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## CHILDHOOD OBESITY

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### Clinical summary

Childhood obesity has important consequences for health and wellbeing both during childhood and also in later adult life. The rising prevalence of childhood obesity poses a major public health challenge in both developed and developing countries by increasing the burden of chronic non-communicable diseases. Despite the urgent need for effective preventative strategies, there remains disagreement over its definition due to a lack of evidence on the optimal cut-offs linking childhood BMI to disease risks, and limited evidence on the most effective components of interventions to prevent childhood obesity. This article reviews the trends in childhood obesity, its genetic, nutritional and other risk factors, and preventative and treatment strategies. Particular emphasis is given to early-onset obesity in pre-school children, which, as a precursor to later childhood and adult obesity, provides insights into the developmental and genetic origins of obesity and also offers the potential for early preventative approaches with long-lasting benefits.

### Prevalence and trends

The prevalence of childhood obesity has almost tripled in US children and adolescents since 1980 <sup>1</sup>, suggesting that it may be increasing at a faster rate than adult obesity with major implications for the population's future health. The proportion of children in the highest percentiles of BMI has seen the most rapid increase. In some western settings such as the US, Western Europe, Australia and Japan, recent data suggest that levels of childhood obesity may have reached a plateau in the last decade (Figures 1 and 2) <sup>1-4</sup>. Even if this were the case, the prevalence of both childhood and adult obesity remains very high and understanding and managing the burden of childhood obesity presents a resilient challenge. Furthermore, the trends may be continuing among children from more disadvantaged social conditions <sup>5</sup> and among those from certain ethnic backgrounds. In the US, between 1971-1974 and 1999-2002 the prevalence of 6- to 11-year olds with a BMI > 95<sup>th</sup> percentile increased by 5-fold (4% to 20%) among black children compared to 3-fold (4% to 13%) among white children, with intermediate rates of increase seen in Mexican-American children.

Increases in obesity levels have been observed even in very young preschool children and are predicted to continue. Based on an analysis of 450 nationally representative surveys from 144 countries, the World Health Organisation (WHO) estimated that the prevalence of children below age 5 years old with a BMI > +2 SD (equivalent to the 98<sup>th</sup> percentile) increased from 4.2% in 1990 to 6.7% in 2010, and is expected to reach 9.1% in 2020 <sup>6</sup>.

#### Disclosures

No conflicts to disclose

Estimates in 2010 were higher in developed (11.7%) rather than developing countries (6.1%), although the relative changes in prevalence have been higher in developing countries, and particularly in African countries (Figure 3) <sup>6</sup>. Nationally, there was wide variation in the prevalence of BMI > 98<sup>th</sup> centile in preschool children; the highest rates were seen in countries such as Albania, Bosnia and Herzegovina, and Ukraine, with prevalences >25% in the most recent surveys. In the US, based on the National Health and Nutrition Examination Survey 1999-2004, 8.3% of under-5 year-olds had a BMI > 98<sup>th</sup> centile using the same WHO reference <sup>7</sup>. These worldwide trends in very young children are dramatic and have raised debate as to whether we can and should diagnose obesity even during infancy <sup>8</sup>.

## Health consequences

### Adult obesity & disease

There is strong evidence that childhood obesity leads to adult obesity and its related comorbidities <sup>9</sup>. Furthermore, many obese children continue to progress in their severity of obesity. In the US National Longitudinal Study of Adolescent Health, nearly 40% of obese adolescents (BMI > 95<sup>th</sup> percentile) became severely obese (BMI > 40 kg/m<sup>2</sup>) by age 30 years, compared to less than 5% of normal weight teenagers <sup>10</sup>. In a recent study of Pima Indians in Arizona US, those with the highest quartile of childhood BMI had double the incidence of death from endogenous causes in adult life compared to those in the lowest childhood BMI quartile (incidence-rate ratio 2.3 [1.46-3.62]) <sup>11</sup>. In the US Bogalusa Heart Study, overweight during adolescence was associated with an 8.5-fold increase in hypertension, a 2.4-fold increase in the prevalence of high total serum cholesterol levels, a 3-fold increase in high LDL cholesterol levels and an 8-fold increase in low HDL cholesterol levels as adults aged 27–31 years <sup>12</sup>. In a study of 276,835 Danish schoolchildren, childhood BMI at ages 7-13 years was positively associated with fatal and non-fatal CHD events during adulthood <sup>13</sup>. The associations were linear at each age indicating that the risk of CHD increases across the entire BMI distribution. Furthermore, the effect of BMI increased with increasing age of the child, and adjustment for birth weight strengthened the results, suggesting that postnatal gains in weight or adiposity may explain these links <sup>13</sup>. There is also evidence that childhood obesity may increase adult morbidity and mortality independently of adult BMI and other confounding factors such as family history of cardiovascular diseases or cancer and smoking <sup>14</sup>.

### Childhood comorbidities

The need to tackle childhood obesity lies not only in the avoidance of poor adult health. Childhood obesity leads to many acute health problems and much suffering during childhood (Figure 4). Therefore parents, healthcare providers and policy-makers should be clearly impressed upon that prevention of childhood obesity is an important outcome in its own right. These BMI-related childhood and adolescent outcomes include type 2 diabetes, hypertension, early puberty, menstrual irregularities and polycystic ovary syndrome, steatohepatitis, sleep apnoea, asthma, benign intracranial hypertension, musculoskeletal disorders and psychological problems <sup>15</sup>. A recent systematic review also found strong evidence for type 1 diabetes as a consequence of childhood obesity; that review identified 9 studies, comprising 2658 type 1 diabetes cases, where the assessment of childhood obesity preceded the diagnosis of diabetes <sup>16</sup>. Some of the consequences of obesity, such as type 2 diabetes, hypertension and hyperlipidemia, were previously only seen in adults, but are now frequently observed in obese children in some populations. For type 2 diabetes the younger age at onset of disease not only prolongs the duration of the disease, but is associated with a more advanced rate of progression to beta cell failure <sup>17</sup> and is likely to lead to earlier

presentation of adult life complications such as cardiovascular disease<sup>18</sup>, kidney failure, visual impairment and limb amputations<sup>19</sup>.

