

Pediatric obesity—Long-term consequences and effect of weight loss

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Childhood obesity is, according to the WHO, one of the most serious challenges of the 21st century. More than 100 million children have obesity today. Already during childhood, almost all organs are at risk of being affected by obesity. In this review, we present the current knowledge about diseases associated with childhood obesity and how they are affected by weight loss. One major causative factor is obesity-induced low-grade chronic inflammation, which can be observed already in preschool children. This inflammation—together with endocrine, paracrine, and metabolic effects of obesity—increases the long-term risk for several severe diseases. Type 2 diabetes is increasingly prevalent in adolescents and young adults who have had obesity during childhood. When it is diagnosed in young

individuals, the morbidity and mortality rate is higher than when it occurs later in life, and more dangerous than type 1 diabetes. Childhood obesity also increases the risk for several autoimmune diseases such as multiple sclerosis, Crohn's disease, arthritis, and type 1 diabetes and it is well established that childhood obesity also increases the risk for cardiovascular disease. Consequently, childhood obesity increases the risk for premature mortality, and the mortality rate is three times higher already before 30 years of age compared with the normal population. The risks associated with childhood obesity are modified by weight loss. However, the risk reduction is affected by the age at which weight loss occurs. In general, early weight loss—that is, before puberty—is more beneficial, but there are marked disease-specific differences.

Keywords: cardiometabolic disease, inflammation, obesity comorbidities, pediatric obesity, weight loss

Introduction

Childhood obesity is a condition which, throughout the last 100 years, has transformed from a sign of wealth and health to a disease that according to the WHO is “one of the most serious challenges of the 21st century” [1]. There are several reasons for the WHO statement. According to the Global Burden of Disease Study [2], health hazards—such as global exposure to unsafe sanitation, household air pollution, childhood underweight, childhood stunting, and smoking—decreased by more than 25% between 1990 and 2015. During the same period, risks associated with high body-mass index (BMI) increased by more than 25%. The prevalence of obesity has doubled in more than 70 countries since 1980. A total of 107.7 million children had obesity in 2015 [2].

Childhood and adolescent obesity is associated with increased risk of premature death [3, 4]. Many

factors contribute, such as cardiovascular disease, [5] type 2 diabetes (T2D) [6], and several endocrine disorders, [7] as well as depression and cognitive disturbances that may contribute to poor school results [8]. Almost all organ systems are affected by obesity in childhood (Fig. 1).

An additional concern for children with obesity is the negative effects obesity may have on social interaction. Bullying is common, and the negative attitudes toward children with obesity may increase the risks for eating disorders, social isolation, and reduced physical activity. Childhood obesity is today associated with stigma to such a degree that, despite it being considered a disease, the health care system is requested to not call the disease “obesity” but to use nonbiased language such as “weight” and “body mass index” [9]. There is also a powerful “body activism” movement claiming that obesity is not a disease and that the

Conditions caused or worsened in children with obesity: all organ systems are affected

Psychosocial – stigmatization

- Depression
- Anxiety
- Poor self-esteem
- Social isolation
- Eating disorder
- Reduced cardio-respiratory fitness
- Lower educational attainment

Endocrine and metabolic disturbances

- Insulin resistance
- Type 2 diabetes
- Dyslipidemia
- Thyroid dysfunction
- Early puberty
- Polycystic ovary syndrome
- Hypogonadism (boys)
- Gynecomastia (boys)

Cardiovascular co-morbidities

- Hypertension
- Left ventricular hypertrophy
- Endothelial dysfunction
- Reduced cardio-respiratory

Pulmonary complications

- Obstructive sleep apnea
- Asthma



Cancer

- Acute lymphatic leucemia

Neurological alterations

- Pseudotumor cerebri
- Cognitive dysfunction
- Reduced eye health
- Hearing loss

Impaired oral health

- Orofacial growth alteration
- Caries
- Periodontitis

Immunologic and autoimmune diseases

- Chronic low-intensity inflammation
- Arthritis
- Diabetes type I
- Multiple sclerosis
- Psoriasis

Renal disturbances

- Glomerulosclerosis
- Hyperfiltration

Gastrointestinal and nutrition complications

- Nonalcoholic fatty liver disease (NAFLD)
- Gallstones
- GERD (Acid reflux disease)
- Vitamin D insufficiency
- Iron deficiency

Musculoskeletal disturbances

- Abnormal bone content
- Altered growth pattern
- Slipped capital femoral epiphysis
- Blount's disease
- Flat feet
- Fractures

Dermatologic complications

- Acanthosis Nigricans
- Stretch marks
- Intertrigo

Fig. 1 Diseases and conditions caused or aggravated by obesity during childhood and adolescence. Childhood obesity is a systemic disease and almost all organs in the body are potentially affected.

