Childhood Obesity – 2010: Progress and Challenges

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Summary

The worldwide prevalence of childhood obesity has increased greatly over the past 3 decades. The increasing occurrence in children of disorders, such as type 2 diabetes, is believed to be a consequence of this obesity epidemic. Much progress has been made in understanding the genetics and physiology of appetite control and from this, the elucidation of the causes of some rare obesity syndromes. However, these rare disorders have so far taught us only limited lessons on how to prevent or reverse obesity in most children. Calorie intake and activity recommendations need to be re-assessed and better quantified, on a population level, given the more sedentary life of children today. For individual treatment, the currently recommended calorie prescriptions may be too conservative given the evolving insight on the "energy gap." Whilst quality of research in both prevention and treatment has improved, there is still a need for high-quality multi-centre trials with long-term follow-up. Meanwhile, prevention and treatment approaches that aim to increase energy expenditure and decrease intake need to continue. Most recently, the spiralling increase in obesity prevalence may be abating for children. Thus, even greater efforts need to be made on all fronts to continue this potentially exciting trend.

Introduction

It has been 8 years since the last Lancet Seminar on childhood obesity.[1] The goal of this Seminar is to review new information relevant to childhood obesity and outline some of the challenges that remain.

Epidemiology

A 2006 review of secular trends in childhood overweight/obesity concluded that its prevalence had increased over the last two to three decades in most industrialized countries except for Russia and Poland and in several lower income countries, particularly in urban areas.[2] The prevalence doubled or trebled between the early 1970's and late 1990's in Australia, Brazil, Canada, Chile, Finland, France, Germany, Greece, Japan, the UK, and the US.[2] It was predicted that by 2010, over 40% of children in the North American and Eastern Mediterranean WHO regions, 38% in the European region, 27% in the Western Pacific region, and 22% in South-East Asian region would be overweight/obese. However, this review predates most recent data, which although it is too soon to be certain, suggests that the increase in childhood obesity in the US, UK and Sweden may be abating.[3–5]

Definition of childhood obesity

There are internationally agreed thresholds of body-mass index (BMI) for defining under-weight, normal weight, overweight, and obesity in adults, but in children, the marked effects of age, gender, pubertal status and race/ethnicity on growth make classification difficult. There are two challenges in defining (i) a standard age-related growth chart; (ii) cut-points for overweight and obesity that are clinically meaningful. The International Obesity Taskforce (IOTF) have developed an international standard growth chart, which enables comparison of prevalence globally.[6] However, many countries continue to use their own country-specific charts, including US, whose standards are based on a national survey from early 1960's, before the current epidemic.[7]

Commonly used cut points for childhood overweight and obesity include: 110% or 120% of ideal weight for height; weight-for-height Z-scores of >1 and >2, and BMI at the 85th, 90th, 95th, and 97th percentiles (based on international or country-specific reference populations). [2] The IOTF recommend using their international growth charts and age and gender specific cut points that, on average, correspond to the adult thresholds. The IOTF classification has been shown to have high specificity but low sensitivity.[8]

Determinants and risk factors for childhood obesity

It is a historical convergence of forces, biological and technological, that has produced the obesity epidemic seen today. Over millennia of frequent food scarcities, natural selection likely favoured those with more parsimonious energy metabolism, known as the "thrifty gene" hypothesis.[9] Although the advent of agriculture about 14,000 years ago ensured stable food supply, activities of daily living still required considerable energy expenditure until about 50 years ago, when radical changes occurred in food availability and required energy expenditures. The current obesity epidemic is then likely the result of our evolutionary legacy interacting with today's technologically-advanced, consumerist society. Population groups in North America who have preserved traditional lifestyles with significant embedded physical activity show considerably lower prevalence of obesity.[10] Likewise, in low and middle income countries the obesity epidemic is largely occurring in urbanized areas with easy access to energy dense cheap foods and less energy requirements in daily life.[2]

More specifically, obesity is a complex condition which is influenced by a wide-range of genetic and non-genetic factors, with interactions between many of these. We focus primarily on current knowledge related to prevention and treatment in this Seminar. Table 1 provides a summary of determinants or risk factors that have been associated with childhood obesity and/or variation in adiposity, with Figure 1 showing a simplified model of the leptin signalling pathway, the key biological pathway that controls energy balance. For several risk

factors, evidence is currently weak and, whilst there have been important advances, it still remains unclear how to incorporate the available information effectively and cost-effectively in prevention programs for children across the world.

Differential diagnosis of childhood obesity

In evaluation of the paediatric patient with obesity, the possibility of endocrine diseases, congenital and acquired hypothalamic defects, genetic syndromes, and usage of medications affecting appetite should be considered (Figure 2). The vast majority of patients, however, will not have any of these identifiable conditions. Regardless of aetiology, all patients should be considered for modifiable lifestyle risk factors and screened for the complications of obesity.

