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Childhood obesity and the associated rise in cardiometabolic complications

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Abstract

Childhood obesity is one of the most serious global public-health challenges of the twenty-first century. Over the past four decades, the number of children and adolescents with obesity has risen more than tenfold. Worldwide, an increasing number of youth are facing greater exposure to obesity throughout their lives, and this increase will contribute to the early development of type 2 diabetes, fatty liver and cardiovascular complications. Herein, we provide a brief overview of trends in the global shifts in, and environmental and genetic determinants of, childhood obesity. We then discuss recent progress in the elucidation of the central role of insulin resistance, the key element linking obesity and cardiovascular-risk-factor clustering, and the potential mechanisms through which ectopic lipid accumulation leads to insulin resistance and its associated cardiometabolic complications in obese adolescents. In the absence of effective prevention and intervention programs, childhood obesity will have severe public-health consequences for decades to come.

Paediatric obesity, in both childhood and adolescence, constitutes a major global public-health crisis of our time[1–5]. Although understanding of its pathogenesis and dynamics has become more nuanced, prevention and treatment remain elusive. Paediatric obesity, particularly in adolescents, is a pervasive disorder with a high risk of continuing into adulthood[6]. The body mass index (BMI) is the accepted standard measure of overweight and obesity for children 2 years of age and older[7–11]. Consensus committees have recommended that children and adolescents be considered overweight or obese if their BMI exceeds the 85th or 95th percentile in curves generated from the 1963–1965 and 1966–1970 US National Health and Nutrition Examination Survey (NHANES)[5,12].

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Author contributions

S.C. drafted the following: Abstract, introduction, 'Epidemiology', 'Environmental determinants', 'The effects of the *FTO* genotype on food intake in children', 'Future outlook', 'Ectopic fat storage in obese youth' and 'Halting the epidemic of childhood obesity'. R.W. drafted the following: 'Bariatric surgery in paediatric obesity' and 'Obesity dynamics and CVRF stability in obese adolescents'. N.S. drafted the following: 'Genetics of childhood obesity', 'Syndromic forms of obesity', 'Non-alcoholic fatty liver disease in obese youth' and 'Pharmacological approaches'. All the authors have read and edited the final version of the manuscript.

Competing interests

The authors declare no competing interests.

Epidemiology

Global prevalence and trends of childhood obesity and underweight from 1975 to 2016: the double burden of malnutrition.

The Non-Communicable Disease Risk Factor Collaboration (NCD-RisC) study, led by Ezzati et al.[11], using a comprehensive global database of BMI from 200 countries, has indicated that the prevalence of paediatric obesity rose dramatically from 4% in 1975 to 18% in 2016. From 1975 to 2016 (Fig. 1), obesity increased from 5 million to 50 million girls and from 6 million to 74 million boys[11]. The largest increases have been in East Asia, the Middle East and North Africa, South Asia and high-income English-speaking regions[11]. Notably, in high-income countries, the rise in childhood obesity has recently plateaued, whereas it continues to rise in low-income and middle-income countries[11].

Undernutrition and obesity commonly coexist side by side within the same country, community or household. The experiences of East Asia, Latin America and the Caribbean have shown that the transition from underweight to overweight and obesity can be rapid, thus creating obstacles to a nation's ability to implement a transition to healthful nutrition. An unhealthful nutritional transition—that is, an increase in nutrient-poor, energy-dense foods—can lead to stunted growth along with weight gain in youth, thus resulting in higher BMI and poorer health outcomes throughout the life course[11,13].

Trends in childhood obesity and its increasing severity in the United States.

NHANES, using calculated BMI from measured weights and heights, has described the history of childhood obesity from 1963–1965 through 2015–2016 in both children and adolescents[14] (Fig. 2).

Substantial ancestral disparities exist in the prevalence of obesity among US children and adolescents: the recent prevalence rates of obesity are 25.1% in non-Hispanic black girls, 23.6% in Hispanic girls, 13.5% in non-Hispanic white girls and 10.1% in non-Hispanic Asian girls[15].

The severity of obesity in adults is subcategorized into class I (BMI 30–35), class II (BMI 35–40) and class III (BMI ≥40). Skinner et al.[15–17] have used a definition of severe obesity applying to only children and adolescents, in which BMI ≥95th percentile is class I obesity, BMI ≥120% of the 95th percentile is class II obesity, and BMI ≥140% of the 95th percentile is class III obesity[15–17]. Under this definition, the prevalence of severe obesity in adolescents was ~10% in non-Hispanic white girls, 20% in non-Hispanic black girls and 16% in Mexican American girls[15]. The rightward shift in the BMI, as classified into class II and class III obesity, is particularly notable in adolescents and in non-Hispanic black individuals[12,16].

Despite evidence that the severity of childhood obesity negatively affects health in youth, current guidelines for screening do not differentiate among degrees of obesity[18].

Risk factors for childhood and adolescent obesity

Environmental determinants.

The root causes of obesity development in childhood and adolescence reflect complex interactions among environmental, socioeconomic, behavioural and genetic factors. The dramatic environmental changes worldwide in recent decades have fuelled the rise in the prevalence of childhood obesity[19–21]. Countless environmental changes that foster eating more frequently have occurred, such as the availability of cheap foods with higher energy content; the growth of soda and fast-food industries generating ultraprocessed foods; and the increased number and marketing of snacks, which continue to play a critical role in the weight and health of youth[6,22]. In the United States and other Western countries, and more recently in underdeveloped countries, in parallel with the rise in obesity, the consumption of added sugars has increased significantly[17,19]. Adolescents are the highest consumers of added sugar[20,21] and are particularly vulnerable to sugar's central reward effects and effects on obesity development. Using functional magnetic resonance imaging, Jastreboff et al.[23,24] have assessed brain perfusion responses to drinking two common monosaccharides, glucose and fructose, in obese and lean adolescents. Obese adolescents show impaired prefrontal executive-control responses to drinking glucose and fructose, whereas their homeostatic and hedonic responses appear to be heightened. Thus, obesity-related brain adaptations to glucose and fructose consumption in obese adolescents may contribute to excessive consumption of both sugars, thereby promoting further weight gain.