Furthermore, childhood obesity can severely influence quality of life via its impact on social and psychological functioning, having been linked with low self-esteem and depression<sup>20</sup>, as well as educational attainment and interpersonal relationships<sup>21</sup>. It is plausible that the causal relationships between many of these obesity-related complications are bi-directional; adverse health, stress or poor psychosocial functioning could lead to sedentary lifestyles and subsequent greater BMI.

## Definition

Obesity is defined as a condition of '*excess body fat which creates increased risk for morbidity and/or premature mortality*' and the adult BMI thresholds 25 and 30 kg/m<sup>2</sup> for overweight and obesity respectively are based on prospective associations between BMI in middle- to late-aged adults in relation to their subsequent mortality<sup>22</sup>. In contrast, there is little consensus as to the best way to operationalize this definition in children.

In many countries, including in the US since 2010<sup>23</sup>, childhood obesity is defined as a BMI above the 95<sup>th</sup> percentile for age and sex (and >85<sup>th</sup> percentile for overweight), however there is a wide range of reference BMI charts available. In contrast, the WHO and UK use statistical based cut-offs corresponding to number of standard deviations above the median. The WHO uses a BMI > +2 SD, which is equivalent to the more extreme 98<sup>th</sup> percentile, to define overweight, while in the UK this same threshold is used to define obesity in clinical practice settings, because 91<sup>st</sup> and 98<sup>th</sup> percentile lines are typically displayed on growth charts, rather than the 85<sup>th</sup> and 95<sup>th</sup> percentiles<sup>24</sup>. A third approach was proposed by the International Obesity Task Force (IOTF) based on identifying the childhood BMI thresholds that correspond with adult definitions. Reference charts were created from international data on 97,876 boys and 94,851 girls from Brazil, America, the UK, Hong Kong, Singapore and the Netherlands. BMI percentile lines were drawn from 2-18 years that pass through the adult overweight and obesity BMI cut-off points of 25 and 30 kg/m<sup>2</sup> at age 18 years<sup>25</sup>. These IOTF criteria are the most stringent of all the current definitions of childhood obesity because relatively few 18 year olds have such high BMI levels, and the IOTF threshold for childhood obesity is roughly equivalent to the 99<sup>th</sup> percentile...

Some may consider that stringent BMI thresholds for childhood obesity are more appropriate in order to better identify those children at highest risk of co-morbidities. However, while the use of higher BMI thresholds will increase specificity and positive predictive values, this should be balanced against the inevitable increase in the likelihood of false negatives (i.e. children with BMI below the 99<sup>th</sup> percentile but who are still at increased risk for obesity-related comorbidities). Currently there are little data on the true shape of the association between childhood BMI and any important child health outcomes to inform the optimal prediction thresholds.

## Childhood risk factors

While the core of the problem of obesity can be simply stated as an imbalance between energy intake and energy expenditure over a prolonged period, the factors behind this are complex. The UK Foresight report described obesity as a '*complex web of societal and biological factors that have, in recent decades, exposed our inherent vulnerability to weight gain*'. That report presented an obesity system map with energy balance at its centre being influenced by over 100 variables acting at the individual, household, community or wider societal levels<sup>26</sup>.

A description of these wide-ranging childhood risk factors is well beyond the scope of this article, and we refer the reader to recent systematic reviews that describe the evidence for a number of individual-level lifestyle factors that affect the energy intake-energy expenditure balance have been shown to have been associated with childhood weight gain and obesity in school-aged children, including the intakes of sugar-sweetened beverages<sup>27</sup>, dietary fat<sup>28</sup>, dietary energy density<sup>29</sup>, physical activity<sup>30</sup>, sedentary behaviours<sup>31,32</sup>, and short sleep duration<sup>31</sup>. In a review of prospective studies, the authors concluded that these classical individual-level lifestyle risk factors do seem to play a role in the development of obesity in school-age children and adolescents, and that the most consistent evidence was for sugar-sweetened beverages<sup>28</sup>. They also commented on the value of studying new risk factors such as short sleep duration, chronic inflammation, anxiety, depression, and behavioural problems as potential targets for future interventions in this age group<sup>28</sup>.

## Early life and inter-generational factors

Considering the rapid rise in prevalence of early-onset obesity in pre-school children, and its links to later childhood and adult obesity, particular attention should be paid to identifying the early life risk factors for obesity with a view to developing strategies for the early prediction and prevention of obesity.

### Birth weight and antenatal factors

There is consistent evidence from large cohort studies of a linear and positive association between birth weight and later life BMI, and this may be equally attributable to correlations with adiposity and lean mass<sup>33</sup>. Furthermore, maternal obesity, gestational weight gain and glycaemia during pregnancy are positively associated with offspring obesity and metabolic disorders<sup>34,35</sup>. Such intergenerational associations may be explained by genetic transmission and shared postnatal environment. In addition, animal models show long-term 'programming' effects of antenatal exposure to maternal diet, and indirect support for this in humans comes from a study of pre-pregnancy bariatric surgery which was associated with a 52% lower risk of offspring obesity<sup>36</sup>.