Complications associated with childhood obesity

Childhood obesity can adversely affect nearly every organ system (Figure 3) and often cause serious consequences, including hypertension, dyslipidemia, insulin resistance/diabetes, fatty liver disease, and psychosocial complications.[11] One study showed that being overweight or obese between age 14 to 19 was associated with increased adult mortality (from age 30) from a wide variety of systemic diseases.[12] Atherosclerotic process[13] appears to be accelerated in the obese child and almost half of children with BMI $\geq 97^{th}$ percentile have one or more of the conditions which comprise the metabolic syndrome.[14] Childhood and adolescent BMI is associated with increased risk of cardiovascular disease in adulthood. [15] Pulmonary disorders, including obstructive sleep apnoea and reactive airway disease[16] are seen more frequently among obese children. Asthma severity, however, does not seem to be altered by obesity,[17] leaving open the possibility that weight-related but non-asthmatic airflow limitations are being misdiagnosed as asthma in some obese children.[18]

Certain nutritional deficiencies often accompany childhood obesity. Higher BMI and greater adiposity have been associated with lower vitamin D levels in children.[19] The mechanism underlying hypovitaminosis D in obesity is unclear, but has been proposed to be greater storage of vitamin D in adipose tissue.[20] Overweight/obese children are also at least twofold more likely to be iron-deficient than normal weight children.[21] Obesity leads to increased production of pro-inflammatory cytokines that in turn promote the release of hepcidin, a peptide hormone produced by the liver and adipocytes, which decreases iron absorption from the gut.[22]

Complications of childhood obesity include acceleration in the timing of thelarche and menarche in girls,[23,24] pubertal advancement in boys[25] and adverse effects on maturation[26] and alignment[27] of developing bones in both. Advanced skeletal maturation has been attributed to increased adipose tissue aromatization of weak androgens into more potent estrogens. Obesity may also impact pubertal timing through nutritionally related signals (e.g., insulin and leptin) on the reproductive axis.[28] Orthopaedic complaints, including fractures, musculoskeletal discomfort, impaired mobility, and lower limb malalignment may be more common in obese compared to non-overweight children.[27] Serious orthopaedic complications of childhood obesity include tibia vara (Blount's disease or adolescent bowing of the legs)[29] and slipped capital femoral epiphyses.[30] By contrast, however, obesity may provide some beneficial effect with regards to bone mineral density. A recent study, using variation in the *FTO* gene as an instrumental variable, suggests that greater fat mass in children is causally associated with greater total, spinal, and limb bone mineral content.[31]

Prevention

Prevention, especially in the young, is universally viewed as the best approach for reversing the rising global prevalence of obesity. Despite the seeming allure of prevention, to date there is limited evidence regarding the most effective means of preventing obesity development in children. This may in part be related to relatively small sample sizes for the expected effect size and insufficient length of follow-up in many prevention trials. These trials have also been criticized for frequently not being based on sound theory of behaviour change and for having inadequate feasibility and pilot work.[32]

Past trials of prevention interventions may also have failed to show notable effects in part because they failed to adequately address the "energy gap"[33] that separates those children who remain lean from those who gain weight throughout childhood.[34] Butte and Ellis calculated that an energy deficit of >250 kcal/day is required to prevent further weight gain in 90% of overweight children[35] – equivalent to a child walking an additional 1–2 hours/day at 1.9 km/hour – or consuming roughly one-fifth fewer calories than usual per day.[35]

Prevention is multi-level and measures can be instituted at individual, household, institutional, community, and health care levels:

Individual level prevention

Caregivers would need to be targeted rather than the children themselves at young age, and there may be reasons for focusing on mothers. First, it has been suggested that developmental or foetal over nutrition as a result of gestational diabetes or maternal obesity may have fuelled the current obesity epidemic (see Table 1).[1] To date, there have been no intervention studies that have examined the long-term effect of reducing gestational diabetes or maternal adiposity on future offspring obesity risk. Second, it has been suggested that breast-feeding might prevent childhood obesity. However, systematic reviews suggest that observational associations might be explained largely by residual confounding and/or publication bias, and a large randomized trial of a breast feeding promotion intervention suggested no causal effect of breast feeding on childhood body weight or obesity risk.[36] Third, mother's might influence offspring diet more so than fathers.[37] However, there are no intervention trials of maternal only interventions to prevent childhood obesity.

Household (family) level prevention

Encouraging parents to offer appropriate food portions, foster physical activity, maximize activities of daily living, and minimize sedentary behaviours are viewed as basic measures of prevention.[38] Most government guidelines have traditionally focused on ensuring adequate nutritional intake.[39] However, these may be less useful for assuring energy intakes that are appropriate for contemporary *sedentary* lifestyles. We are unaware of any randomised controlled trials to date that focus solely on household/family based interventions to prevent childhood obesity.