Sedentary behaviours are key contributors to the development of obesity. Opportunities in daily life to increase energy expenditure have diminished: children have many hours of 'media time' per day, physical education has markedly decreased in schools, many neighbourhoods lack sidewalks for safe walking, and bicycles have been replaced by motorized bicycles and scooters[6].

Genetics of childhood obesity: from twin studies to the exome era to GWAS.

Since 1970, several studies have tested the hypothesis that human obesity is a heritable trait[25–27]. Seminal studies by Stunkard et al.[26,27] have estimated BMI heritability to be 0.77 by age 20 and 0.84 by age 25 (refs.[26,27]). As stated by the authors: "the concept of 'heritability' does not refer to a constant genetic effect, rather it describes the genetic effect under certain environmental exposures, thus for the same individuals under different environmental conditions, different estimates of heritability may be obtained"[27].

One of the milestones that propelled the field of genetics of obesity came in 1994 with the discovery of the leptin gene (*LEP*) and its product, the leptin hormone, which is synthetized mainly by adipose tissue and acts in the hypothalamus by decreasing appetite and increasing satiety[28].

Soon after the cloning of the *LEP* gene in humans, O'Rahilly et al. described two severely obese children homozygous for a frame-shift mutation in codon 133 of the *LEP* gene[29]. One of the children (a 9-year-old girl) was successfully treated with recombinant leptin for 12 months (ref.[30]). After leptin's discovery, studies of individuals with severe early-onset obesity indicated the importance of the melanocortigenic pathway in modulating

leptin's action. Subsequently, α-melanocyte-stimulating hormone, a compound derived from proopiomelanocortin (POMC), was clearly implicated in the control of appetite through its receptor, melanocorin-4-receptor (MC4R)[31]. Furthermore, mutations in the *MC4R* gene are the most common monogenic cause of severe obesity[32]. The prevalence of mutations in the *MC4R* gene ranges from 0.5% to 5%, with an average of 3%, among obese individuals[32–35].

The discovery of the melanocortinergic system has been extremely important, because it has led to the development of drugs targeting this system that are effective in people with *MC4R* mutations and leptin deficiency[36,37].

The second pivotal landmark in the study of the genetics of obesity was the availability of genome-wide association studies (GWAS). In 2007, a key large GWAS study discovered a locus within the *FTO* gene that is strongly associated with BMI and obesity risk[38]. GWAS have used anthropometric measures as outcomes, such as BMI, waist-to-hip ratio adjusted for BMI (WHRadjBMI) and percentage body mass[39–41]. More than 500 genetic loci have been associated with obesity-related traits in a recent GWAS performed in nearly 700,000 individuals[41]. In a recent study, 346 loci and 463 signals associated with WHRadjBMI were identified[41], but the combined variants explained only 3.9% of the outcome variance[41]. The investigators also observed a sex-dependent effect, in which the heritability of WHRadjBMI was found to be stronger in women than in men[41]. Of note, loci associated with WHRadjBMI appear to be enriched in genes involved in adipose tissue biology[40], whereas loci associated with BMI primarily affect brain-expressed genes involved in appetite regulation[39].

Although most GWAS discoveries have been made in adults, studies in children have been performed in recent years[42–45]. The main difference between studies in adults and children is the smaller sample size in the latter. GWAS in paediatric groups have shown that most of the loci discovered in adults can be replicated in children, thus suggesting an overlap between the genetic architecture of obese children and obese adults[42,43]. Some paediatric studies have shown that the *FTO* locus is strongly associated with obesity, although the strongest association was not consistently observed in all the studies[42], contrary to the results from studies in adults. Paediatric GWAS have also served as a discovery tool for new signals not identified in adult populations (such as *OLFM4* at chromosome 13q14 and *HOXB5* at chromosome 17q21)[42,43]. Very recently, a large paediatric GWAS meta-analysis in groups of children with different ancestries has confirmed that adult and paediatric obesity may share the same genetic underpinnings and that not all the loci found in adults can be replicated in children, primarily because of the smaller sample size of the latter group[46]. Overall, in children, as in adults, the relevant loci together explain a small portion of heritability[46].

Despite the lack of functional studies for most the genes or loci associated with obesity, in 2019, a polygenic risk score, using gene variants associated with obesity through GWAS, was derived and shown to be associated with the degree of obesity as well as the development of obesity over time, starting from the age of 12 years (ref.[47]).

The possibility of selectively sequencing all coding regions of the genome (exome) enables examination of whether rare variants (with a minor allele frequency <1%) rather than common variants (explored through GWAS) may explain the so-called 'missing heritability'. A recent exome-wide search for low-frequency and rare genetic variants associated with BMI has been performed by using exome-targeted genotyping arrays in 718,734 individuals[48]. Interestingly, the investigators discovered 14 new variants in 13 genes and found that the rare variants had an effect size ten times larger than the common variants previously identified by GWAS[48]. This finding suggests that rare and low-frequency variants rather than common variants may play major roles in the genetics of obesity.

The effects of the *FTO* genotype on food intake in children: a potential contributor to obesity.

GWAS studies have reliably established that single-nucleotide polymorphisms in the first intron of *FTO* are strongly associated with greater BMI across different ages and populations[38,49,50]. People homozygous for the A allele of *FTO* rs9939609 have an obesity risk 1.7-fold greater than that of people homozygous for the low-risk T allele[22]. The association between *FTO* and BMI is predominantly driven by an increased drive to eat, probably because of impaired satiety[51,52]. *FTO* is highly expressed in brain regions controlling feeding, such as the hypothalamus, particularly the arcuate nucleus, which is critical for the appetite-stimulating effect of ghrelin[53–56]. A preference for energy-dense foods among children has been found to be associated with the *FTO* genotype independently of body weight[22,57,58].