In contrast to the *positive* birth weight associations with obesity, studies of the major comorbidities of obesity generally report *inverse* birth weight associations. For example, each 1 kg higher birth weight was associated with a 10-20% lower risk of ischaemic heart disease<sup>37</sup>, and with a 1.5 mmHg lower systolic blood pressure in men and 2.8 mmHg lower in women<sup>38</sup>. A meta-analysis of the association between birth weight and type 2 diabetes identified increased risks associated with both low (<2.5 Kg, odds ratio 47% higher) and high birth weights (>4 kg, odds ratio 36% higher) compared to the reference group (birth weight 2.5-4 kg)<sup>39</sup>.

These contrasting associations with both low and high birth weight might be explained by the co-existence of two separate early life pathways to obesity and later metabolic disease.

### The 'thrifty' or 'mismatch' pathway

Barker and Hales proposed that the relationship between low birth weight and later disease susceptibility was a result of fetal adaptations, such as insulin resistance, to survive antenatal undernutrition, but which were then inappropriate in the face of a subsequent affluent postnatal environment<sup>40</sup>. To better explain why they should persist into postnatal life, Gluckman and colleagues proposed that these adaptations were 'predictive adaptive responses'; i.e. that the fetus exposed to poor nutrition anticipates a similar harsh postnatal environment<sup>41</sup>. These responses include: a preference for a high-fat diet, hyperphagia, less investment in muscle mass and greater deposition of visceral adipose stores. The term '*thin-fat baby*' has been coined to describe this phenotype in some South Asian babies, and which

is exacerbated by an obesogenic childhood environment<sup>42</sup>. Thus later life obesity and metabolic risk may be determined by the mismatch between the intrauterine and subsequent postnatal environment<sup>41, 43</sup>.

### The 'early life hyper-nutrition' pathway

The second proposed developmental pathway to obesity follows the effects of hypernutrition during fetal and/or early postnatal life. Maternal hyperglycemia leads to increased glucose transport across the placenta, and in turn leads to increased insulin secretion by the fetal pancreas. Insulin is adipogenic in late fetal and infant life, and probably increases both fat cell number and content<sup>44</sup>. Increased fetal adipogenesis is believed to underlie the macrosomia observed in infants of diabetic mothers<sup>45</sup>. The relevance of this pathway may be of increasing importance in settings of rising maternal obesity, gestational weight gain and hyperglycemia.

### Weight gain during infancy

Infancy is the period of life with the highest rates of weight gain, both in absolute terms (approximately 6 kg in the first year) and also relative to body size (the average infant triples in size during the first year). Faster infancy weight gain is consistently associated with increased risk of childhood and adult obesity, and there is increasing evidence from randomised controlled trials to support the existence of long-term 'programming' effects of infant nutrition and weight gain on later obesity and obesity-related diseases<sup>46</sup>.

Overall, there appears to be a two- to three-fold increase in childhood obesity risk in those infants who cross upwards through at least one major weight centile band on their growth chart (e.g. 2<sup>nd</sup> to 9<sup>th</sup> or 9<sup>th</sup> to 25<sup>th</sup> centile etc.), which is equivalent to a gain in weight z-score > 0.67, between birth to age 1 year (Figure 5)<sup>47</sup>. In a meta analysis of 7 studies, this rapid early growth pattern also predicted adult obesity up to age 66 years<sup>47</sup>. In addition to higher BMI, rapid infancy weight gain is associated with greater total adiposity, central adiposity, and higher metabolic syndrome risk markers in young adults<sup>48-50</sup>.

In historical cohorts, being thin at birth and thin until around age 2 years, but then showing rapid childhood weight gain after this period, was associated with increased risk for later cardiovascular disease<sup>51</sup> and impaired glucose tolerance<sup>52</sup>. In contrast, in a contemporary cohort, rapid weight gain (> 0.67 z-score) within the first 3 months of life had an even greater influence on markers of cardiovascular disease and type 2 diabetes in early adulthood compared to a similar rate of rapid weight gain spread over the first 12 months of life<sup>50</sup>. Hence both the degree and timing of infant and childhood weight gain may be important in conferring later disease risk.

### Infant nutrition

In most developed settings, formula milk fed infants are heavier and grow faster than breastfed infants. Indeed, these early growth differences form the rationale for the WHO 2006 International Growth Standard for 0-5 year old children, which is based on predominantly breastfed children<sup>53</sup>. Accordingly most observational studies report that obesity risk at school age is 15-20% lower in breastfed compared to formula milk-fed infants<sup>54</sup>. Systematic reviews have also shown that breastfeeding is associated with a lower risk of type 2 diabetes<sup>55</sup>, lower cholesterol levels<sup>56</sup> and blood pressure<sup>57</sup> in adulthood. However, breastfeeding is strongly socially patterned and is associated with other healthy behaviours and therefore it is possible that observational links between breastfeeding and better health outcomes are confounded by these and other unmeasured factors<sup>58</sup>. A randomised controlled trial of breastfeeding promotion found no effect on childhood

obesity<sup>59</sup>, however in that setting breastfed infants were heavier than formula milk fed infants, which could explain the lack of protection against childhood obesity.

Among formula milk fed infants, higher intakes of milk and other sources of energy are positively associated with infancy weight gain and childhood BMI<sup>60</sup>. Indeed, as a percentage of total energy intake, the energy demands for growth are substantially higher during infancy than during later childhood. Energy deposition as a percentage of total energy requirements decreases from: 40% at 1 month, to 17.5% at 3-6 months, 6% at 6 to 12 months, 3% at 12 months, 1-2% from 12 months until mid-adolescence, and gradually disappears by 20 years of age<sup>61</sup>. Therefore infancy weight gain is more closely related to energy intake, than is weight gain in childhood or in later life.