Institutional (nursery or school) level prevention

Most randomized prevention trials have been in the school setting since it is viewed as a universal "encatchment" for children. Most prevention programs involve altering the caloric content of school meals and increasing physical activity. One area hotly debated in the US involves the removal of vending machine from schools to curb the availability of energy dense snack foods. However, a national survey in the US revealed that snack foods from vending machines contributed only 1.3% of total daily calories from snacks, while home snacks contributed 69.1 %.[40] There have been at least 9 systematic reviews of randomised controlled trials of school-based childhood obesity prevention programmes[32,41] (see also

citations of other systematic reviews within these). Earlier reviews noted a lack of evidence of effectiveness and the poor quality of studies; whereas more recent reviews suggest that school based interventions may be effective. A recent review identified 19 high-quality trials of school based interventions and found reduced odds of being overweight or obese in intervention compared to control groups (pooled odds ratio 0.74 (95%CI: 0.60, 0.92).[41] The majority of studies were conducted in the US. There is a need to determine what the key effective characteristics are of such programmes and whether they are effective outside of the US. Although initiatives have also been aimed at children in kindergarten/nurseries,[42] the relatively few controlled trials in this setting have yet to be systematically reviewed. One area yet to be addressed is the built environment of schools/nurseries. Architectural designs of school buildings and their environment can be re-examined for opportunities to impose increased energy expenditure. A multistory building with purposefully designed class schedules could lead to significant stair (or ramp) climbing during the school day.

Community-level prevention

Prevention at the community level includes public policies and mass media campaigns.[43,44] For the past decade, there has been increasing pressure for labelling caloric contents on restaurant menus, especially at fast food restaurants. However, there are limited data regarding the effectiveness of such labelling for preventing childhood obesity.[45] In 2002, the Centers for Disease Control launched a 2-year marketing campaign in the US via media advertisements to promote physical activity in children aged 9–13 years.[46] Children's physical activity (assessed by self-report) increased,[43,44] but effects on BMI were not assessed. Currently, there is a strong movement toward government involvement in several countries for addressing the "toxic environment" by levying taxes on sugared beverages and fast foods, though the effectiveness of such measurements is currently unknown.[47]

The popular media in several countries have given much attention to the topic of obesity, but there is no objective information on the effect of these messages on the public.

Public health surveillance and screening for childhood obesity has been implemented in some communities. In the US, Arkansas was the first state to pass legislation in 2003 for mandatory BMI assessments of children in public schools with annual reporting to parents. This approach has subsequently been followed in thirteen other states.[48,49] In 2005, an annual National Child Measurement Programme was introduced in the UK for *surveillance* of two school year groups. In 2007, the British government introduced legislation to give parents the results of their child's measurements. Evidence to date is unclear as to whether surveillance or screening of childhood obesity will be valuable in its prevention.

Health care settings for prevention

Infants and young children are seen frequently in medical settings for well child and acute care. These visits present a potentially unique opportunity to detect upward deviations in a child's growth rate, thus, placing the primary care provider at the strategic first line of defence before BMI exceeds recommended levels. However, data for the efficacy of such counselling for obesity prevention are lacking.

Critical periods for prevention

Certain periods during childhood present both challenges and windows of opportunity for obesity prevention as they have been observed to be associated with notable changes in adiposity growth velocity or obesity related behaviour. They include the first year of life,[50] the period of "adiposity rebound" (between ages 3–7), and menarche.[51] The transition years from childhood to adolescence are a time of marked behavioural changes, which include a precipitous decline in physical activity.[52] Although it is unclear whether preventive

measures instituted during these times will prevent excessive growth, these should be investigated further.

Discussion on prevention

Common sense supports a key role for decreased energy intake and increased energy expenditure in humans who have adapted through evolutionary processes to a parsimonious energy metabolism. Thus, prevention programs should aim to decrease energy intake, increase activity, and decrease sedentary behaviour. To balance the need for more definitive research on which interventions best achieve changes in these behaviours with the "pressure to act now" to halt and reverse the obesity epidemic, we need to continue with both prevention activities and research to better understand the means of inducing behavioural changes and their impact on childhood obesity.

In closing, for prevention, one might recall the words of Rudolph Virchow, a 19th century German pathologist, who wrote that "epidemics appear, and often disappear without traces, when a new culture period has started" and that mass diseases are "due to … disturbances of human culture."[53] Geoffrey Rose promulgated the notion further that whole populations can be sick (such as the case of obesity), and that political action may be needed to improve population health.[54] Thus, we must continue to seek opportunities for prevention at all levels of society including having responsible public policies to modifying our manner of living since there remain many untapped resources and untried venues.

Treatment of childhood obesity

We recommend that children with BMI $\geq$ 95th percentile or BMI $\geq$ 85th percentile accompanied by co-morbidities of overweight, such as hypertension, hyperlipidaemia, or impaired glucose tolerance be considered for treatment.

