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EDITORIAL

Treatment and prevention of obesity—are there critical periods for intervention?

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Why obesity?

Both professionals and the public view obesity, increasingly apparent in childhood, and already highly prevalent in adults in the Western world, as one of, if not, the most important public health problem of our times. The considerable effort expended on researching risk factors for obesity (a Medline search for studies examining risk factors for obesity conducted at the time of writing this editorial (November 2005) resulted in 264 326 hits) contrasts starkly with the simplicity of the key underlying problem, that obesity is largely a consequence of over-nutrition and under-activity. Despite the clarity of this message, there is little evidence-based guidance on successful, viable long-term strategies to prevent or treat obesity. We believe there is a need to develop findings from epidemiological research into coherent decisions regarding prevention and treatment interventions and ultimately appropriate polices for the improvement of public health. Our intention was that a themed issue on obesity in the *International Journal of Epidemiology* would contribute towards this aim.

In the first half of this editorial we review the current evidence for the treatment of adult obesity and conclude that to date there is no strong evidence that such treatments have long-term benefits in terms of health gain. Clearly, lack of evidence does not equate to lack of effect and there is no doubt that most trials to date have not been large enough or had sufficiently long-term follow-up to answer these questions. On the other hand treating established obesity in adulthood may be '*shutting the gate after the horse has bolted*'. Further, epidemiology tells us that obesity is socially patterned, varies between countries, but in recent years has shown marked increases in all countries, and that what we eat and the exercise we take is largely determined by the food industry, transport policy, and the built environment (see for example the piece by Cummins and Macintyre in this issue[1]). Thus, a population approach to the primary prevention of obesity and to the prevention of its associated diseases is more likely to be beneficial than an individual or small group level approach such as treating established obesity.

Animal studies suggest that brief interventions during critical or sensitive periods of development can have lasting effects in terms of disease prevention. This seems such an exciting prospect to us that we spend the second half of this editorial considering whether there is sufficient evidence relating critical/sensitive periods of development to the risk of later obesity and its associated diseases to warrant trials in humans of such interventions.

Treating obesity

Ideally, any treatment for obesity should assess long-term impacts on obesity associated cardiovascular risk factors, such as hypertension, dyslipidaemia, and insulin resistance, as well as disease outcomes such as cardiovascular disease, diabetes, and osteoporosis. However, to date, few studies of any intervention have been sufficiently powered and sufficiently long-term to go beyond the assessment of weight loss itself.

Diets

Several systematic reviews and meta-analyses have examined the effect of a variety of dietary interventions on weight reduction in adults with obesity. Very low energy density diets (<800 kcal/day) resulted in the greatest weight loss, ~15–25% of initial weight, over a short period, in those who completed the programme.[2,3] However, the authors noted that these programmes were associated with high financial cost, high attrition rates and high odds of regaining 50% or more of the lost weight over 12–24 months of follow-up. With the exception of weight-watchers (a weekly support group activity in the UK), for which three randomized controlled trials suggested moderate weight loss (up to 3% of original weight) over 2 years of follow-up, trials of self-help programmes and programmes available over the internet do not suggest benefits in terms of weight loss or other outcomes.[3]

In the long-term only low fat diets have been found to be beneficial, with a pooled weight loss of −3.55kg (95% CI −4.54 to −2.55kg) at 36 months compared with control groups.[4] There were also long-term beneficial effects on dyslipidaemia and blood pressure for low fat diets in obese individuals. The long-term effects of other diets, including very low calorie diets were unclear, and the authors concluded that large long-term randomized trials of different dietary regimes with disease outcomes were required to determine the true health benefit of any diet.[4]

Over-the-counter dietary supplements

As well as the numerous fad-diets that are available to the public there is a burgeoning market in over-the-counter remedies that

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make extravagant claims about their weight loss potential. Max Pittler and Edzard Ernst recently undertook a review in order to '*... assess the evidence from rigorous clinical trials, systematic reviews and meta-analyses on the effectiveness of dietary supplements.*'[5] They identified five systematic reviews/meta-analyses and an additional 25 trials, which were not included in any previous review. None of these studies provided convincing evidence to support the use of supplements, with one exception. *Ephedra sinica* (also known as ma-huang) was associated with modest short-term weight loss (in the order of 0.9 kg /month) when compared with placebo. However, this is an ephedrine-containing supplement and has been found to be associated with a 2-fold to 4-fold increase in the odds of psychiatric, autonomic or gastrointestinal symptoms, and heart palpitations.[5] Unsurprisingly, Pittler and Ernst concluded that none of the reviewed supplements could be recommended for over-the-counter use.[5]

Pharmocological treatment

Over recent decades there has been increased interest in the use of drug treatment for obesity. Two anti-obesity drugs—orlistat and sibutramine—have been widely assessed in a number of randomized controlled trials.