A few studies have investigated the role of age at introduction of complementary foods (weaning) in childhood obesity. The evidence suggests that complementary foods displace milk intakes, with no clear effect on energy intake or obesity risk<sup>62</sup>. Furthermore reverse causality cannot be ruled out because infants who gain weight rapidly are more likely to be weaned earlier<sup>63</sup>.

## Genetic factors

### Monogenic obesity

Over the last 15 years, profound insights into the biological regulation of appetite, food intake and weight gain have been gained by identifying and characterising the rare genetic mutations in individuals and families with extreme obesity. Deleterious mutations have been detected in genes encoding leptin, the leptin receptor, pro-opiomelanocortin, melanocortin-4 receptor, and brain derived neurotrophic factor<sup>64</sup>. Other causes of severe monogenic obesity associated with hyperphagia and disorders of learning and behaviour arise due to large chromosomal deletions<sup>65</sup>. It is noteworthy that many of these advances in the understanding of the genetics of obesity have been achieved through studies of extremely obese children with early-onset obesity, and this possibly reflects stronger effects of these rare mutations on BMI gains in children than in adults<sup>66, 67</sup>.

### Common genetic variants

Advances in understanding the polygenic basis of common obesity and normal variations in BMI have only occurred much more recently. Genome-wide association studies (GWAS) in large-scale population-based studies have identified several common genetic variants that are robustly associated with adult BMI and obesity. The first BMI locus was found in the *FTO* locus in 2007, followed by *MC4R* in 2008, and loci in or near to *TMEM18*, *SH2B1*, *KCTD15*, *MTCH2*, *NEGR1*, *BDNF*, *SEC16B*, *GNPDA2* and *ETV5* in 2009 and 18 further loci in 2010<sup>68</sup>. While the focus of those studies was on BMI or obesity in adult populations, those reports also showed that several of these variants showed significant associations with childhood BMI<sup>68, 69</sup>. Indeed, recent follow-up studies have reported that most of these variants have comparable effect sizes in children and adolescents compared to adults, in terms of age standardised BMI Z-scores (Figure 6)<sup>70</sup>.

Other studies have explored longitudinal BMI and growth associations with these BMI loci. In the prospective 1946 British Birth Cohort, associations between the *FTO* and *MC4R* variants and BMI and body weight loci strengthened during childhood and adolescence, peaked at age 20, and then weakened into adulthood<sup>71</sup>. In larger studies, the *FTO* variant has a surprising inverse association with infancy BMI; rather it confers an earlier adiposity rebound in early childhood and subsequent higher childhood BMI<sup>72</sup>, but then appears to have no further positive effect on weight gain during adult life<sup>73</sup>. In combination, the GWAS obesity variants appear to have little influence on birth weight, but promote more

rapid weight gain and growth from even the earliest weeks of postnatal life, and prevent against risks of underweight and failure to thrive, which may point to a potential evolutionary advantage of genetic obesity susceptibility<sup>74</sup>. These findings of the childhood timing of action of genetic mutations and common variants are supported by the observation that the heritability of BMI changes with age, increasing with age in childhood and decreasing with age in adults, and in general is higher in children than in adults<sup>75</sup>.

With regard to its mechanism of action, the obesity susceptibility variant at *FTO* has been associated with increased dietary energy intake in children<sup>76</sup> and associated traits, such as lower levels of satiety<sup>77</sup> and a greater intake of dietary fat<sup>78</sup>. However there is some discordance with the results of animal models which highlight a role of *FTO* in the regulation of energy expenditure<sup>79</sup>. While the use of further genomic approaches hope to explain substantially more of the heritability of BMI, the current findings are already helping to direct new avenues of research into the biological regulation of body weight<sup>79</sup>.

## Prevention

In 2010, Michelle Obama launched the 'Let's Move' childhood obesity prevention campaign in the US, with the aim to '*solve the childhood obesity problem within a generation*'. In 2009, the UK government set a target to reduce the proportion of overweight and obese children to 2000 levels by 2020<sup>80</sup>. Such ambitious targets require health and education policies that are based on well-evidenced intervention components.

## Interventions in school-age children

Schools have been a popular setting for obesity intervention, as they offer continuous and intensive contact with children. School infrastructure and physical environment, policies, curricula and staff all have the potential to positively influence knowledge and lifestyle. A recent systematic review found strong evidence for beneficial effects of childhood obesity prevention programmes based on 27,946 children and adolescents in 37 studies<sup>81</sup>. A large majority of the identified studies were based in school settings among children aged 6-12 years old and these appeared to be more effective in reducing BMI (mean change in BMI z-score: -0.17; 95% CI: -0.25 to -0.09) than studies that took place in non-educational or mixed settings (-0.07; 95% CI: -0.24 to 0.10). The most promising school-based intervention strategies were: inclusion of teaching on healthy eating, physical activity and body image within the school curriculum; more school-based sessions on physical activity and movement skills; better nutritional quality of schools food; and better support for teachers and staff to implement health promotion. However, the studies usually used complex interventions and there was wide heterogeneity in the results, which made it very difficult to identify the most effective intervention components, but suggest that combined diet and physical activity school-based interventions may help prevent children becoming overweight and there was no evidence for any adverse effects<sup>81</sup>.