“medicalization” of someone’s body is harmful [10]. Consequently, children with obesity should be left alone and treatment postponed. Although such a statement will be misleading, it is important to carefully evaluate the psychosocial risks of stigmatization associated with childhood obesity treatment and compare these risks with the potential health benefits of successful treatment.

In this article, we will go through the long-term medical and psychosocial consequences of childhood obesity and discuss to what extent comorbidity markers during childhood are associated with disease in adulthood. We will demonstrate how much can be gained if effective treatment of obesity is initiated already during childhood.

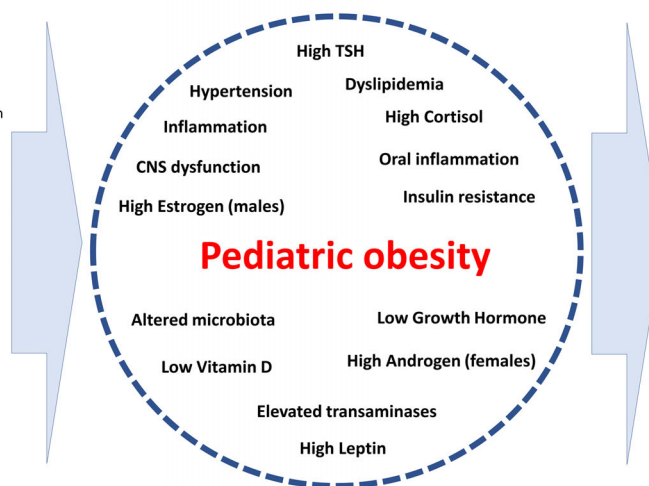
Immunological consequences

As mentioned, almost all organ systems are affected by childhood obesity. Many different factors contribute and interact. Together they create complex vicious circles, which makes it difficult to evaluate the specific importance of one single factor (Fig. 2). One factor of major importance is that obesity—directly due to immunological effects in the adipose tissue and indirectly via endocrinological alterations—affects the immune system. The altered immune system contributes to all long-term obesity-associated comorbidities such as T2D and other metabolic diseases, cardiovascular disease, cancer, and autoimmune diseases.

Risk factors

- Genetics
- Epigenetics
- Obesogenetic environment
 - 24/7- food availability, affordability of energy-dense foods
 - Sedentary activities
 - Limited access to recreation areas
- Unhealthy eating habits
 - Large portion sizes
 - High intake of sugar-sweetened beverages
 - High glycemic foods
 - High intake of fast foods
 - Low fiber content
 - Low intake of fruits and vegetables
 - Irregular food intake
- Lifestyle factors
 - Low physical activity
 - Sedentary lifestyle
 - Insufficient sleep
 - Stress and depression

Mechanisms



Long-term consequences

- Type 2 diabetes
- Type 1 diabetes
- Cardiovascular disease
- Nonalcoholic fatty liver disease
- Cognition defects
- Multiple sclerosis
- Periodontitis and Caries
- Cancer – malignancies
- Mb Crohn
- PCO syndrome
- Gynecomastia
- Premature mortality
- Pseudotumor Cerebri
- Asthma
- Arthritis

Fig. 2 Many different factors contribute to the long-term effects of childhood obesity. They interact in a complex pattern and it is difficult to identify one specific mechanism responsible for one long-term consequence. The low-intensity inflammation caused by obesity in young children already contributes to many obesity-associated diseases.

Obesity and the immune system

The effects of obesity on the immune system have been described previously [11, 12]. Briefly, when pathological amounts of fat accumulate in the adipose tissue, the fat cells become larger, and a pathological immune activation takes place, resulting in low-grade chronic inflammation. Both cytokines secreted from the adipocytes and an increased number of macrophages, lymphocytes, and other immunologically active cells contribute. This condition, which is not due to infection or tissue damage, is sometimes called metabolic inflammation or metinflammation. Also, during normal conditions, the adipose tissue—both adipocytes and immune cells—secretes several endocrine and immunologically active adipokines, but the secretion pattern is altered in children with obesity [12]. Thus, the secretion of pro-inflammatory cytokines—such as tumor necrosis factor- α (TNF- α), resistin, and retinol binding protein-4 (RBP-4)—increases, whereas the secretion of anti-inflammatory adipokines such as adiponectin is reduced. Leptin is an adipokine that is mainly secreted from adipose tissue and circulating leptin levels increase with the growth of the adipose tissue [13]. Leptin is involved in appetite regulation in the central nervous system and puberty devel-

opment, but also has multiple pro-inflammatory effects such as stimulation of the release of IL-6 and TNF- α . The adipokines also interact with cytokines from the liver and muscle tissues, which further increases the complexity [14].