Orlistat, a pancreatic lipase inhibitor that reduces the absorption of dietary fat, is effective both in the short-term and long-term at reducing weight, particularly when combined with dietary and exercise interventions.[6,7] The combination of orlistat and physical activity advice has been found to have long-term (18–24 months) beneficial effects on dyslipidaemia and hypertension, though it is unclear whether this effect is primarily due to the drug or the increase in physical activity.[6,7] To date there are no results of the long-term effects of orlistat on disease endpoints or disease and disability free survival.[6,7] Orlistat is associated with a higher incidence of gastrointestinal adverse events, which have in some trials resulted in poor compliance. Further, there is some evidence that the effect of orlistat, in terms of weight loss and improvements in cardiovascular disease risk factors, is weaker for obese individuals who are also diabetic than for non-diabetic obese individuals.[6]

Sibutramine is a centrally acting serotonin–norepinephrine reuptake inhibitor that enhances satiety and promotes energy expenditure. Short-term trials, and one trial over 2 years of follow-up, demonstrate sustained effects on weight loss.[8] Beneficial effects of sibutramine on triglyceride, high-density lipoprotein cholesterol, and glycaemic control have also been reported, but there is no direct evidence that sibutramine reduces obesity-associated morbidity and mortality. Because of its norepinephrine effect it has been anticipated that sibutramine could increase blood pressure. This hypothesis is supported by some, though not all trials.[8,9] Nevertheless, it is not recommended for use in obese individuals with hypertension, which, given the concordance between obesity and hypertension, somewhat limits its usefulness.

Many new pharmacological approaches are under investigation. These include gut hormones, such as cholecystokinin that normally signal satiety, other centrally acting serotonin agents, the anticonvulsant medications topiramate and zonisamide, cannabinoid receptor antagonists, and drugs that act on other peptide neurotransmitters. The first randomized controlled trial (n = 1507) in humans of a selective cannabinoid-1 receptor antagonist (rimonabant) was recently published.[10] It found a marked reduction in weight and waist circumference and improvements in high density lipoprotein cholesterol, triglycerides, insulin resistance, and the prevalence of the metabolic syndrome at 1 year of follow-up when rimonabant was given at a dose of 20 mg per day, but much weaker effects on weight reduction of a 5 mg dose and no effects on metabolic syndrome components at this lower dose.[10] Despite the marked weight loss with the higher dose there was no effect on blood pressure, total cholesterol, or low density lipoprotein cholesterol. Further, there is evidence from animal studies that low dose cannabinoid therapy reduces progression of atherosclerosis,[11] and it has, therefore, been suggested that blocking cannabinoid receptors might actually increase the risk of atherosclerosis.[12] There is biological evidence that blocking cannabinoid receptors might result in demyelination and one participant treated with rimonabant in this trial developed multiple sclerosis.[13] This may have been a chance occurrence, but there is clearly a need to aggressively investigate potential side-effects of all new drugs.

Surgery

In most populations surgery is reserved for morbid obesity [Body mass index (BMI) of 35 kg/m^2 together with obesity related morbidity or BMI of 40 kg/m^2 in the absence of associated morbidity] and is considered when other non-surgical treatments have failed, though there is evidence of extensive use of surgery to reduce weight outside of these criteria in privately funded health care systems. A systematic review identified 26 studies, of which just 5 (2 randomized controlled trials and 3 cohort studies) compared surgery with non-surgical management, with the remaining 21 (all randomized controlled trials) comparing the effectiveness of different surgical procedures to each other.[14] The quality of the studies was noted to be generally poor, with just 3 of the 24 trials having adequate allocation concealment. The authors concluded that '*the limited evidence suggests that surgery is more effective than conventional management for weight loss in morbid obesity. The comparative safety and effectiveness of different surgical procedures is unclear.*'[14]

A population approach to the primary prevention of obesity and its related morbidity and mortality