Only a few studies have tested obesity prevention strategies in older school-age children aged 13-18 years old, and together they provide only weak evidence for effectiveness as assessed by reduction in BMI (mean change in BMI z-score: -0.09; 95% CI: -0.20 to 0.03)<sup>81</sup>. Furthermore, in this age group who are potentially more sensitive to issues related to body image, such as stigmatisation, low self-esteem and unhealthy dieting patterns, none of the studies explicitly reported on the potential harms of intervention<sup>81</sup>.

## Interventions in infants and pre-school children

There have been far fewer intervention studies in pre-school compared to school-age children, although the limited evidence suggests that larger treatment effects may be achieved in this age group<sup>81</sup>. In particular, very early intervention during infancy could

present a 'window of opportunity' for obesity prevention as it is a period of developmental plasticity, rapid weight gain and habit formation. Interventions in early life could potentially influence feeding patterns before they have been established and become more difficult to modify<sup>82</sup>.

Long-term follow-up of earlier RCTs in preterm and small for gestational age infants have reported that standard versus nutrient-enriched formula milks prevent faster infancy weight gain and lead to lower adiposity and cardiovascular risk factors in adolescence<sup>83, 84</sup>. The STRIP trial (the Special Turku Coronary Risk factor Intervention Project) showed that reduced saturated fat intake from age 7 months onwards had beneficial effects on serum cholesterol levels and lowered blood pressure during adolescence, although in that study the active intervention was continued well beyond infancy and pre-school ages<sup>85</sup>.

Other trials of 'childhood obesity prevention' during infancy are in progress. Two RCTs are testing modified compositions of formula milk, while eight are testing behavioural interventions to promote breastfeeding, longer sleep duration, physical activity or healthy eating. For example, ERNEST (the multi-centre European Childhood Obesity Project) randomised 1000 infants to high- versus low-protein formula milks. Infants on the low-protein formula had lower weight gain, similar to the reference breastfed group<sup>86</sup>. The US SLIMTIME pilot trial taught parents soothing strategies to reduce feeding for 'non-hunger related fussiness', to prolong sleep duration, to delay introduction of solid food and to increase acceptance of healthy foods through repeated exposure and has reported promising results<sup>87</sup>.

In the slightly older pre-school age group, recent systematic reviews<sup>88, 89</sup> found an absence of effective interventions to prevent obesity. The first review<sup>88</sup> included only three studies that reported BMI as an outcome, while the second review included 23 studies that reported BMI, diet or physical activity as an outcome<sup>89</sup>. It is interesting to note that the second review found that parental involvement was important, that parents were receptive to intervention programs and in some cases made positive changes to diet and physical activity in young children.

## Treatment

The US Preventive Services Task Force (USPSTF) recently positively reviewed the evidence for lifestyle interventions in obese children<sup>90</sup>. In 13 trials comprising 1258 overweight or obese children and adolescents they found adequate evidence for short-term (up to 12 months) improvements in BMI from moderate- to high-intensity (but not low intensity) comprehensive interventions that include dietary, physical activity, and behavioural counselling components in obese children and adolescents aged 6 years and older, with only small risks of harm. It is notable that no studies were identified that targeted those younger than 4 years. Based on these findings, and the adequacy of BMI as an acceptable measure for identifying children and adolescents with excess weight, the USPSTF were bold enough to recommend routine screening for obesity in children aged 6 years and older<sup>90</sup>. Harms of screening were judged to be minimal and therefore, the net benefit of screening was judged to be at least moderate. However, how widely these recommendations are taken up will also depend on much needed health economics analyses to demonstrate the cost-effectiveness of such strategies.

The disappointing side-effect profiles and withdrawal of appetite suppressant medications, such as fluoxetine, rimonabant and sibutramine<sup>91</sup>, have left limited pharmacological options for weight management in obese adults, let alone in obese children in whom the longer treatment durations needed to avoid disease end-points may lead to less favourable risk:benefit calculations. Orlistat, a gastric and pancreatic lipase inhibitor, modestly reduces



BMI (by approximately  $-0.24$  z-scores) in children and adolescents, but has an unacceptably high prevalence of gastrointestinal adverse effects leading to frequent premature discontinuation in the absence of adequate dietetic support<sup>92</sup>.

Finally, there is limited evidence that the insulin sensitizing agent metformin has moderate efficacy in obese children, reducing BMI by on average  $1.42 \text{ kg/m}^2$ <sup>93</sup>. In small randomised trials of girls presenting with precocious pubarche and history of low birth weight, who tend to have high central adiposity and insulin resistance, low-dose metformin during the peri-pubertal years has been reported to have remarkable benefits both on reducing short-term symptoms of oligomenorrhoea and hirsutism and also on long-term increases in lean body mass and height and reductions in adiposity and other markers of metabolic disease<sup>94</sup>. Similar trials of metformin in other groups of insulin-resistant children are warranted to confirm these potential re-programming effects of insulin sensitisation therapy during puberty.

## Conclusions

The promising signs that the rates of increase in obesity in children and adolescents are starting to slow have been attributed to wider awareness of its adverse health effects<sup>26, 95</sup>. However, in order to turn the corner from plateau to steady decline in obesity rates will require informed and decisive actions, which, considering its complex causes and contributing factors<sup>26</sup>, will need to involve multi-component and multi-sector policy interventions. Increasing understanding of the early developmental origins of obesity has led to a growing interest in the development and trials of interventions starting in early life, which have the potential for larger and longer-lasting benefits.