Non-pharmacologic treatment

Non-pharmacologic treatment should be the foundation of all obesity treatments, especially in children and should always be considered as Step 1 therapy. A recent systematic review of randomised controlled trials of treatments for childhood obesity identified 64 trials, 54 of which assessed non-pharmacological lifestyle intervention.[55] The 54 lifestyle intervention trials were generally of small sample size (16 to 218 participants), with 70% including fewer than 30 participants. The majority of trials had significant methodological limitations and were of relatively short-term follow-up. Despite these limitations the authors concluded that "*… this review shows that family-based, lifestyle interventions with a behavioural program aimed at changing diet and physical activity and thinking patterns provide significant and clinically meaningful decreases in overweight in both children and adolescents … in the short- and the long-term"* These findings are encouraging and provide a useful guidance for treatment of currently obese children, but they also highlight the need for additional large randomised controlled trials with long term follow-up. The following is a summary of approaches that form the basis of most non-pharmacologic intervention strategies.

Energetics (thermodynamics) of weight reduction

Inducing weight loss requires a catabolic state of stored energy. The latest guidelines from the American Academy of Pediatrics recommend that weight reducing diets contain "less energy than that required to maintain weight but not less than 1200 kilocalories a day."[56] Equivalent UK guidance emphasises energy balance between intake and expenditure but does not specify amounts of intake.[57] Another recommended approach is to construct a diet that is 300–400 kcal/d below weight–maintenance requirements as assessed by dietary

history or as calculated on the basis of a formula relating anthropometry to energy expenditure, such as the Harris-Benedict equation. Given the magnitude of the "energy gap," a sizeable energy deficit would be needed to induce appreciable weight reduction in an obese child, and many of the currently used weight loss diets may be energy neutral in a young child or even lead to weight gain in a sedentary female adolescent.[33,35]

Some guidelines (e.g. UK) and commentators emphasize behavioural strategies that do not specify actual caloric intake amount. A well-conducted randomized trial of behavioural treatment without specified calorie limits showed no effect on BMI.[58,59] The protein-sparing modified fast has a very low calorie regimen (600–800 kcal/day) and appears to be promising, but this concept has not progressed since it was first reported.[60] Transient growth deceleration was observed but growth was normalized by 14 months.[61] However, this was not a randomized trial and had limited follow-up data.

Fostering increased energy expenditure for weight reduction has not received the same attention as dietary prescriptions. We found only one randomized controlled trial of 6–11 year old obese children that compared hypocaloric diet, 90 minutes of moderate exercise 3 days/week, or both. Weight loss was greater in the diet or diet plus exercise group (being similar in these two) than the exercise-only group, but there was no "control" group and follow-up was for just 9-months.[62] Interventions to decrease sedentary activity, such as limiting television viewing, has been examined and shown to be promising.[63]

Macronutrient composition of weight reducing diets

The macronutrient composition of diets has been examined for differential weight loss benefits. Several popular diets such as the Atkin's diet have emphasized increasing protein but not changing the energy content of the diet. Although some studies show greater weight loss with this diet in adults[64–66] long-term studies generally show no difference in weight loss between diets of varying macronutrient contents that do not change total energy intake.[67,68] Demol et al, found no differences in BMI decrease in obese adolescents on different macronutrient diets.[67]

The glycaemic index of diets has also been implicated in weight reduction.[69] Two small, short-term studies of obese adolescents reported greater weight loss on a reduced glycaemic load diet, but the numbers were small and long-term effects are unknown.[70,71]

Behavioural strategies

Strategies to alter dietary habits to a more calorie-reduced intake are based on behavioural principles with Bandura's social cognitive model as the most widely used.[72] It is based on the notion that lifestyle changes succeed through cognitively driven, intentional behaviours such as self-monitoring, goal setting, and rewarding successful change. A widely adopted approach in children uses the "traffic light" system developed by Epstein et al.[73]

Motivational interviewing has been recently advocated as an especially useful technique for those who may not feel ready for change.[74] It is an empathetic "way of being", including reflective listening, shared decision making, and agenda setting.[75] A recent guideline from the American Heart Association recommends motivational interviewing for paediatric weight management.[76] However, the efficacy of this approach versus other behavioural approaches is not known.

Venues for weight reduction programs

Most weight reduction programs are provided by outpatient clinics. One study examined an inpatient intervention and found no evidence of its efficacy.[77,78] Although the school setting has not been regarded as a site for treatment of childhood obesity (as opposed to its prevention), the promising results from a randomized trial of classroom-based weight reduction in obese Mexican-American children suggest that this venue needs further examination.[79] Residential summer camp for obese adolescents has been examined and shown to have short-term efficacy,[80] but long-tem effects after camp remain unknown. Internet intervention for obese adolescents has been examined without promising results to date.[81]

Discussion on non-pharmacologic treatment

In summary, there is urgent need to improve research on non-pharmacologic treatment, especially on the extent of caloric restriction and the effectiveness of increasing energy expenditure. Consensus guidelines for age-appropriate safety monitoring of weight reducing regimens are also needed to ensure appropriate height growth and biologic and social development. Since randomized clinical trials are costly, multi-centre collaborative research with common protocols might be cost-effective and more generalizable. Given the aging populations worldwide and increasing use of technology-intensive medical treatments, allocation of increasingly scarce medical resources will demand more evidence-based information for treatment of childhood obesity. Questions such as how often an obese child should go for dietary counselling will not find ready answers unless better evidence is made available.