Obesity is no longer a health problem confined to adults. The prevalence of childhood obesity has increased ~3-fold in most industrialized countries over the last 20 years.[15] In the US, often perceived as an extreme example, around a quarter of all children are overweight or at risk of being overweight.[16] The rest of the developed world is, however, not far behind.[17] Obese children often become obese adults. Childhood obesity increased the risk of adult obesity 4-fold in men and 3.2-fold in women in the British 1958 birth cohort, although child to adult BMI correlations across the range were modest.[18] Among contemporary children and adolescents obesity is associated with elevated blood pressure, dyslipidaemia, glucose intolerance, hyperinsulinaemia, and greater left ventricular mass,[19–23]

though the evidence linking childhood overweight/obesity with adult cardiovascular disease events is weak, perhaps in part because these studies are based on individuals who were born several decades ago at times when childhood obesity was less common.[24,25] Increasingly, frank type 2 diabetes is being diagnosed in obese adolescents.[26,27] Further, obesity and its associated cardiovascular disease risk factors are associated with atherosclerosis in autopsy studies of adolescents and young adults.[28] Thus, there is evidence that obesity in contemporary children and adolescents has already resulted in metabolic and vascular abnormalities that may be long-lasting. As a consequence attempts to treat established obesity in adulthood may be too late to have important impacts on disease prevention or health improvement.

Standard approaches to obesity prevention in children and adolescents

One review of interventions to treat or prevent obesity in children found that, as with adult obesity, there was no strong evidence that interventions to treat obesity in children had long-term benefits in terms of weight loss or associated morbidity.[15] The authors asked '*Why is substantial long-term weight loss so difficult to obtain?*'[15] They concluded that increasing funds were required for research into new behavioural, environmental, and pharmacological approaches for the prevention and treatment of obesity in children, but emphasized that the epidemic of childhood obesity was unlikely to be resolved without concerted political action to detoxify the obesogenic environment in which we live.

A recent Cochrane systematic review identified just 22 controlled (with or without randomization) trials of interventions in childhood and adolescence to prevent obesity.[29] Most were school based and most assessed outcomes over a short time period only. Important methodological weaknesses were noted in many studies, and in particular the authors noted that '*. . .many of the studies included in this review have unit of allocation errors, since allocation was often by institution (e.g. school) but assessment was by individual child. The results of these studies . . .are likely to be misleadingly optimistic.*'[29] Even with this caveat regarding their possible exaggeration of true effects, most studies found that combined promotion of healthy eating and physical activity were not effective at preventing childhood obesity. The impact of these interventions on the adverse sequelae of obesity, such as glucose intolerance, hypertension, and dyslipidaemia, were rarely assessed. While better designed studies of these interventions may provide evidence of effectiveness in terms of both weight control and metabolic and disease outcomes we believe there is also merit in exploring whether brief interventions during key periods of development might have long-term benefits in terms of obesity and obesity related disease prevention.

Critical and sensitive periods for the primary prevention of obesity

Three periods in early life may be particularly important for the development of obesity and its associated morbidity and mortality: the perinatal period; the period of adiposity rebound; and puberty/adolescence.[30,31]

The perinatal period

There is increasing evidence that intrauterine over-nutrition predicts life long obesity.[32,33] According to this hypothesis high maternal glucose, free fatty acid, and amino acid plasma concentrations result in over-nutrition of the fetus which, through permanent changes in appetite control, neuroendocrine functioning, or energy metabolism in the developing fetus, leads to obesity in later life.[32,33] Since maternal obesity itself is associated with insulin resistance and glucose intolerance, and, therefore, higher plasma concentrations of glucose and free fatty acids, maternal obesity is seen as the prime factor in fetal over-nutrition. Recent evidence supports this hypothesis, with two studies demonstrating a relationship between greater weight gain during pregnancy and obesity in the offspring at 2–4 years.[34,35] The consequences of these finding are potentially formidable: '*the obesity epidemic could accelerate through successive generations independent of further genetic or environmental factors*'.[36] The mechanisms of such an association between maternal weight and weight gain during pregnancy and obesity in her offspring are becoming clearer. Offspring of female rats with diet-induced obesity have been found to be heavier than the offspring of rats with the same genotype, but without the diet-induced maternal obesity.[37] *In vitro*, animal and human studies have demonstrated that fetal pancreatic development and fat stores are influenced by the availability of fetal fuels—in particular glucose, lipids, and amino-acids—which are in turn determined by maternal insulin secretion and responsiveness, and maternal plasma levels of glucose and free fatty acids.[33] These *in vitro* findings are confirmed by studies of women with gestational diabetes whose offspring have considerably greater birth weights and a greater risk of obesity and diabetes in later life.[33,38] There is also evidence that these adverse sequelae are not confined to maternal diabetes; rather there is a linear trend of increasing offspring birth weight with increasing maternal gestational glucose concentration across the population distribution.[39]