In addition to these direct effects of adipose tissue alterations on the immune system, endocrine alterations secondary to obesity also affect the immune system. Growth hormone (GH) is down-regulated in childhood obesity [15], whereas IGF-1 levels are normal. Both GH and IGF-1 have effects on proinflammatory cytokines. GH deficiency has been associated with high TNF- α , but conflicting results are found, probably due to a different disease background and varying balance between GH and IGF-1 [16, 17]. Another important key player is cortisone, which is converted to cortisol by means of the enzyme 11- β -HSD in several tissues. Increased total body adipose tissue will result in enhanced conversion and thereby higher bioavailability of cortisol, which also affects the immune system [18, 19]. This association is bidirectional as high cortisol levels may predict later development of childhood obesity [20].

Sleep disturbances may also affect the immune system [21], and there is an association between

disturbed sleep and obesity. The causality is unclear, but disturbed sleep in children 2–10 years of age may precede later obesity [22, 23], and it is well established in adults that sleep disturbances induce a different and more unhealthy eating pattern [24]. Again, there is a bidirectional association as obesity also may negatively affect sleep quality [25].

The gastrointestinal microbiome may also contribute to an altered immunological response. An obesogenic food intake with saturated fat and low fiber content may alter the microbiome and induce an inflammatory response [26]. Further, low physical activity—a common problem among individuals with obesity—also contributes to an altered inflammatory response [27], and may also affect the microbiome [28].

Child obesity comorbidities due to an activated immune system

Increased C-reactive protein levels and other signs of chronic inflammation can be detected already in preschool children with overweight and obesity [29, 30], and several diseases are probably affected by the low-grade inflammation. Some of them—nonalcoholic fatty liver disease (NAFLD)/metabolic dysregulation to metabolic (dysfunction)-associated fatty liver disease (MAFLD), insulin resistance and T2D, atherosclerosis, and hypertension—are described elsewhere in this review. The prevalence of asthma is higher among children with obesity compared with normal-weight children [31]. Most probably both mechanical and immunological factors contribute, as two types of asthma phenotypes associated with obesity are described—one early-onset allergic and one late-onset nonatopic asthma type [32].

To which extent the altered immune response among children with obesity will negatively affect the outcome of infections remains unclear. This has been a concern during the COVID-19 pandemic, and it is plausible that obesity and obesity-associated chronic inflammation and other obesity-related factors such as oxidative stress and insulin resistance contribute to the worse outcomes observed among critically ill children with obesity [33, 34].

Osteoarthritis is a well-established comorbidity to obesity in adults [35]. However, there is also

an association between pediatric obesity and osteoarthritis and knee pain in adulthood, independent of weight status in adulthood [36]. This may indicate that although mechanical factors and bone growth alterations may contribute, chronic inflammation is probably a major contributing factor.

Child obesity and autoimmune diseases

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system leading to demyelination and neurodegeneration. Chronic inflammation is probably the most important factor behind the association between childhood obesity and MS [37, 38]. As there is a strong association between early development of obesity and later MS, and also mechanistic data supporting a causal relationship, it is likely that early prevention and treatment of obesity can reduce the MS prevalence [39]. On the other hand, if childhood obesity is not treated, given the high childhood obesity prevalence, childhood and adolescent obesity is projected to contribute to up to 14% of overall risk of MS in 2035 [40].

Type 1 diabetes (T1D) is also an autoimmune disease with increasing prevalence worldwide [41]. It is a disease where genetics and environmental factors contribute, but it is unclear why the prevalence varies markedly between countries [42]. It has been proposed that obesity is involved in the increased incidence of T1D primarily via obesity-induced insulin resistance. The so-called “accelerator hypothesis” proposes that individuals with autoimmune destruction of insulin-producing cells who are more insulin resistant will be more prone to develop clinically manifested diabetes [43]. However, the association between obesity and T1D is complex, and the genetic HLA pattern affects the association between BMI and T1D incidence [44]. Obesity-induced inflammation also seems to increase the risk of developing clinical T1D with only one type of autoantibody present [45]. Furthermore, already long before the T1D is clinically apparent, obesity increases the shift from one to two autoantibodies in childhood and adolescence, but only in specific genetic groups [46].