Pharmacologic treatment

The recent Cochrane review identified 10 randomised controlled trials of pharmacological treatments for obese children.[55] These trials were largely of small sample size (range 24 to 539 participants, with 60% including fewer than 30 participants), but most were high quality. With one exception, all of the pharmacological treatment trials were in older children/adolescents (minimum age 12 years); the one exception included individuals aged 9–18 years. Trials meeting criteria for pooled meta-analysis included only two drugs: orlistat (a lipase inhibitor that prevents absorption of dietary fat from the gut) and sibutramine (an inhibitor of serotonin, norepinephrine, and dopamine reuptake). The additional effect of orlistat over placebo when given in combination with a lifestyle intervention was a difference in BMI of $-0.76 \, \text{kg/m}^2$ (95% CI: -1.07 to -0.44) at 6 months follow-up. The additional effect of sibutramine over placebo when given in combination with a lifestyle intervention was difference in BMI of $-1.66 \, \text{kg/m}^2$ (95% CI: -1.89 to -1.43) at 6 months follow-up. For long-term outcomes, there has been only one randomized trial of orlistat, which reported a change in BMI of $-0.55 \, \text{kg/m}^2$ with orlistat versus $+0.31 \, \text{kg/m}^2$ with placebo at 12 months (p=0.001),[82] and only one randomized trial of sibutramine, which reported a change in BMI of $-2.9 \, \text{kg/m}^2$ with sibutramine versus $-0.3 \, \text{kg/m}^2$ with placebo at 12 months (p<0.001).[83] Side effects (reported as prevalence in excess of that reported for placebo) of orlistat included oily stool (42%), abdominal pain (11%), faecal incontinence (9%), and new cholelithiasis (2%).[82] Side effects of sibutramine included tachycardia (6%), dry mouth (5%), constipation (4%), dizziness (4%), insomnia (3%), and hypertension (2%). [83] Thus, whilst there is evidence for modest effectiveness of orlistat and sibutramine when combined with lifestyle intervention, treatment with these medications is associated with more adverse effects than lifestyle intervention alone.

Surgical treatment

To date there are no randomised controlled trials of bariatric surgery in children or adolescents.[55] A recent systematic review of observational studies reporting outcome data in patients ≤ 21y (range 9–21y, mean 16.8y) with a minimum of 12 months follow-up identified 4 studies of Roux-en-Y gastric bypass (RYGB, a restrictive and malabsorptive procedure, Figure 4a) and 6 studies of laparoscopic adjustable gastric banding (LAGB, a purely restrictive procedure, Figure 4b) that met inclusion criteria for meta-analysis. [84] For RYGB, the 95% CI for change in BMI compared to baseline was −17.8 to −22.3 kg/m^2 at 1–6.3y follow-up. [84] For LAGB, the 95% CI for change in BMI compared to baseline was −13.7 to −10.6 kg/m^2 at 1–3y follow-up.[84] For RYGB, complications included pulmonary embolism, shock, intestinal obstruction, postoperative bleeding, staple line leak, and severe malnutrition.[84] For LAGB, complications included band slippage/erosion, micronutrient deficiency, port/tube dysfunction, hiatal hernia, wound infection, and pouch dilation.[84] Long-term prospective studies are needed to establish the safety and efficacy of restrictive and malabsorptive procedures and to determine whether reductions in morbidity and mortality outweigh the risks of serious surgical complications and life-long nutritional deficiencies.

Discussion on pharmacologic and surgical treatment

There is a need for large trials that are sufficiently powered to examine long-term effects and that allow direct comparisons of non-pharmacologic, pharmacologic, and surgical treatments. In light of the paucity of data and limited efficacy and unknown risks for long-term medication use, we suggest following the conservative approach, namely to employ pharmacotherapy only in those with BMI ≥ 95th percentile who have significant medical complications of obesity and after a reasonable period of behavioural intervention. The risks of bariatric surgery are considerable, and its long-term safety and efficacy in children remain largely unknown. Therefore, surgery should be reserved for only the most severely obese (BMI ≥ 50 kg/m^2 or BMI ≥ 40 kg/m^2 with significant co-morbidities), and even then, considered with extreme caution.

Conclusion: progress, challenges, and future directions

There has been much progress made in understanding the genetics and physiology of appetite control and from this, the elucidation of the causes of some exceedingly rare obesity syndromes. Much work still remains to be done since these rare disorders have so far taught us only limited lessons about how to prevent or reverse obesity in most children. There is currently no evidence-based, clinically meaningful definition of childhood obesity. Calorie intake and activity recommendations need to be re-assessed and better quantified, at a population level, given the more sedentary life of children today. For individual treatment, the currently recommended calorie prescriptions may be too conservative given evolving insight on the "energy gap." The quality of scientific reports needs to improve to permit comparisons between interventions and pooling of studies. Because obesity is a chronic condition in need of ongoing management, long-term clinical trials are needed to demonstrate safety and efficacy of treatments not only for a few months but over the critical period of active growth and maturation. In children, the safety of treatments needs to be examined as a co-equal outcome to their efficacy.