Highlighting the mechanistic link between FTO and ghrelin in energy homeostasis, Karra et al.[59], in a group of lean men, have shown that people homozygous for the *FTO* A allele, compared with people homozygous for the major allele, have attenuated suppression of ghrelin levels and hunger as well as diminished hypothalamic neural responses after consuming a meal. Rosenbaum et al.[60] have suggested that even before the development of obesity, children carrying the rs9939609 A risk allele exhibit greater food intake, and each copy of the A allele is associated with approximately 65 additional calories consumed, thereby explaining 3% of variance in intake[60]. The influence of genotype dose on energy intake adds support to the hypothesis that *FTO* genotypic associations with body weight may be mediated by effects on food intake rather than on energy expenditure. Despite these observations, Claussnitzer et al. have proposed that the *FTO* effect may be mediated by a different gene variant that decreases energy expenditure[61]. This intriguing observation contrasts with findings from another study indicating that the *FTO* rs9939609 variant is not associated with any phenotype related to energy expenditure[62].

Syndromic forms of obesity: what they can teach us about bodyweight regulation.

Although the above-mentioned studies tested the effects of common and rare variants on the risk of developing essential non-syndromic obesity early in life, some complex genetic syndromes are characterized by early-onset obesity. Among these, Prader–Willi syndrome (PWS) is the most common syndrome associated with severe obesity[63]. PWS is a congenital multisystem disorder characterized by neonatal hypotonia and feeding problems, developmental delay, short stature, hypogonadotropic hypogonadism and diminished resting

energy expenditure. PWS results from a defect in the expression of genes in the paternally inherited chromosomal region 15q11.2–q13. Although the genetic defects underlying PWS are known, their relationships with the PWS phenotype remain unclear. Recent findings suggest that the *PCSK1* gene might be responsible for early-onset obesity[64]. Indeed, Burnett et al., using induced pluripotent stem cells from people with PWS, have shown that the *PCSK1* gene, which encodes the enzyme prohormone convertase 1 (PC1), is weakly expressed in PWS[64]. This finding is extremely interesting because a defect in the *PCSK1* gene was originally found to cause early-onset obesity by affecting the melanocortinergic pathway[65].

Further insights into the pathophysiology of paediatric obesity have come from Alström syndrome (AS) and Bardet–Biedl syndrome (BBS), two ciliopathies characterized by early-onset obesity. AS is an autosomal recessive disease caused by mutations in the *ALMS1* gene[66] characterized by hearing and visual impairment, early-onset obesity, high plasma triglycerides, severe insulin resistance (IR), diabetes and fatty liver[66], along with developmental delays[66]. Knockout of *Alms1* in mice suggests that *Alms1* deficiency leads to insulin hypersecretion, owing to a β-cell glucose-sensing defect. Consequent hyperinsulinaemia leads to β-cell exhaustion, thus resulting in diabetes[66]. This model suggests that body-fat accumulation in these patients may be caused by hyperinsulinaemia, and studies comparing people with AS and BMI-matched controls have highlighted the extreme insulin-resistance characteristic of AS[67].

BBS is characterized by ciliary dysfunction along with obesity, early-onset diabetes, retinitis and kidney disease[68]. Mutations causing BBS result in obesity through a dysregulation of food-seeking activity[69]. People with BBS experience severe leptin resistance[70], probably because the underlying ciliopathy affects leptin signaling[70]. Variable BBS gene mutations are associated with different degrees and distribution of adiposity, thus suggesting that fat accumulation has a different pathogenesis in BBS and nonsyndromic obesity[70].

Overall, these observations imply that insights from syndromic obesity must be taken into account in the study of non-syndromic obesity, because they can provide essential clues regarding the complex pathophysiology of weight regulation.

Cardiometabolic complications and their burden in childhood

Paediatric obesity is increasingly associated with type 2 diabetes, fatty liver and cardiovascular disease[71–76]. The clustering of cardiovascular risk factors (CVRFs) in early childhood is concerning, given that ~80% of obese youth remain obese in adulthood[77–79]. Below, we describe the role of IR, the key element linking obesity and CVRF clustering, and potential mechanisms leading to its development in obese children.

Ectopic fat storage in obese youth: a potential cause of IR.

The subcutaneous adipose tissue (SAT) has been proposed to act as a ‘sink’ accommodating excess energy as triglycerides and thus preventing the flow of lipids to other organs[80–82]. Of note, not all obese youth develop metabolic complications; in fact, many obese youth have favourable metabolic profiles[83]. One hypothesis explaining this paradox is that total

body fat is not the culprit of an unfavourable metabolic profile; instead, the relative proportion of lipids in various fat depots is the determinant of metabolic risk. In other words, inadequate SAT expansion results in lipid overflow into visceral adipose tissue (VAT) and non-adipose tissues[84,85]. The 'adipose expandability hypothesis'[86,87] suggests that after AT storage capacity is exceeded, the net lipid flux to non-adipose tissues increases, thus causing lipotoxicity and leading to IR[87]. Our studies in obese adolescents have indicated that IR is related to a particular abdominal fat distribution and ectopic fat accumulation[88,89]. To unravel the mechanisms responsible for the inefficient storage of fat in the abdominal SAT, fat-cell size and the transcription of genes regulating lipogenesis and adipogenesis have been measured in two groups of obese adolescents with similar degrees of obesity but profound differences in abdominal fat distribution (low VAT/SAT ratio versus high VAT/SAT ratio)[83]. Compared with obese adolescents with low VAT/SAT, obese adolescents with high VAT/SAT showed coexistence of large and small adipocytes, downregulation of key lipogenic and adipogenic genes, and an inflammatory profile characterized by macrophage infiltration and decreased *SIRT1* expression[90].

To gain further insights into the potential causes of inefficient storage of triglycerides in the SAT and gluteal depots, we measured in vivo dynamic fluxes of SAT triglycerides, de novo lipogenesis and adipocyte turnover in obese girls with distinct differences in abdominal fat distribution but similar degrees of obesity[91]. We found that obese girls with a high VAT/(VAT + SAT) display increased in vivo rates of lipolysis and unaltered de novo lipogenesis in both abdominal and gluteal SAT; higher adipocyte turnover, with no difference in preadipocyte proliferation; and a strong relationship between the increased lipolytic rates and intrahepatic lipid accumulation. These findings suggest that increased turnover of triglycerides and mature adipocytes in SAT, rather than decreased triglyceride deposition capacity or proliferation of new adipocytes, contributes to the development of fatty liver and related metabolic impairment.