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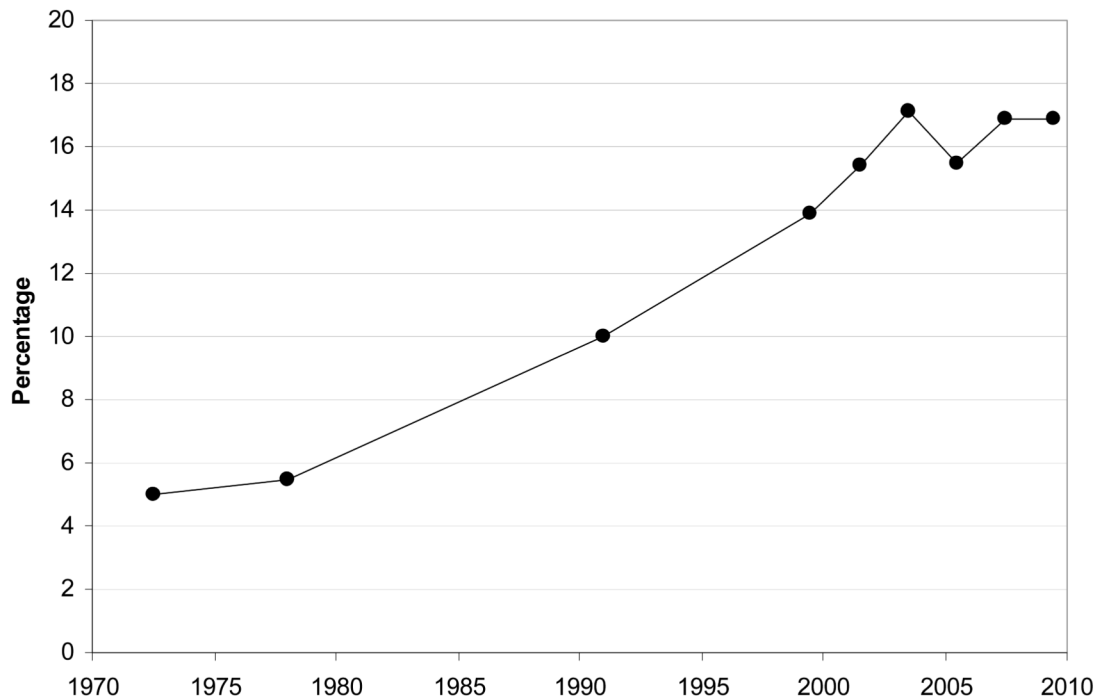
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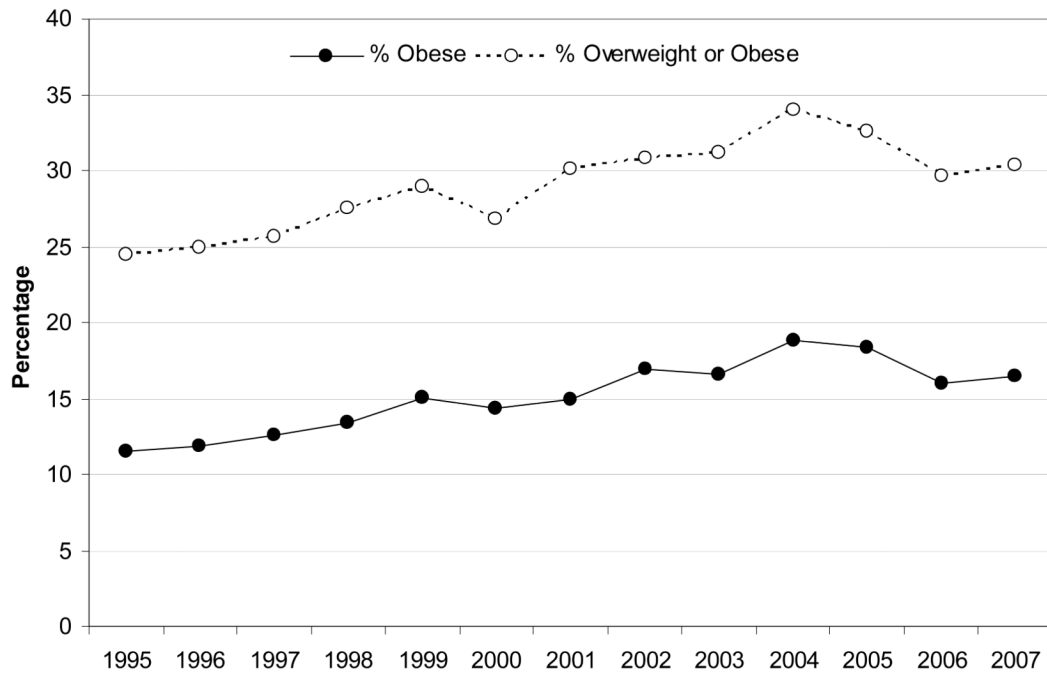


**Figure 1.**

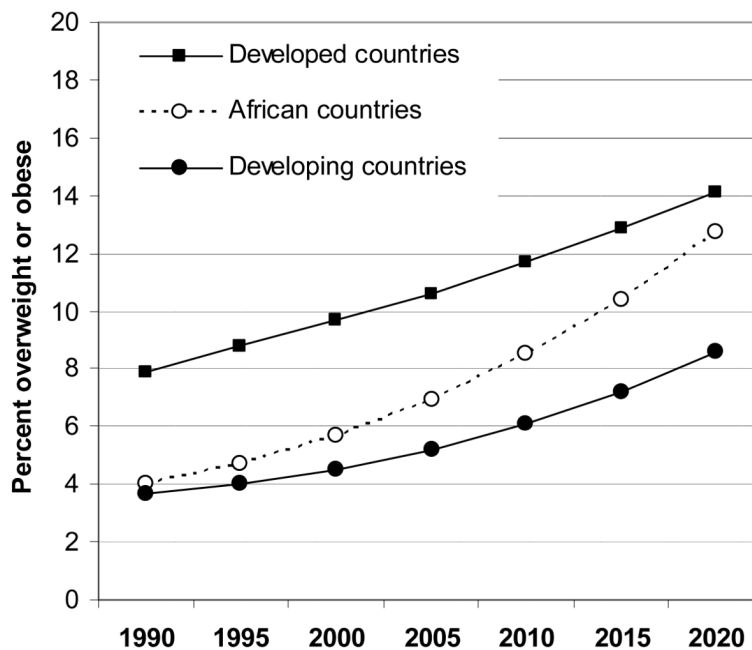
Prevalence of obesity (BMI > 95<sup>th</sup> centile) among children and adolescents aged 2-19 in the United States between 1971-74 to 2009-10 shows a recent plateau from 2003-04 onwards.