The long-term follow-up of the offspring of mothers who have been involved in randomized trials of the effectiveness of strict glycaemic control during pregnancy will provide particularly valuable insights into the potential of intervening during this period to improve outcomes in the offspring. In the short term, improved perinatal outcomes have been observed amongst those women with gestational diabetes randomized to intensive glycaemic control vs those on standard care.[40] There were fewer large for gestational age infants amongst those in the intervention group (13% vs 22%, $P < 0.001$) and fewer infants with macrosomia (10% vs 21%, $P < 0.001$). However, these differences may have been largely driven by the shorter period of gestation among the intensively treated group, due mainly to the greater rate of inductions of labour in that group. Nevertheless, long-term follow-up of these infants to determine whether a brief intervention during the intrauterine period has long-term beneficial effects on the offspring in terms of the development of obesity and its associated diseases is important for testing the fetal overnutrition hypothesis and determining

whether a brief intervention during the intrauterine period among this high-risk group has a lasting effect.

Infancy

In normal physiological circumstances, during the first year of life BMI increases rapidly, but then decreases, reaching a minimum usually ~5–6 years of age. This point of minimum BMI has been called the *adiposity rebound*, though would be more accurately termed BMI rebound. Following this nadir, BMI then starts to increase again. Several studies have found that an earlier 'adiposity' rebound (based on the assessment of BMI) increases the risk of later obesity.[41–43] However, the meaning and usefulness of these findings are unclear. BMI is not a true measure of adiposity and other markers of adiposity do not show the same patterns as BMI over early life. Thus, ponderal index (kg/m^3) and percentage body fat both decrease to about age 6 years and remain constant thereafter, whereas triceps skinfold thickness shows two nadirs (at ages 6–8 and 15–17 years).[44] It has also been demonstrated that early age at adiposity rebound predicts later fatness as it identifies children whose BMI centile is high and/or moving upwards across centiles, suggesting that BMI centile crossing or actual BMI in childhood is a more useful measure for predicting later fatness than is age at adiposity rebound.[45] This is consistent with findings from the Bogalusa study, which, although finding an association between early age at adiposity rebound and adult BMI, also noted that BMI at age 7–8 years was a stronger predictor of adult BMI than age at minimum BMI.[46] As age at adiposity rebound can only be determined in retrospect, prevention *per se* is difficult to implement and assess.[44] One could try to identify modifiable risk factors associated with early adiposity rebound, but in one study that aimed to do just that the only independent predictor of early adiposity rebound was parental obesity, which is a known risk factor for offspring obesity.[47]

Several studies have found that breast-feeding is protective against later adiposity, but a recent systematic review and meta-analysis concluded that while mean BMI in later life was lower among breast-fed subjects, the difference was small and likely to have been strongly influenced by publication bias and confounding factors.[48] These conclusions are supported by findings from a large cluster randomized controlled trial of the promotion of breast-feeding,[49] which failed to show marked differences in obesity or cardiovascular disease risk factors in later childhood. Thus, evidence to date does not support infancy as a critical period during which interventions might have long-term effects on the risk of obesity and its associated diseases.

Puberty and adolescence

Puberty is a time of rapid change in size and shape for both females and males. In females earlier age at menarche is associated with obesity, independently of childhood BMI and other potential confounding factors.[50] Puberty is associated with a physiological increase in insulin resistance[51] and is thought to contribute to a peak of incidence in type 1 diabetes at that age. In relation to these changes in insulin metabolism, post-pubertal fat deposition in both females and males tends to be more central rather than general. In addition, behaviours such as dietary patterns and levels of physical activity are largely formed in adolescence and persist into adulthood.[44] Adolescence may also be a critical period for the development of atherosclerosis. Lipid rich deposits (fatty streaks) are found in the aortae of almost all children >3 years of age, irrespective of ethnicity, sex, environment, diet, or later CHD.[28] Consequently, while these lesions may be the seed for atherosclerosis, their relationship to extent of adult atherosclerosis is disputed. Autopsy studies in humans show that late adolescence (i.e. from ~15–19 years) is the key time when fatty streaks convert to raised atherosclerotic lesions.[28] Intriguingly, this also corresponds to the age at which BMI and skinfold thickness increase in young adults who go on to develop the metabolic syndrome,[52] suggesting that the development of nascent metabolic syndrome may be linked to the generation of raised atherosclerotic plaques. By the age of 30, raised atherosclerotic lesions are present in arteries of 1 in 3 adults and are associated with the same risk factors (central adiposity, dyslipidaemia, hypertension, glucose intolerance/insulin resistance, chronic inflammation)[28] that predict diabetes and cardiovascular disease. These data suggest that adolescence offers a therapeutic window with a unique opportunity to modify the risk of future obesity, diabetes, and cardiovascular disease and achieve long-term prevention, perhaps via short-term interventions.