The deposition of lipids within insulin-responsive tissues, such as the skeletal muscle, liver and adipose tissue, is associated with localized IR in molecular pathways related to glucose metabolism, thus leading to hyprinsulinaemia[92]. In insulin-responsive tissues, a selective resistance to the effects of insulin is observed in pathways related to glucose metabolism, whereas other insulin-mediated pathways respond normally to the resultant hyperinsulinaemia (such as hepatic lipogenesis or renal sodium reabsorption)[93]. This selective IR is largely caused by intracellular fatty acid derivates such as fatty acyl-CoA, diacylglycerol and ceramides[94]. In skeletal muscle, the result of such IR is decreased trafficking of the glucose transporter GLUT-4 to the cellular membrane and thus lower uptake of systemic glucose. In the liver, the result is increased hepatic glucose production mediated by a decreased suppression of gluconeogenesis[85]. Similarly, adipose tissue IR is manifested increased lipolysis and decreased glucose uptake, thereby resulting in increased systemic flux of free fatty acids ('lipotoxicity') into the skeletal muscle and liver[95]. These cellular and molecular defects of IR are manifested early in life in obese youth[88,91,95–97]. First, obese adolescents who develop impaired glucose tolerance have profound IR and are characterized by increased intramuscular and intra-abdominal lipid deposition despite being as obese (according to anthropometric and percentage-body-fat indices) as obese adolescents with normal glucose tolerance[95]. Second, obese youth with greater degrees of

intrahepatic steatosis (despite comparable degrees of obesity to their peers) have been found to have higher 2-hour glucose levels and profound whole-body IR, and most have substantial CVRF clustering[98]. Adipose IR in this context is tightly related to increased 2-hour glucose levels and decreased postprandial suppression of free fatty acid levels[99]. Importantly, in the presence of IR, the β-cells in obese youth are challenged by an increased allostatic load[100]. The presence of baseline insulin secretion defects, together with continuous weight gain, further aggravates β-cell failure and ultimately leads to further deterioration of glucose metabolism[101].

The systemic response to IR related to altered lipid partitioning is thus manifested as altered glucose metabolism and, in parallel, as the appearance of adverse cardiovascular biomarkers such as elevated concentrations of triglycerides, small particles containing oxidized-low-density-lipoprotein cholesterol[102] and markers of subclinical inflammation[103], along with diminished levels of high-density lipoprotein (HDL) cholesterol and adiponectin[104]. Together, the cluster of CVRFs such as altered glucose metabolism, dyslipidaemia, elevated blood pressure and subclinical inflammation has been named insulin-resistance syndrome and is highly prevalent in obese youth[75]. The clinical correlates of obesity-related CVRF clustering are increased intima–media thickness and left-ventricular hypertrophy[105] in childhood[106], which continue into adulthood[107], thus suggesting the presence of accelerated atherogenesis.

Non-alcoholic fatty liver disease in obese youth: pathogenesis and genetic underpinnings.

Non-alcoholic fatty liver disease (NAFLD) defines a spectrum of disease including intrahepatic fat accumulation, steatohepatitis, fibrosis and cirrhosis[108]. Its prevalence in children increases with BMI and is approximately 38% in obese adolescents[109]; however, the prevalence differs according to ancestry and is highest in Hispanic (45%) and in non-Hispanic white people (~30%) and lowest in non-Hispanic black people (~13%)[110]. The natural history of paediatric NAFLD is poorly understood, given the paucity of longitudinal data. A retrospective study has shown that adolescents with NAFLD at the age of 13.9 years have a survival free of end-stage liver disease lower than that expected in the general US population of the same age and sex[111]. Obese youth with NAFLD are more insulin resistant than those without NAFLD[112], and have a higher prevalence of prediabetes, type 2 diabetes[113] and dyslipidaemia[114]. NAFLD and IR are intrinsically linked, although which precedes the other is unknown. A recent longitudinal study has shown that youth who develop NAFLD within 2 years tend to have higher levels of insulin and c-peptide at baseline than those who do not develop NAFLD[110], thus suggesting that IR may precede the development of NAFLD.

Although a certain degree of IR is present in all obese youth, not all of them develop NAFLD, and the heritability of NAFLD ranges between 35% and 50% (refs.[115–117]). The first gene variant associated with NAFLD through a GWAS was the rs738409 variant in the *PNPLA3* gene[118], which encodes a substitution of isoleucine with methionine in a highly conserved codon (I148M)[118]. The *PNPLA3* gene encodes the protein adiponutrin, which promotes the transfer of essential fatty acids from triglycerides to phospholipids in hepatic lipid droplets[119]. Although the mechanism through which this variant predisposes people

to NAFLD has not yet been elucidated, this is the strongest genetic signal associated with NAFLD[120,121]. Along with this variant in *PNPLA3*, other variants in genes expressed in the liver have been consistently associated with NAFLD in youth[122–124]. Notably, the effects of these gene variants on the development of NAFLD are amplified by the degree of adiposity, thus indicating that the effect of the genotype on the phenotype increases with increasing BMI[125]. In Fig. 3, we propose potential mechanisms linking NAFLD to IR and cardiac dysfunction in obese adolescents.

Obesity dynamics and CVRF stability in obese adolescents.

CVRF clustering (CVRFs, altered glucose metabolism, elevated blood pressure and triglycerides, low HDL-cholesterol levels and elevated biomarkers of inflammation) is tightly associated with IR and is common amongst obese youth[75]. As described above, altered lipid partitioning is the main mechanistic driver linking obesity and the development of IR in obese children. Adolescents with BMI greater than the 99th percentile for age and sex have a significantly greater risk of having CVRF clustering than those with lower degrees of obesity[126]. Using conservative thresholds for prediabetes, dyslipidaemia and elevated blood pressure, a large multi-ancestral cohort has demonstrated that the prevalence of the CVRF is directly and independently linked to the degree of both obesity and IR[75]. Across a spectrum of BMI, each half unit of the BMI *z* score increases the risk of having CVRF clustering by 55% (hazard ratio, 1.55; 95% confidence interval, 1.16–2.08). Independently of the degree of obesity, increasing IR (an additional unit of homeostatic model assessment of IR) increases the risk of CVRF clustering by 12% (hazard ratio, 1.12; 95% confidence interval, 1.07–1.18). Skinner et al., using NHANES data[16], have shown that values for some but not all CVRFs are higher in people with increasing severity of obesity, while also demonstrating that after adjustment for age, ancestry and sex, a greater degree of obesity increases the risk of lower HDL-cholesterol levels, high systolic and diastolic blood pressure and elevated plasma triglycerides. In an obesity-clinic-derived cohort[127], greater adiposity has been shown to be associated with greater risk of CVRF clustering, yet this risk tends to plateau and not increase further in people with BMIs greater than 40 kilograms per square metre.