An association has also been observed between obesity, higher prevalence, and worsened prognosis of several other autoimmune conditions such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel diseases, and psoriasis

[26, 47]. This has also been observed in children, but whether diet contributes to the risk is still unclear [48].

In conclusion, obesity-induced low-grade inflammation is of importance for the development of almost all obesity-related comorbidities and increases the prevalence and severity of several other immunological and autoimmune diseases. The associations between obesity and disease are found already before puberty, which may indicate that early treatment of obesity is required to reduce the incidence of immunologically related diseases.

Cardiovascular health

It is well established that there is an association between long-term cardiovascular health and obesity in general. Cardiovascular diseases and atherosclerosis develop slowly over time, and it is therefore reasonable that the associated mortality rate is higher if obesity develops in young adults compared with later in life [4]. This is of course dependent on the obesity remaining, which unfortunately is regularly the case. Weight loss reduces the cardiovascular risks in adults [49].

Cardiovascular disease in adulthood is associated with childhood and adolescent BMI [50]. In Denmark, it was found that the risk of any cardiovascular event was positively associated with BMI at 7–13 years of age for boys and 10–13 years of age for girls. The risk increased across the entire BMI distribution [5]. However, to what extent individuals with childhood and adolescent obesity have higher cardiovascular risk than individuals who develop obesity as young adults is unclear.

Cardiovascular risk markers with a clear-cut association to cardiovascular morbidity in adults can be found in prepubertal children. Already in 7–8-year-old children there is an association between early signs of atherosclerosis and BMI [51]. Also, endothelial cell dysfunction is associated with obesity in young children [52].

Blood pressure—another factor of importance for later cardiovascular disease and stroke—is frequently increased in children with obesity already before puberty [53]. It has been estimated that 37% of all hypertension in children is attributed to obesity [54]. Night-time systolic blood pressure normally drops more than 10% from daytime blood pressure, so-called nocturnal dipping

[55]. Nocturnal reduction of less than 10% is defined as nondipping, and studies have consistently shown an association between nondipping and increased incidence of fatal and nonfatal cardiovascular events in adults [56]. Among both prepubertal and pubertal children, nondipping occurs frequently [57, 58].

Several factors act in concert to increase the cardiovascular risk (Fig. 2). In addition to the effects of low-grade inflammation discussed above, long-term hypercholesterolemia is probably of major importance for the development of atherosclerosis [59]. Atherosclerosis is thought to develop early in childhood with fatty streaks, and it has been demonstrated in a series of Brazilian studies that cholesterol levels in adolescence are of major importance for fatal heart disease in adulthood [59].

Weight loss in childhood seems to be even more beneficial for long-term cardiovascular health than weight loss in adulthood. A weight loss of 0.2 BMI Z-score units (corresponds to approximately 5–6 kg weight loss for an adult) is associated with reduced cardiometabolic risk markers [60]. Hypertension is effectively reduced provided that marked weight loss is achieved [53, 61]. Moreover, obesity in childhood that does not remain till adulthood does not seem to be associated with increased long-term morbidity compared with children who have had normal weight during childhood [62]. The importance of pubertal BMI is also supported by the finding that a BMI increase from 8 years of age to 20 years is associated with increased cardiovascular risk [63]. Weight loss from adolescence to adulthood effectively reduces diabetes risk to some extent, but the association with coronary heart disease remains [64].

In conclusion, there is a strong association between childhood obesity and cardiovascular morbidity in adulthood. However, normalization of weight status before puberty seems to eliminate these risks. The earlier the treatment is initiated, the better the effect on long-term health, provided that the treatment leads to a normalized weight. As previously mentioned, risk markers for cardiovascular disease are with an alarming frequency found in prepubertal children. The epidemiological data may indicate that these cardiovascular risk markers are reversible and of limited prognostic value before puberty. Furthermore, it is still unclear when these comorbidity

markers and high blood pressure should be pharmacologically treated in children if the goal is to maintain long-term cardiovascular health.

