylglycerol; HDL, HDL-cholesterol; Chol, fasting total cholesterol; BP, blood pressure. (From Sjostrom *et al.* 2002.)

16·3 kg compared with no loss in a medically-treated control group (Sjostrom *et al*. 2000). The unadjusted prevalence of diabetes among the controls followed for 8 years shows an increase from 7·8 % to 24·9 % while in the surgically-treated group the prevalence rate is stable at 10·5 %. The course of the blood pressure shows a different pattern, with an initial marked fall in blood pressure in the surgically-treated group associated with rapid weight loss. Despite continuing weight loss during the next 6 years, the reduction in diastolic blood pressure was found to cease, and to be accompanied by a small rise in systolic blood pressure (Fig. 1). As a result, no difference was observed in systolic blood pressure between the two groups at 8 years; the diastolic pressure was found to be 2·5 mmHg higher in the surgically-treated group compared with the controls despite the weight loss. Furthermore, the initial improvement in all variables of serum lipid profiles is not sustained in the surgically-treated group at 8 years; although HDL-cholesterol levels increase, there is no change in total cholesterol from the pre-operative values (Sjostrom, 2001).

A review of evidence from randomised controlled trials confirms that surgery for obesity is an option for carefully-selected patients with clinically-severe obesity (BMI $\geq 40\,kg/m^2$ or BMI $\geq 35\,kg/m^2$ with co-morbid conditions) when less-invasive methods of weight loss have failed, and the patient is at high risk for obesity associated morbidity and mortality, most particularly diabetes. The National Institute for Clinical Excellence (2002*b*) has issued guidance about surgical treatment for morbidly-obese patients and confirms that the nature of the surgical procedures necessitates long-term hospital follow-up for such patients; a 'patient for life'.

Lifestyle interventions for the treatment of obesity

Lifestyle modification remains the most important tool for the management of the overweight and obesity. There have been a number of national public education campaigns that have succeeded in raising awareness and understanding of the issues and promoting healthier eating and more active living; the most notable example is in Finland's North Karelia Project (Puska *et al*. 1995). Physical inactivity is a major risk factor for the development of type 2 diabetes. Prospective studies suggest that the more exercise taken each week, the lower the risk of developing type 2 diabetes (Kesaniemi *et al*. 2001). Individuals who are physically inactive are more likely to have impaired glucose tolerance, and type 2 diabetes is more common among individuals who are physically inactive. Intervention studies have demonstrated that a programme of lifestyle change focusing on improved diet and increased activity can delay, or possibly prevent, the development of type 2 diabetes in individuals with impaired glucose tolerance (Tuomilehto *et al*. 2001; Knowler *et al*. 2002). The Diabetes Prevention Programme in North America involved 3234 men and women with impaired glucose tolerance (mean age 50 years; mean BMI $34\,kg/m^2$) randomised either to placebo, metformin treatment or an intensive lifestyle intervention, with goals of ≥7 % weight reduction from starting weight and 150 min physical activity each week. The individualised intensive lifestyle intervention was found at 3 years to result in a 58 % reduction in the incidence of type 2 diabetes in the lifestyle intervention group, compared with a 33 % reduction in the metformin-treated group. The level of the reductions led to the cessation of the trial. Interestingly, identical results have been demonstrated by a similar study in Finland (Tuomilehto *et al*. 2001). Such findings strongly support the hypothesis for reversibility of the vicious cycle of events that follow increasing adiposity with increasing insulin resistance and systemic hyperinsulinaemia, provided that the lifestyle changes occur sufficiently early and before islet cell failure. Preliminary publication of the results from the use of the anti-obesity drug orlistat in patients with impaired glucose tolerance and/or established metabolic syndrome indicate a benefit from the addition of orlistat to a programme of lifestyle change. The results from the Xenical in the Prevention of Diabetes in Obese Subjects study (Torgerson *et al*. 2004) show a 37 % reduction in relative risk for all subjects, and 45 % reduction in subjects with impaired glucose tolerance alone. Subjects with the metabolic syndrome show a 36 % reduction in risk of developing type 2 diabetes at 4 years.

Financial costs and economic consequences

Overweight and obesity, and their associated health consequences, result in a huge financial burden for governments and society as a whole. The Chief Medical Officer for England (Chief Medical Officer, 2002) has estimated that a general practice with 10 000 patients and five doctors will have to cope with eighty new obese patients each year, based on current trends of increasing prevalence, and acknowledges the substantial increase in National Health Service costs. The National Audit Office (2001) has estimated the costs to the National Health Service to be $\geq £0{\cdot}5 \times 10^9$ per year in treatment costs, and possibly $> £2 \times 10^9$ to the wider economy. Recalculation of this estimate by the UK Parliamentary Health Select

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Table 1. Assessment criteria to determine the need for early medical and/or surgical intervention for overweight and obesity

Criteria for early intervention
BMI
Waist circumference
Blood pressure
Metabolic indices (blood glucose, lipids etc.)
Associated risk factors
Established co-morbidities
Family history (CHD, diabetes etc.)
Motivation and likely adherence to treatment regimen

Committee on Obesity (House of Commons Health Committee, 2004) suggests that these values underestimate the total direct health costs by ≥50%.

All these costs relate to the present generation of adults and take no account of the impact of the rapidly-rising prevalence of obesity in children and young people. There are immeasurable effects on young people that may affect later employment, earnings and social prospects as well as physical and mental health care needs. This position underlines the importance for clinicians to identify overweight and obese patients most likely to benefit from drug or surgical treatment. Factors that need to be taken into account are summarised in Table 1.

Importantly, the progressive rise in the prevalence of obesity will inevitably mean that only a small proportion of patients will be treated by long-term drug therapy or surgery.

Conclusions

Biological mechanisms have evolved to prevent weight loss; thus, the likelihood of a pharmacological solution or 'magic bullet' is small. Present therapeutic and surgical interventions do provide opportunities to assist weight reduction in selected obese patients, but they need to be applied in the context of lifestyle change. Clinicians should identify those patients most likely to benefit medically from such approaches through a careful clinical assessment that takes account of medical risk and likely response to intervention. Additional resource must be applied to developing effective population-wide interventions that halt the increase in fatness and ensure that future generations maintain and enjoy a healthy weight.

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