Weight loss, resulting in decreased ectopic lipid deposition, is expected to reverse the presence of such risk factors. Multiple clinical trials combining dietary modifications, physical activity and family-oriented therapy have demonstrated that modest weight loss, or even cessation of weight gain, may significantly improve metabolic phenotypes[128,129]. Linking the clinical-marker improvement associated with weight loss has revealed that a decrease of 0.30 BMI s.d. in obese adolescents is associated with a significant decrease in intrahepatic and intramuscular lipid deposition[130], thus resulting in significantly increased insulin sensitivity[131]. Moreover, an exercise program leads to weight loss, better insulin sensitivity and improvements in clinical biomarkers of atherogenesis such as intima–media thickness[132].

The studies described above led to a critical question: what magnitude of BMI s.d. score (or percentage body weight) decrease is needed in obese adolescents to improve insulin sensitivity sufficiently to enable recovery from obesity-related metabolic morbidity? The

amount of weight loss needed to induce substantial changes in insulin sensitivity that translate to normalization of clinical risk markers has been postulated to be approximately 0.25 BMI s.d., and achieving weight loss >0.50 BMI s.d. has the greatest benefit[133,134]. Importantly, such improvements may be sustained months after the completion of an intervention program[135].

However, longitudinal changes in insulin sensitivity are strongly related specifically to fat-mass accrual over time[136], thus highlighting the mechanistic role of adipose tissue excess in the development of IR. Specifically, weight gain is tightly associated with decreased insulin sensitivity and is the best predictor of deteriorating glucose tolerance[137]. The relationship between weight dynamics and insulin sensitivity is best appreciated when interventions are evaluated upon completion, and their sustainability is determined over time. In such studies, weight loss immediately after the completion of a successful intervention program is paralleled by improvements in proxies for insulin sensitivity, yet after subsequent weight regain, insulin sensitivity returns to its low baseline level[138].

Interventions for reversing the obese state in youth

Recently published guidelines recommend that therapeutic approaches to paediatric obesity be limited to counselling about physical activity and lifestyle changes[7]. Yet, noncompliance and high attrition rates are highly frequent among obese youth[139,140]. Therefore, the addition of pharmacological treatments to lifestyle-intervention programmes may be an effective therapeutic strategy in paediatrics.

Pharmacological approaches.

In children, unlike adults, few US Food and Drug Administration (FDA)-approved obesity drugs are available, owing to the difficulty in demonstrating the safety profiles of centrally acting drugs in to the context of growth and development. Among the few pharmacological options in paediatric medicine, orlistat, an inhibitor of pancreatic lipase (limiting fat absorption from the gut)) is currently the only FDA-approved medication for treatment of paediatric obesity for children from 12 years of age[141]. However, its effect on weight loss is very modest[142].

Recently, in a clinical trial in obese adolescents with type 2 diabetes, liraglutide, a GLP-1 agonist, has shown similar safety, tolerability and pharmacokinetic profiles to those in adults[143]. The investigators have demonstrated the superiority of liraglutide over placebo in decreasing haemoglobin A1c and plasma glucose, although they did not show the superiority of liraglutide in decreasing the BMI *z* score after 26 weeks. Testing of the effect of liraglutide on the BMI *z* score in 24 prepubertal obese children (7–11 years of age) has demonstrated that liraglutide is superior to placebo in decreasing the BMI *z* score (−0.28; $P = 0.0062$)[144]. Therefore, GLP-1 agonists may be a promising medication for treating obesity in children. The mechanism through which GLP-1 causes weight loss is not entirely clear yet seems to be related to an effect on the central nervous system. GLP-1 crosses the blood–brain barrier and reaches regions critical for the control of appetite, such as the hypothalamus. In particular, animal studies have suggested that GLP-1 acts in the arcuate

nucleus of the hypothalamus, where it stimulates POMC/CART neurons and inhibits AgRP neurons, thereby determining satiety[145].

The discovery of the melanocortinergic system as a key pathway in appetite control has led to the development of drugs targeting MC4R. In particular, recent trials using setmelanotide, an MC4R agonist, have been performed in obese individuals carrying rare variants in the *MC4R*, *POMC* and leptin-receptor genes[36,37,146]. Specifically, the first trial was performed in two people with a *POMC* deficit and showed a loss of 51.0 kilograms after 42 weeks in one patient and 20.5 kilograms after 12 weeks in the other[146]. In another phase 1b clinical trial, 49 obese adults were enrolled and randomized to treatment with either setmelanotide or placebo for 14 or 28 days (ref.[37]). Significant weight loss was observed in obese people receiving ≥0.01 milligrams of setmelanotide per kilogram in 24 hours, compared with placebo[37]. Setmelanotide has also effectively led to weight loss in three adults with leptin-receptor mutations[36] and is well tolerated[36,37,146].

Importantly, monogenic causes of obesity are rare, and thus agents such as setmelanotide do not provide a solution for most obese children.

To address the metabolic effects of altered lipid partitioning in obese youth, several trials have used rosiglitazone. This agent induces preadipocyte differentiation and thus expands subcutaneous fat while diverting lipid from the liver and skeletal muscle. In a 4-month randomized intervention in obese youth with prediabetes, rosiglitazone indeed improved insulin sensitivity in association with increased subcutaneous fat, decreased intrahepatic fat and normalized glucose metabolism in 58% of those who received it[147].