Cardiorespiratory fitness

Low levels of cardiorespiratory fitness (CRF) are associated with a high risk of cardiovascular disease and all-cause mortality [65]. It is to some extent an integrated measure of several factors with negative effects on cardiovascular health such as obesity, T2D, smoking, and sedentary activity, but there are genetic factors that contribute to individual variations of CRF. These familiar and genetic factors are also of major importance for the association between CRF and disease in young males [66].

There is a modest correlation between BMI and CRF in young males, indicating that individuals with obesity may have a normal CRF [67]. A low CRF increases the risk of future cardiovascular disease in young males with obesity [67]. There is also an association between cognition and physical fitness in children [68].

Indirect evaluation of oxygen consumption during a bicycle test is often used as a measure of CRF. In children with obesity, the relative oxygen consumption per kilogram of body weight is invariably low compared with normal-weight children whereas the total maximum oxygen consumption is relatively normal [69, 70], and similar results are found with direct measurement of maximum oxygen uptake [71].

In adolescents, weight loss after bariatric surgery results, as expected, in improved maximal oxygen consumption per kilogram body mass. In addition, pain associated with movement was reduced. More surprising, despite a marked reduction of fat-free mass, absolute oxygen consumption increased. These results suggest that bariatric surgery in adolescence might add specific benefits of importance for future health [72]. The lungs are expanded after weight loss (Fig. 3) but it is unclear whether this improvement is due to changes in the heart, microcirculation, or the lungs.

Glucose homeostasis

Hyperinsulinemia and a disturbed glucose homeostasis are key features of obesity. Glucose homeostasis depends on the balance between β -cell function, that is, insulin release, and target organ

insulin sensitivity. Insulin has several biological effects, and the sensitivity may differ in different organs. As the effect of obesity on insulin sensitivity is also organ specific, it is difficult to predict the pathophysiological picture in hyperinsulinemic conditions.

Insulin resistance usually refers to reduced glucose uptake in the presence of insulin. When the insulin release can no longer compensate for the insulin resistance, T2D occurs. Hyperinsulinemia in obesity is usually considered a compensatory elevation of insulin to achieve the required biological effect on glucose uptake so normal blood glucose is maintained.

Insulin resistance is problematic to measure. The key peripheral tissues affected by insulin include the skeletal muscle mass (the largest insulin-responsive organ that modulates glucose metabolism in the postabsorptive state), the liver (which has the capacity to produce glucose in the fasting state), and the adipose tissue (the source of free fatty acids in fasting and a storage depot during the postabsorptive state). Resistance to the effects of insulin results in reduced glucose uptake in skeletal muscle and adipocytes and reduced suppression of hepatic glucose production. Insulin resistance also results in increased adipose tissue lipolysis. Taken together, the results are elevated circulating insulin, glucose, and free fatty acids, the typical markers of the insulin resistant state.

Obesity in childhood drives insulin resistance together with several other factors. Genetic and epigenetic factors are of crucial importance [73, 74]. Almost all children who develop T2D have family members with the same disease [75]. Several lifestyle factors also contribute, such as physical inactivity, eating habits, stress, and psychosocial problems such as depression [75].

T2D is preceded by a range of glucose-related phenotypes characterized by a progressive decline in β -cell function and an increase in insulin resistance. These conditions are defined as intermediate hyperglycemia or prediabetes. Common markers of dysregulated glucose homeostasis include acanthosis nigricans (isolated hyperpigmentation of the skin), elevated HbA1c, impaired fasting glycemia, and impaired glucose tolerance measured with the oral glucose tolerance test. In adults, intermediate