Despite the challenges that remain, there are glimmers of hope. Recent statistics suggest the prevalence of childhood obesity may be stabilizing in Western countries. All past efforts made in the prevention and treatment of obesity, though not of evident individual notable effect in trials, may still have contributed collectively to this trend.[54] The increased attention

directed to obesity by the media may have helped increase the public's awareness regarding energy balance. The private sector's expanding food product availability and increasing food labelling may have also helped the consumer to make better informed choices. One cannot wait to delineate the complex "causal web" of the obesity epidemic. Unravelling even one thread of the causal web may allow for an important degree of prevention.[85] Thus, prevention efforts should continue at all levels with the goal that the outcome should be greater than the sum of its parts. These efforts should be in tandem with an increased commitment to more robust research.

We anticipate that the next 10 years will be a time of new discoveries and collective societal actions that will help eliminate this scourge of the new millennium.

Acknowledgments

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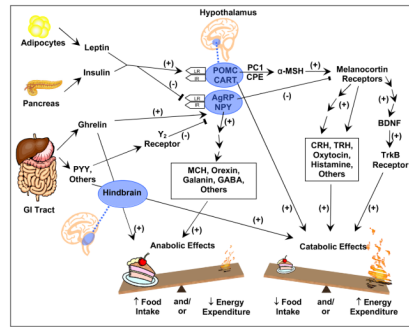
Figure 1. A simplified model of the leptin signalling pathway

Since the discovery of leptin, understanding of the mechanisms that control energy balance has rapidly advanced. Unfortunately, except for leptin replacement therapy in a handful of leptin deficient individuals, there is yet to emerge any interventions that effectively prevent or treat obesity in the general population. Both insulin and leptin are secreted in proportion to body fatness and serve as adiposity signals, acting on the same neurons of the hypothalamic arcuate nucleus to regulate energy homeostasis. Ghrelin, which is secreted by the stomach and duodenum, serves as a hunger signal at the hypothalamus and brainstem, while other peptides secreted by the GI tract, including PYY, act as satiation signals. The ligands leptin,[120] POMC, [121,122] CART,[123] and BDNF,[91,124] the receptors for leptin, [125,126] melanocortins,[127–130] and BDNF,[131] and the enzyme PC1[132,133] have been found to have function-altering mutations associated with obesity in children. Mutations in the ligands and receptors for NPY,[134] AGRP,[135] CPE,[136,137] and MCH[138] have been found to alter energy balance in rodents, but have not been as convincingly shown to be associated with human obesity. Lines with arrowheads indicate stimulatory action. Lines ending with a perpendicular end-block indicate inhibitory action. Abbreviations: GI, gastrointestinal; PYY, peptide YY, IR, insulin receptor; LR, leptin receptor, NPY, neuropeptide Y; AGRP, agouti-related protein; POMC, pro-opiomelanocortin; CART, cocaine-amphetamine related transcript; PC1, prohormone convertase 1; CPE, carboxypeptidase E; MSH, melanocyte stimulating hormone; TRH, thyrotropin-releasing hormone; MCH, melanin concentrating hormone; GABA, gamma amino butyric acid; BDNF, brain-derived neurotrophic factor; TrkB, tyrosine kinase receptor B.
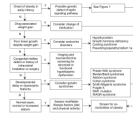
Figure 2. Recommended evaluation of childhood-onset obesity
The clinical history and examination of the patient should guide the care provider in forming a differential diagnosis. Onset of marked obesity during early infancy raises the suspicion for function-altering genetic mutations affecting the leptin signalling pathway, but these are exceedingly rare conditions, with the most common, melanocortin-4 receptor defects, comprising <5% of children with early-onset obesity.[130] When evaluating new onset of excessive weight gain, potential side effect from a recently initiated medication should be taken into consideration, as weight gain may be associated with administration of insulin or insulin secretagogues, glucocorticoids, hormonal contraceptives (e.g., depot medroxyprogesterone acetate), psychotropic medications (including atypical antipsychotics (e.g., clozapine, olanzapine, risperidone), mood stabilizers (e.g. lithium), tricyclic antidepressants (e.g., amitriptyline, imipramine, and nortriptyline), and anticonvulsants (e.g., valproic acid, gabapentin, and carbamazepine)), antihypertensives (e.g., propranolol and clonidine), and antihistamines.[139] In patients with decreased growth velocity despite continued weight gain, an endocrinopathy should be considered; measurement of TSH and free T4, and referral to a paediatric endocrinologist are recommended. All patients, regardless of the aetiology of obesity, should be assessed for modifiable lifestyle factors, including physical activity and diet, and screened for complications of obesity, including measurement of fasting lipids, fasting glucose, and alanine amino transferase. If fasting glucose is 100 – 126 mg/dL, an oral glucose tolerance test is recommended. Screening for vitamin D and iron deficiency should also be considered.
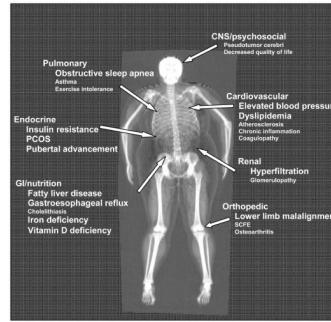
Figure 3. Complications associated with childhood obesity
Image obtained by dual energy X-ray absorptiometry from a teenage girl with BMI 38 kg/m^2. Conditions that are of high prevalence and are well-established in their association with childhood obesity are shown in larger font size.
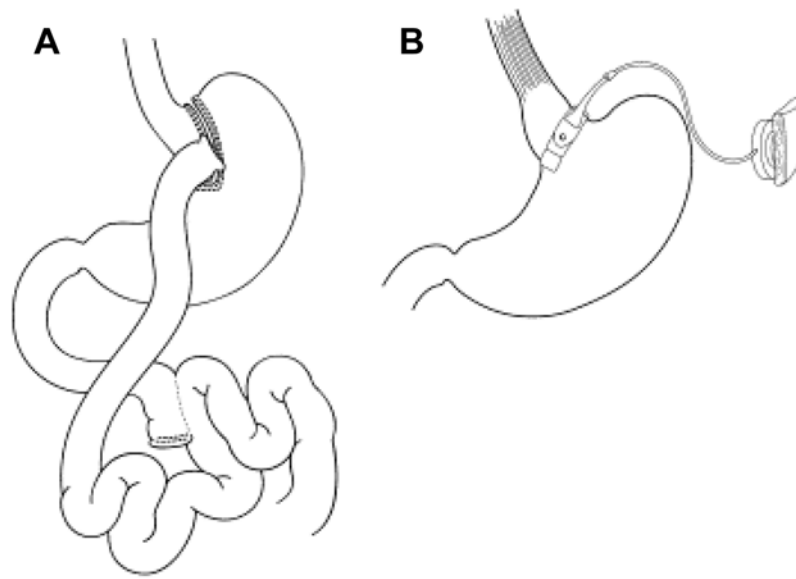
Figure 4. Operations performed for weight loss
(A) Roux-en-Y gastric bypass, (B) Adjustable gastric band. (Reprinted from Inge TH, Zeller MH, Lawson ML, Daniels SR. A critical appraisal of evidence supporting a bariatric surgical approach to weight management for adolescents. *J Pediatr* 2005;**147**(1):10-9 with permission from Elsevier Limited.)[140]