Bariatric surgery in paediatric obesity.

The important long-term morbidity associated with severe obesity in children and adolescents and the modest effects of conservative interventions in this age group have led to more aggressive interventions such as bariatric surgical procedures. Bariatric procedures differ in their degree of anatomical modification, thus resulting in variable relative combinations of mechanical and hormonal effects. Nonetheless, they will be discussed herein as a group regarding their effects on weight and insulin sensitivity in morbidly obese adolescents. Patient selection for bariatric surgery in adolescents requires candidates to have reached >95% of their projected height and to have severe obesity-related complications (BMI ≥35 kilograms per square metre or 120% of the 95th percentile with clinically relevant comorbid conditions such as obstructive sleep apnoea (apnoea hypopnea index >5), type 2 diabetes, idiopathic intracranial hypertension, steatohepatitis, Blount’s disease or hypertension; or BMI either ≥40 kilograms per square metre or 140% of the 95th percentile, whichever is lower). Surgery candidates must be assessed by a multidisciplinary team to decide whether the patients and families have the ability and motivation to adhere to preoperative and postoperative regimens[148]. Bariatric surgery is contraindicated in adolescents with medical or psychiatric problems that may hamper adherence to postoperative dietary and pharmacological regimens, recent substance abuse, planned pregnancy or a medically correctable cause of obesity. In the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) consortium, a multicentre observational study, data from 242 morbidly obese adolescents showed a significant weight loss (26–

28%) postsurgery (for both Roux-en-Y gastric bypass and sleeve gastrectomy). Weight loss was associated with type 2 diabetes remission (95% of patients), and recovery from dyslipidaemia (66% of patients) and hypertension (74% of patients)[149]. The main conclusion from Teen-LABS was that the 5-year outcomes of bariatric surgery in obese adolescents are similar to those demonstrated in adults regarding weight and are slightly better regarding remission from obesity-related comorbidities[150]. Similarly, The Adolescent Morbid Obesity Surgery (AMOS) study has reported the superiority of 5-year outcomes in adolescents receiving Roux-en-Y gastric bypass compared with conservative treatment[151]. AMOS demonstrated a significant weight loss, which was maintained for 5 years and was associated with a 74–100% resolution of altered glucose metabolism, hypertension, dyslipidaemia and inflammatory markers. Despite the clear and impressive short-term effects of bariatric procedures on weight and related comorbidities, these clinical benefits should be balanced with the potential comorbidities associated with such surgical interventions, including the need for additional surgical procedures (25% of people in the AMOS study) and the development of nutritional deficiencies (72%) that might affect future bone health if they occur during a critical period of bonemass development. Inge et al. have reported nutritional deficits after 2 years of follow-up in ~50% of adolescents and 26% of adults, whereas the rate of a second surgery was higher in adolescents than in adults[151]. A 5-year follow-up study has highlighted a high prevalence of gastroesophageal reflux symptoms, especially in adolescents receiving vertical sleeve gastrectomy[152]. A tendency towards a higher prevalence of alcohol abuse and self-harm after surgery has also been described[153].

Importantly, substantial ethical issues exist regarding these procedures: they are irreversible (with the exception of gastric banding), the long-term effects on morbidity and mortality (specifically in people without major obesity-related morbidity in adolescence) are unknown, and not all adolescents seem to benefit from them[154]. One of the main concerns relates to future bone health, because such procedures have been shown to be associated with substantial early bone loss in adolescents and adults[155] as well as with an overall increased risk of fractures[156]. Most patient-selection guidelines for such procedures in adolescence highlight the importance of prior participation in a lifestyle intervention (to demonstrate adherence), thus ruling out major psychiatric conditions and demonstrating a viable family support system. Because adherence to obesity-management programs in this age group is notoriously low[157], and given the high prevalence of psychiatric morbidity in obese youth[158], strict adherence to such guidelines results in very few suitable surgical candidates[159].

In cases of syndromic or hypothalamic obesity, the results of bariatric procedures are less promising. In patients with PWS compared with those with non-syndromic obesity, the results of surgery are poorer, specifically in weight regain[160]. Similarly, in patients with hypothalamic obesity after resection of craniopharyngioma, surgery outcomes are quite variable[161]. Therefore, in cases of syndromic or hypothalamic obesity, given the lower success rates, bariatric surgery should be considered only as a last resort in patients with substantial comorbidity.

Halting the epidemic of childhood obesity: reasons for patchy progress.

To understand the beginning of the epidemic of obesity in the United States, using NHANES data from the early 1970s, Rodgers et al.[162] have noted that in most obese adults and children in the United States, the excess weight gain began at approximately the same time (1970s)[162]. Further, they have argued that the precipitous global spread of obesity could not have been driven by changes in genetic predisposition, which do not occur over short periods of time[162]. Hence, to determine the potential drivers of the rise in obesity, they focused on the changes in US farm bills in 1970, which caused an increase in food production, thus increasing the availability of cheap food and fast food, and allowing restaurants to serve larger portions[163]. Another important role has been played by the expanded use of inexpensive sweeteners such as high-fructose corn syrup[164].

Given the complex nature of obesity, it has become increasingly clear that confronting and reversing obesity trends should be addressed through comprehensive multisectoral action[165]. The World Health Organization has been, and still is, at the forefront of the problem in developing global strategies for the prevention of childhood obesity and non-communicable diseases[166], and improving maternal and child health[167]. As a result of its global efforts to prevent childhood obesity, the World Health Organization established the Commission on Ending Childhood Obesity (ECHO). Although not entirely novel, the plan and recommendations of the ECHO program are well developed, described and illustrated in the Commission's report[166], which proposes a range of governmental recommendations aimed at reversing the rising trend in children becoming obese. As a result of these global efforts, high-level policies, strategies and targets for addressing childhood obesity have been agreed upon, yet translating these recommendations into specific policies at the national level has been challenging[168]. Roberto et al. have described the implementation of these strategies as being "patchy" at best[168]. The reasons for the poor translation of global recommendations into national policies lie mainly in the imbalance between the private sector and government/society. The prioritization of free-market goals has influenced the deregulation of markets in many countries, and privileged commercial interests are affecting policy-making[169]. Indeed, fast-food and soft-drink conglomerates have had critical roles in halting efforts to introduce public-health regulation of these industries[170].