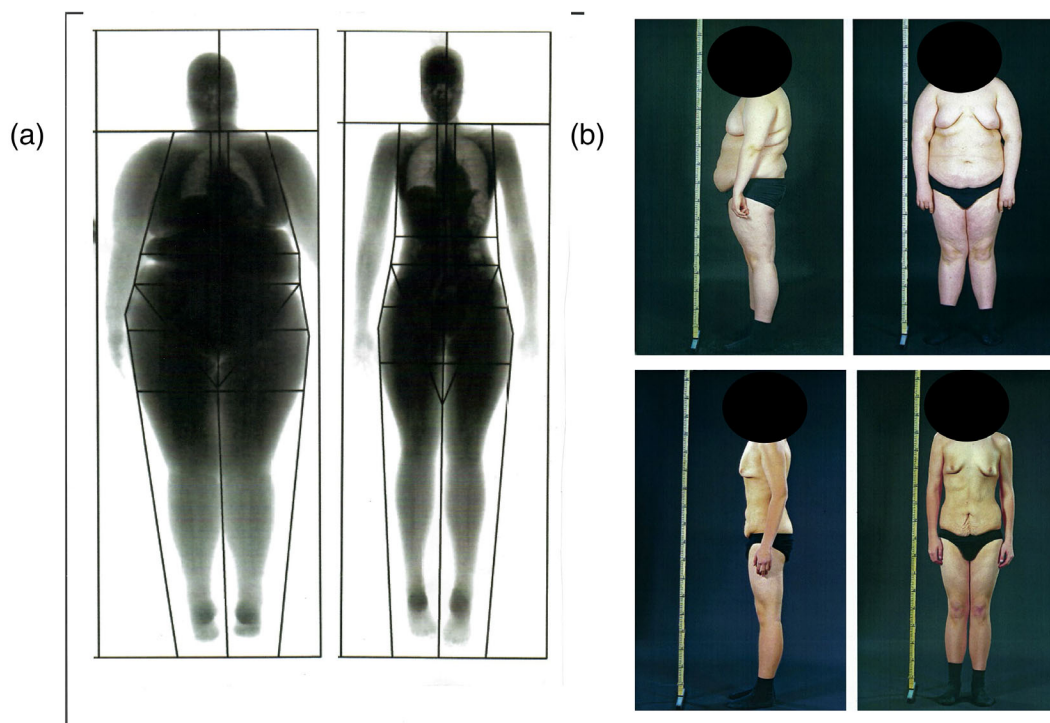


Fig. 3 Effect of severe adolescent obesity and weight loss on lung volume, posture, and gynecomastia in adolescents. (Panel a) Adolescent before and 2 years after gastric bypass surgery and 40 kg of weight loss. The lung volume is markedly restored. (Panel b) One year with 30 kg weight loss as an effect of successful lifestyle support. The posture is normalized and the lipomastia is reduced but the gynecomastia remains despite weight loss. Written approval obtained from the patient to use the photos of him before and after weight loss presented in Fig. 3.

hyperglycemia has been associated with increased risk for cardiovascular disease, cognition, cancer, and premature death even in the absence of the development of T2D [76–80].

T2D in children and adolescents was extremely rare before the present obesity epidemic, that is, only a few decades ago. The prevalence of prediabetes and diabetes in the pediatric obesity population varies greatly across countries and ethnicities but an increase is generally observed [81–85].

Among children and adolescents with obesity, impaired fasting glycemia and elevated HbA1c increase the risk for adult T2D with a hazard ratio of 3.7 and 3.1, respectively [6]. However, the degree of obesity is a major risk factor for future T2D, independent of the presence of intermediate hyperglycemia [6, 62, 86]. Not only obesity, but also overweight in adolescents without any apparent metabolic disturbances, confers a sixfold increase

in the risk of T2DM more than 20 years later, compared with normal-weight controls [87].

The complications of T2D are like the ones of T1D. However, the early onset of T2D, that is, among adolescents and young adults, is fiercer with a much faster progression of the disease compared with T2D with middle-age onset [88]. Moreover, early-onset T2D, that is, in adolescence and young adulthood, is a much more severe disease than T1D diagnosed in the same age range. Diabetes complications such as nephropathy, retinopathy, and neuropathy come earlier and more frequently and together this results in a much higher mortality rate [85, 89–91]. Further, youths with T2D have a more deteriorated fluid cognition than youths with T1D, but the association seems to be mediated by obesity and depression [92].

In conclusion, it is imperative to prevent early development of T2D. While increased BMI in childhood is associated with high risk for future T2D

[93], normalization of childhood weight by late adolescence/adulthood eliminates the increased risk to develop T2D in adulthood [62, 64, 94]. Further, successful obesity treatment in childhood and adolescence improves insulin sensitivity, fades acanthosis nigricans, and lowers the risk for future T2D [6, 95].

Nonalcoholic fatty liver disease

Pediatric NAFLD is a chronic disease and is defined as a condition where $\geq 5\%$ of hepatocytes have vesicular fatty infiltration upon examination of liver histology, provided that it is not secondary to infections, metabolic or genetic disorders, alcohol consumption, or medications [96, 97]. Insulin resistance is a key factor for fatty liver development and visceral adipose tissue is the dominant source of fat accumulation in the liver. Inflammation, diet, and gut microbiota are also involved in the clinical progression and manifestation of NAFLD [98].