Source: Based on data from the National Health and Nutrition Examination Survey (NHANES) published in Ogden et al., *Health E-Stat* 2010 <sup>1</sup> and Ogden et al., *Journal of the American Medical Association* 2012 <sup>4</sup>.



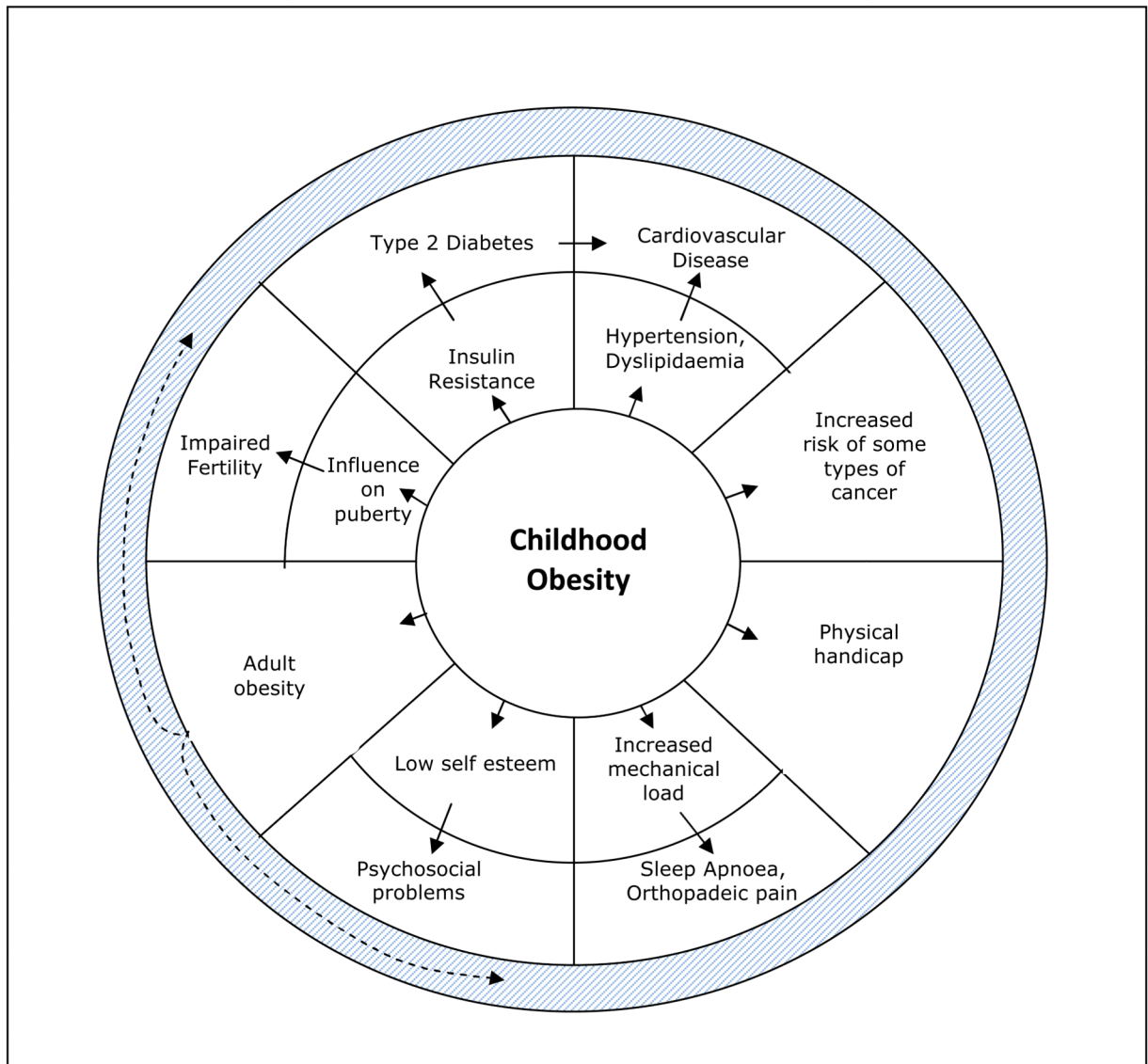


**Figure 2.** Recent plateau in the prevalences of obesity (BMI > 95<sup>th</sup> centile) and 'overweight or obesity' (BMI > 85<sup>th</sup> centile) among children aged 2-15 in England, 1995-2007  
Source: Based on data published by the Association of Public Health Observatories <sup>2</sup>