Future outlook.

A major concern related to childhood obesity is that obese children tend to become obese adults with all the associated risks and comorbidities (including diabetes, fatty liver disease and cardiovascular disease, among many others). A recent study[171] has estimated that among children between the ages of 2 and 19 years in 2016, more than half (57.3%) will be obese by the age of 35 years. Early development of obesity predicts obesity in adulthood, especially for children who were severely obese. Thus, these findings highlight the importance of promoting healthy weight throughout childhood and adulthood. A narrow focus solely on preventing childhood obesity will not avert potential future damage to health that may be induced by the ongoing obesity epidemic[171].

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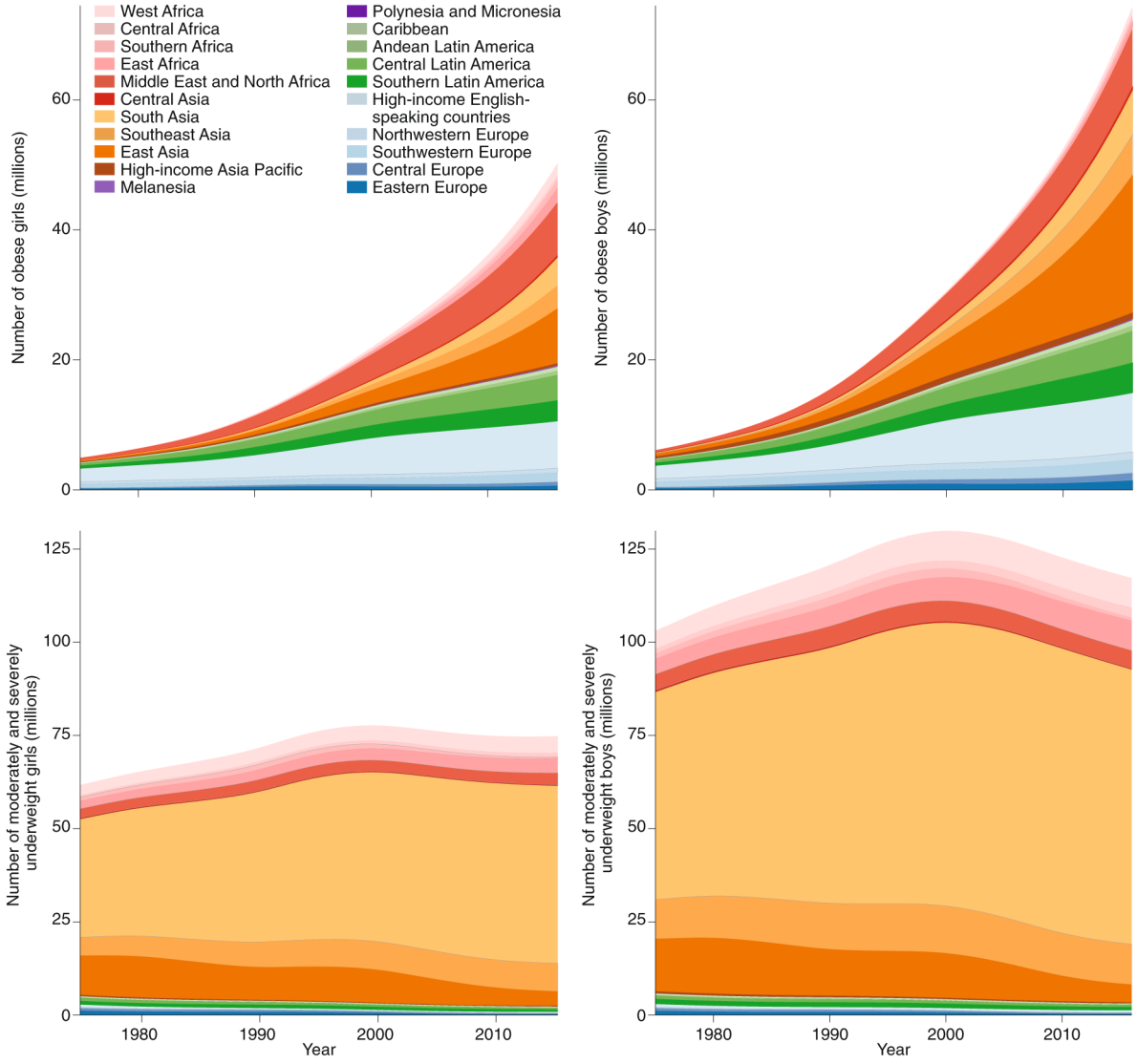

Fig. 1 |. Trends in the number of children and adolescents with obesity and with moderate and severe underweight by region.