Table 1

Determinants or Risk Factors for Development of Childhood Obesity or Greater Adiposity

Risk factor	Nature of association	Currently potentially modifiable	Type of evidence*
Genetic variation	Rare single gene defects in which obesity is the specific abnormality, e.g. those related to the leptin signaling pathway (Figure 1).	No, except for leptin replacement in the handful of leptin-deficient individuals	Basic science studies, case series, family linkage, and genetic-association studies[86]
	Obesity is a manifestation of several genetic syndromes (Figure 2). Prader-Willi syndrome is associated with hyperghrelinemia, but the mechanism of hyperphagia remains unclear.[87,88] Animal models of ciliopathies (Bardet-Biedl and Alstrom syndromes) have defects in leptin pathway signaling.[89,90] Haploinsufficiency of BDNF, a downstream mediator of leptin action, is associated with hyperphagia and obesity in children with WAGR syndrome.[91]	No	Genetic-association studies[86]
	Genome wide association studies have identified several common genetic variants associated with greater adiposity and obesity; each with weak/modest effects.	No	Genome wide association studies[92]
Epigenetics	The mechanism whereby in utero factors (see below) can produce heritable changes in adiposity has been suggested to be due to DNA methylation or histone modification of DNA in gene regulatory regions. However, evidence from humans is currently lacking.	Possibly, in animals, maternal consumption of folate, methionine, and vitamin B12 during pregnancy can affect DNA methylation in offspring	Non-systematic review of evidence (largely from basic science and animal studies)[93]
Endocrine disease	Classically, hypothyroidism, growth hormone deficiency or resistance, and cortisol excess. Polycystic ovarian syndrome (PCOS) is a consequence of but also possible contributor to obesity. The obesity associated with pseudohypoparathyroidism (caused by Gα_s inactivating mutation) may be due to defective signaling at G-protein coupled receptors, including the melanocortin receptor of the leptin pathway.[94]	Some, e.g. thyroxine and growth hormone replacement, surgical treatment of Cushing syndrome; for PCOS, oral contraceptives, anti-androgens, and insulin-sensitizers have been used, but long-term large RCTs lacking in adolescents[95]	Non-systematic review of evidence (basic science, epidemiology, clinical)[96]
Central nervous system pathology	Congenital or acquired hypothalamic abnormalities have been associated with a severe form of obesity in children and adolescents.	Possibly, but still under investigation; hyperinsulinemia due to increased vagal tone has been postulated as a contributing factor prompting studies using octreotide, which prevented further weight gain in a small RCT, but long-term larger RCTs are needed.[97]	Non-systematic review of evidence (basic science, epidemiology, clinical)[98]
Intrauterine exposure to gestational diabetes	In populations at high risk of obesity and diabetes (e.g. Pima Indians) exposure to gestational diabetes is associated with increased risk of childhood and early adult obesity in offspring. Evidence for similar associations in other populations is currently lacking.	Yes	Review of observational studies in Pima[99] Prospective cohorts in other populations[100] (and other studies cited in this reference)
Intrauterine exposure to greater maternal adiposity	A study comparing obesity in children whose mothers had received bariatric surgery for extreme morbid obesity found siblings born before surgery (when mother was extremely obese) were more obese than their siblings born after weight loss in response to surgery. Evidence that less extreme variation in maternal adiposity affects offspring obesity is lacking.	Yes	Within sibling comparisons,[101] prospective cohort studies,[99,102] and Mendelian randomization study[102]
Birth weight	Higher birth weight is associated with increased offspring fat and lean mass. Small-for-gestational age babies who exhibit catch-up growth may	Safe means of modifying birth weight to improve health are unknown	Prospective cohort studies[50,103]