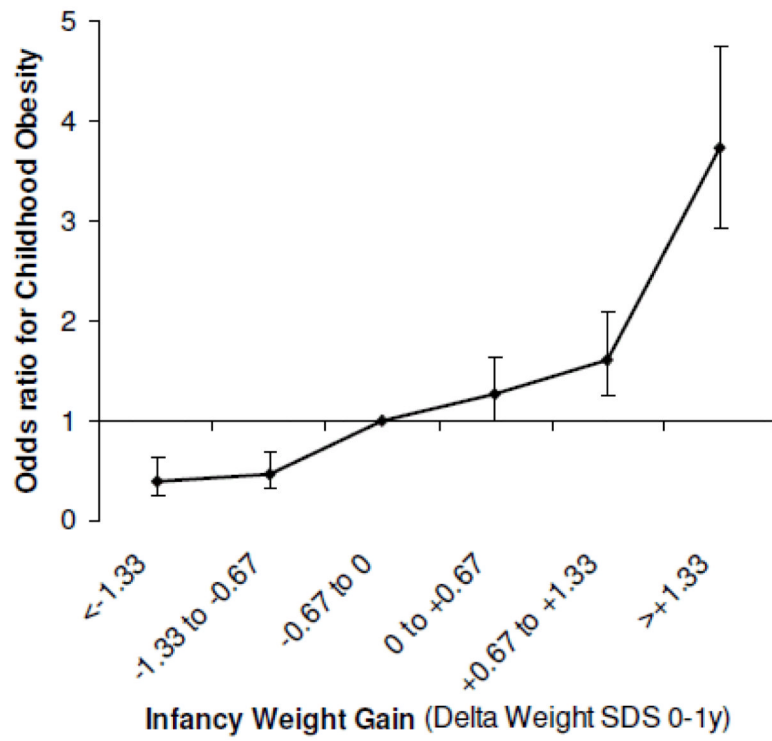


**Figure 3.** Trends between 1990-2010 and predicted ongoing rise 2010-2020 in the prevalence of BMI  $> +2$  SD (equivalent to the 98<sup>th</sup> centile) in preschool children in developed and developing countries.

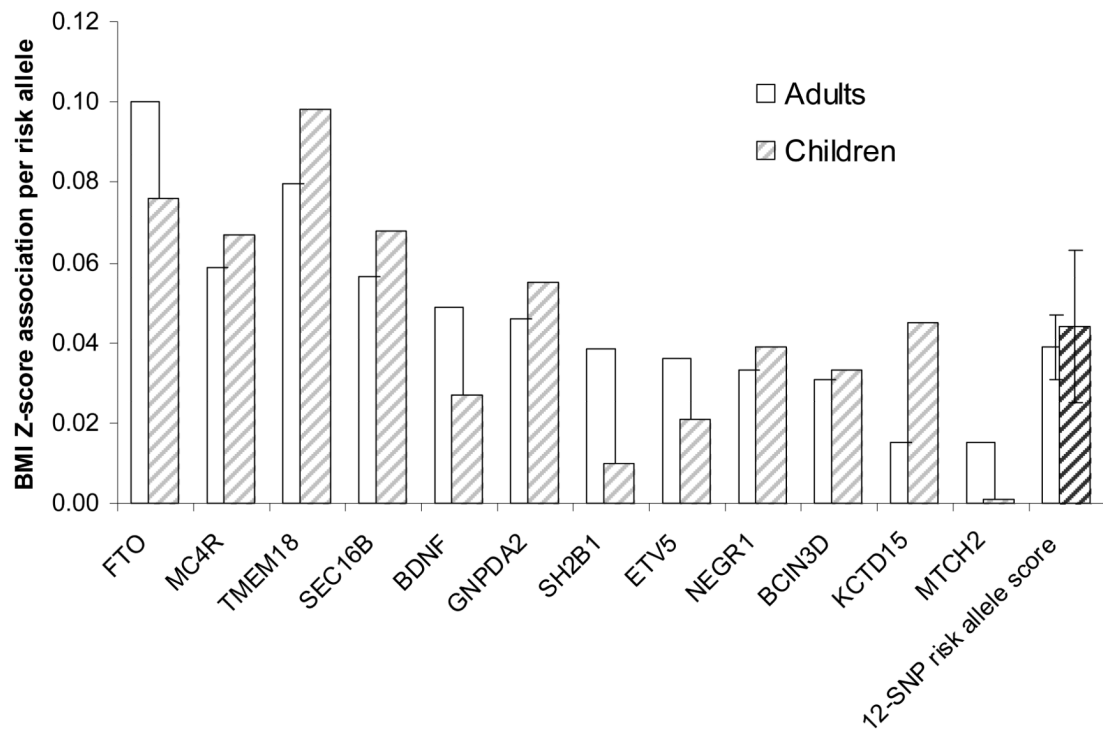
Source: Based on data published in de Onis et al., Public Health Nutrition 2010 <sup>6, 74</sup>



**Figure 4.** Schematic summary of the complications of childhood obesity. Comorbidities of childhood obesity are depicted in the outer ring with their intermediate processes in the inner ring. Childhood obesity also increases the risk of adult obesity, which in turn also increases the likelihood of those comorbidities.



**Figure 5.** Odds ratio for childhood obesity by infant weight gain between 0-1 year, adjusted for sex, age and birth weight.  
Source: Figure reproduced from Druet et al, Paediatric and Perinatal Epidemiology, 2012 <sup>47</sup>



**Figure 6.**

Comparison of the effect sizes on BMI Z-score in adults versus in children of various obesity-related genetic variants.

The 12 single nucleotide polymorphism (SNP) risk allele score represents the effect of each additional obesity risk allele averaged across all 12 variants (error bars represent 95% CI).

Source: Based on data published in den Hoed et al., Diabetes 2010<sup>70</sup>