Due to its association with obesity, it has become the most common liver disease in children [96], with an estimated prevalence of 28%–41% among children and adolescents with obesity [99]. Among pediatric obesity population, NAFLD is more prevalent among males, those with severe obesity, and those having impaired glucose metabolism [100–103]. Recently, it has been suggested by an international expert group that the condition should be renamed and redefined. The definition, “non-alcoholic,” is primarily problematic for children, for whom alcohol consumption is usually not a concern. MAFLD is therefore suggested with age-appropriate definitions based on sex and age percentiles [104].

It remains unknown whether or to what extent children with fatty liver disease are more likely to have progressive fibrosis or increased risk of cardiovascular disease as adults [97, 104]. It has recently been demonstrated that children and young adults with NAFLD in Sweden have a higher mortality rate compared with age-matched individuals from the normal population [105]. However, children with obesity in Sweden also have higher mortality rate compared with the normal population [3]. Thus, as the children with NAFLD were not BMI matched, it is impossible to estimate whether or how much pediatric NAFLD contributes to increased mortality.

NAFLD is associated with increased risk to develop T2D in adults. The liver is essential in glucose regulation and a disturbed liver function in combination with inflammatory factors associated with NAFLD increases the diabetes risk [106]. However, the association is bidirectional as they so frequently are in this review. T2D is also associated with impaired liver function with increased progression of NAFLD to fibrosis and nonalcoholic steatohepatitis [106].

In the pediatric obesity population, NAFLD is not rarely accompanied by T2D [107], but may also predict future T2D. Two recent studies show that NAFLD and elevated ALT markedly increase the risk for later development of T2D in children and adolescents, respectively, with obesity. After adjustments, the risk for later T2D increased with a hazard ratio of 2.6 in both studies [108, 109]. This is an increase only slightly lower than that observed for children and adolescents with impaired fasting glycemia [6]. The mechanism for the progression to T2D is complex, but hepatic fat infiltration, independent of visceral fat and intramyocellular lipid content, reduces the insulin-induced suppression of endogenous glucose production, which is of major importance for insulin resistance in adolescents with obesity [110].

Treatment options for pediatric NAFLD are limited. There are some studies demonstrating promising effects of probiotics both in adults and children [111, 112] but no long-term studies are available. There is currently no other accredited treatment for NAFLD but decreasing the degree of obesity improves NAFLD [97]. Several studies with a duration of up to 15 months suggest that weight loss is efficacious in reducing NAFLD prevalence [113–116]. Among teenagers who have undergone gastric bypass, transaminases are normalized 5 years past surgery [61]. One recent study has shown that a weight loss of 0.25 BMI standard deviation score or z-score (SDS) units almost eliminates the long-term risk for future NAFLD in pediatric years [117]. Similarly, despite childhood obesity being associated with increased risk for adult NAFLD, the increased risk can be largely reduced by obtaining a normal adult BMI [118].

In conclusion, pediatric NAFLD/MAFLD is associated with increased risk for later development of T2D and effective weight loss seems to eliminate that risk. It remains to be established whether

pediatric NAFLD/MAFLD is associated with liver disease in the adult.

Other endocrine alterations

Thyroid

Elevated thyroid stimulating hormone (TSH) levels as a sign of disturbed thyroid function are regularly observed in individuals with obesity. Usually, thyroid hormone levels, T3 and T4 are within the normal range [119] and weight loss results in normalization of the TSH levels. The situation is similar in children [120]. The mechanisms are unclear but a modest and reversible obesity-induced thyroid gland dysfunction or an increased turnover of thyroid hormones might contribute. Elevated TSH among children with obesity is associated with cardiometabolic markers in childhood and later cardiovascular disease [120, 121]. TSH may have other effects in the body beyond the stimulation of thyroid hormone production [121–123] but based on the present knowledge, there are no signs of a causal association between increased TSH levels in childhood and later disease.

Vitamin D

Low vitamin D levels are often found in children with obesity. Vitamin D deficiency in childhood has been associated with the development of several diseases such as MS [124] and prediabetes [125, 126], that is, two conditions also associated with obesity. Whether supplementation of vitamin D affects T2D, prediabetes, and the metabolic syndrome has been investigated, but with contradictory results [127] and the pathophysiological significance of vitamin D deficiency for the development of T2D is unclear. A large double-blind intervention study in adults failed to identify any beneficial effect on glucose metabolism of vitamin D substitution [128] whereas a modest effect has been noted in children and adolescents [129]. Yet, most likely the association between vitamin D insufficiency and disturbed glucose metabolism in obesity is primarily due to that similar factors contribute to both low vitamin D levels and insulin resistance, that is, sedentary indoor life and unhealthy food intake [130, 131].