Risk factor	Nature of association	Currently potentially modifiable	Type of evidence[*]
	be at risk for childhood obesity, but this may simply reflect greater growth resulting in larger size.		
BMI rebound	Early age at BMI rebound is associated with greater risk of obesity, but this may be statistical artifact.	No, since can only be determined retrospectively in individuals	Non-systematic review of largely prospective cohort studies[104]
Diet	Breast feeding is unlikely to be causally protective of childhood obesity.	Yes	Systematic review of prospective cohort studies,[105] RCT[106]
	High quality prospective evidence is sparse. Available evidence suggests that high energy intake in early infancy and high consumption of sweetened drinks in childhood is prospectively associated with childhood obesity risk. Lack of evidence for other dietary characteristics may reflect poor study design and difficulties of accurately assessing diet in children.	Yes	Non-systematic review of observational studies[107]
Energy expenditure	Low levels of physical activity are associated with childhood obesity risk.	Yes	Systematic review of observational studies[108]
Television viewing	Greater hours spent screening viewing associated with childhood obesity risk.	Yes	Systematic review of observational and experimental studies[109]
Sleep	Shorter sleep duration in infancy and childhood associated with childhood obesity risk.	Possibly	Prospective cohort study[110]
Microbial infection	Potential role of microbial infection (*e.g.* adenovirus Ad-36) and composition of gut flora (*e.g.* ratio of *Firmicutes* to *Bacteroidetes* species) in the pathogenesis of obesity. However, epidemiological evidence in the non-selected general population is lacking.	Yes	Cross-sectional studies [111,112]
Iatrogenic	Cranial irradiation or surgery causing hypothalamic damage (see above). Psychotropic medication (e.g., olanzapine and risperidone), chemotherapeutics (e.g. treatment acute lymphocytic leukemia even without cranial irradiation), and hormonal contraception (e.g., depot medroxyprogesterone acetate) have been associated with greater weight gain in children and adolescents.	Depends upon disease/treatment and risk-benefit considerations	Non-systematic review of evidence (basic science, epidemiology, clinical)[98] and prospective cohort studies[113_115]
Ethnic origin	Some ethnic groups, e.g. Hispanic and South Asian, appear to be more likely to become obese. At a given BMI children and infants of South Asian origin have higher adiposity.	No	Cross-sectional studies[116,117]
Country of birth	Children from low and middle income countries tend to be stunted and underweight but with sufficient nutrition gain healthy weight and with overnutrition are prone to obesity.	No	Cross-sectional and ecological studies[118]
Urban versus rural area of residence	Children in urban areas are more likely to be obese than those in rural areas in many countries including high and low-middle income countries.	Unlikely to be able to change where families live but may be able to modify underlying reasons for association	Cross-sectional studies[2]
Socioeconomic position	In high income countries generations born prior to 1950's–1960's did not show socioeconomic differentials in adiposity/obesity in childhood (though do as adults). Some evidence that contemporary populations of children do show higher rates of obesity in those from lowest socioeconomic groups in high income countries.	Yes with major political and cultural changes. May be able to modify the underlying reasons for association	Prospective two-generational cohort study[119]

*
The most recent systematic review of highest level of evidence is cited for most risk factors rather than providing a comprehensive list of all papers for each risk factor which would be beyond the scope of this seminar.

Abbreviation: RCT, randomized controlled trial. This table has been modified and updated from a similar table published previously.[4]