Pregnancy

The role of pregnancy in determining offspring obesity has already been discussed. But in addition, there is increasing evidence that weight gain during pregnancy, and post-partum weight retention, may be an important predictor of the mothers' risk of subsequent obesity and diabetes.[53] It has been proposed that the antenatal period therefore offers a unique period in the life course during which women at risk of future diabetes and cardiovascular disease might be identified, at a time when they might be particularly receptive to health promotion or disease prevention interventions.[53]

Studies of interventions during key developmental periods: proof of concept

The idea that an intervention during a key developmental period can persistently modify risk factors is supported by studies in animal models of human disease. Brief treatment with angiotensin-converting enzyme (ACE) inhibitors[54] or a selective angiotensin II receptor antagonist[55] in young (prior to their development of hypertension) genetically spontaneous hypertensive rats causes a reduction in blood pressure that persists throughout life and is associated with a reduction in target organ damage. In humans, as a result of these findings in animal studies, there are now two on-going trials investigating whether treatment of 'pre-hypertension' with an angiotensin receptor antagonist for a brief period only in young adults (average age ~35 years) may delay or prevent subsequent hypertension: the Trial of Prevention of Hypertension (TROPHY) and the Danish Hypertension Project.[56] Similarly, animal models of type 1 diabetes indicate that intensive prophylactic treatment from weaning to 180 days of life in genetically programmed diabetic mice is effective at reducing the risk of development of

diabetes.[57] In a non-randomized controlled study of non-diabetic school children who had islet cell antibodies (and thus increased risk of type 1 diabetes) brief treatment in childhood with nicotinomide reduced the risk of future diabetes.[58] Similarly, a small trial of prophylaxis with insulin therapy among non-diabetic children with relatives who had type 1 diabetes produced promising results.[59] However, larger randomized trials of these agents have been negative.[60,61] Nevertheless, given the difficulty of establishing the correct therapeutic window, duration of therapy, dose, and agent, these disappointing findings should not curtail attempts to pursue this approach in this and other disease areas.

The future

Data on childhood obesity from the developing world are sparse, but indicate that not only is obesity on the increase but also that obesity co-exists with the long-standing problem of under-nutrition (see, for example, the paper by Andrew Prentice[62] in this themed issue). The impact of interactions between these conditions is not known and difficult to predict. In Asian Indians, long-term adaptation to scarce food supplies has, in times of abundance, resulted in a classically insulin resistant population, with central obesity, dyslipidaemia, glucose intolerance, and cardiovascular disease. Yet, perhaps as a consequence of persistent maternal malnutrition (both under-provision of critical nutrients, and overprovision of obesogenic foods), Indian Asian babies are both short and thin, and are already more glucose intolerant, insulin resistant, dyslipidaemic, and, importantly, have a greater percentage of body fat, than their European counterparts.[63,64] That this population has, in settings of food abundance, one of the highest rates of diabetes and cardiovascular disease in the world, suggests that the intergenerational effect of over-nutrition superimposed on under-nutrition may be particularly toxic. This observation underlines the fact that we must be cautious when extrapolating findings from studies performed largely in Western settings to the developing world, where triggers for obesity and their outcomes may be very different. In addition, in many developing countries, obesity in women is particularly prized as a sign of affluence, and is often achieved at the cost of relative malnutrition for other members of the family. Given the suggested vicious spiral between obesity during pregnancy and childhood obesity, this has potentially dire implications for the likely future patterns of obesity in these countries.

Standard approaches to obesity prevention in the long term have been disappointing. Targeting the prevention of obesity during the key periods of development may be of particular relevance in reducing subsequent risks of adult obesity and associated chronic disease. To our knowledge there are no trials in humans that have examined the long-term effects of maternal glycaemic control during pregnancy on the risks of obesity and associated morbidity in their offspring (to provide causal evidence for the fetal overnutrition hypothesis and to provide evidence on the possible prolonged and long-term benefit of a brief intervention during a critical period of future health) and beyond the trials of school-based health promotion interventions (described above) we are not aware of other trials in adolescence (a possible critical period for the development of obesity, metabolic disorders, and atherosclerosis) that have assessed brief interventions aimed at permanent beneficial effects on obesity and cardiovascular risk factors. It is possible that most investigators feel that the epidemiological evidence is still not sufficiently robust to proceed with such trials. But we feel that the animal studies in hypertension and diabetes discussed above and the progress from these to undertaking trials of brief interventions in young adults offer exciting prospects for the future. Perhaps if we undertake another themed issue of the journal in 10 years time we will be able to report on the benefits of a brief intervention in a critical period of human development on future obesity and health risk.

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