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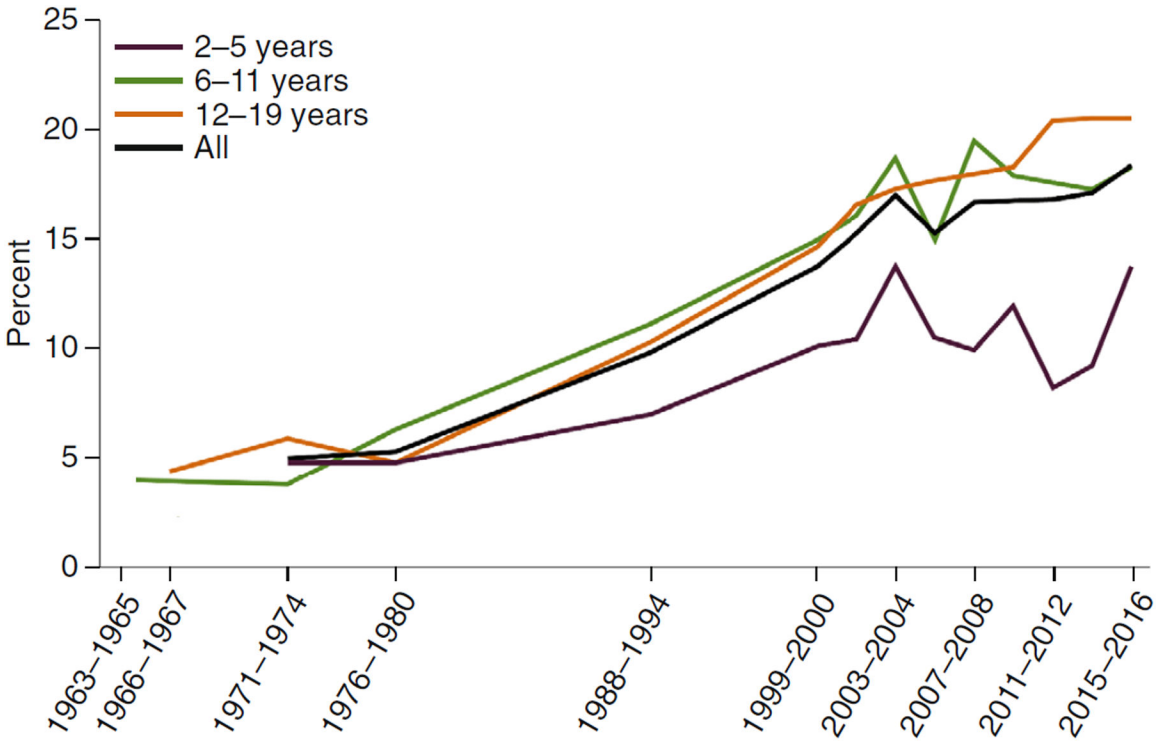

Fig. 2 |. Trends in the prevalence of childhood obesity in the United States from 1963 to 2016.
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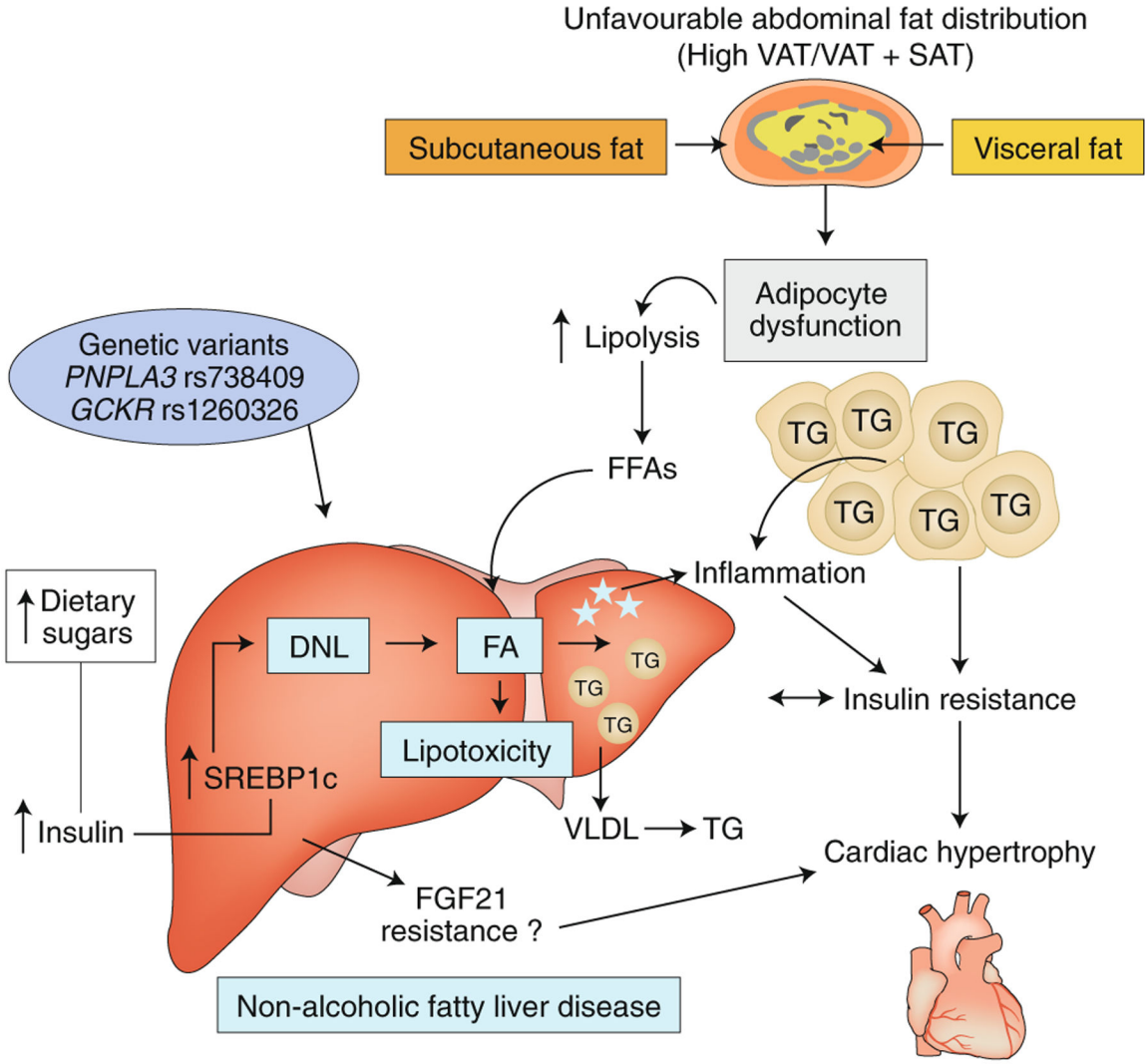

Fig. 3 |. Proposed pathophysiological mechanisms linking NAFLD to IR and cardiac dysfunction in obese adolescents.

NAFLD is a result of genetics and environmental factors (dietary habits, IR, increased de novo lipogenesis and adipose tissue lipolysis). FFAs, free fatty acids; FA, fatty acid, VLDL, very low-density lipoprotein; TG, triglyceride; DNL, de novo lipogenesis; FGF21, fibroblast growth factor 21; SREBP1c, sterol regulatory element–binding protein 1c. Image adapted with permission from ref.[172], American Association for the Study of Liver Diseases.