The mechanisms behind low vitamin D levels are unknown. Both increased storage in the adipose tissue and increased metabolism have been proposed [130] and it has been suggested that there is no true deficiency since the levels are

low due to increased accumulation in the adipose tissue [132]. It has also been suggested that the metabolism of vitamin D is disturbed [133]. Vitamin D can be metabolized in the adipose tissue and the expression of 25-hydroxylase CYP2J2 and the 1 α -hydroxylase CYP27B1 are decreased in subcutaneous adipose tissue from obese subject [134]. But as mentioned, both indoor activities and poor eating habits probably contribute as well.

GH, IGF-1, and longitudinal growth

GH has many effects on bone growth, metabolism, immune responses, and the central nervous system [16, 135–137]. Many functions are mediated via IGF-1, but some organs, such as the liver and adipocytes, have only GH receptors and no IGF1-receptors. GH levels are markedly downregulated in obesity to levels usually found in severe GH deficiency conditions. Despite that, IGF-1 levels are normal. Most probably, adipose tissue is the main source of circulating IGF-1 in children with obesity and GH levels are downregulated due to negative feedback [15]. Weight loss normalizes GH secretion.

Children with obesity grow faster than normal-weight children despite low GH levels. During puberty, when normal-weight children have a growth spurt, children with obesity have a lower growth velocity and they end up with a similar final height as normal-weight children [138].

The relatively low GH levels in obesity may contribute to the psychosocial effects of obesity. GH deficiency is associated with shyness, inhibition, and memory dysfunction, and memory dysfunction has also been observed in adult females [139, 140]. Given the effects of GH on metabolism and immune response the low GH levels may also contribute to the association between cardiovascular dysfunction and obesity.

Bone health

Osteoporosis is a skeletal disorder characterized by low bone mass, micro-architectural deterioration of bone tissue leading to bone fragility, and increased fracture risk [141]. This is a disease associated with malnutrition and ageing and not with childhood obesity. The bone mass is positively correlated with body weight both in children and adults probably due to greater excess weight activation of bone growth. However, endocrine or paracrine factors associated with the metabolic syndrome and

obesity may negatively influence bone mass. They are released from the adipose tissue and they may have both systemic and local effects within the bone marrow [142–144].

Contrary to expectations, children with obesity have a higher fracture rate than normal-weight children [145, 146]. Mechanistic factors such as a heavier body in combination with altered body proportions may contribute to increased risks for children with obesity when specific fractures are studied [147] in combination with other obesity-related factors such as reduced motor skills and balance problems, as previously suggested [146]. However, it is also possible that bone density is negatively affected in children with obesity [148]. Several factors may contribute to disturbed bone synthesis such as low levels of vitamin D, low-grade inflammation, reduced physical activity, poor eating habits, and insulin resistance [149].

Adolescents with severe obesity who undergo gastric bypass surgery may constitute a risk group for later osteoporosis especially if bone quality is reduced and dual energy X-ray absorptiometry (DEXA) measurements are somewhat misleading. Peak bone mass is usually reached between 22 and 26 years of age [150]. Thus, these individuals have not reached their peak bone mass before surgery. They have a bone mass above normal before surgery but the weight loss in combination with low vitamin D levels results in a very rapid loss of bone mineral content, which may be a future concern [151].

Puberty, polycystic ovary syndrome, gynecomastia, and fertility

Puberty often starts early in females with obesity whereas it is somewhat delayed in males [152]. In females, the menstruations are often irregular, and the insulin resistance seems to trigger a hyperandrogenic state, which may trigger the development of a polycystic ovary syndrome with higher androgen levels and infertility [152]. This is reversible and weight loss during adolescence, causing unexpected increased fertility, may result in unwanted pregnancies [61].

Among pubertal boys with obesity, gynecomastia is relatively common (Fig. 3b). As this occurs together with lipomastia, the breast enlargement may affect the psychosocial well-being. The gynecomastia is primarily thought to be due to aromatization of

testosterone to estrogen in the adipose tissue—a process that is increased in individuals with obesity [153]. Mild gynecomastia is reversible, but often surgical treatment is required [153].

Fertility is reduced both among males and females with obesity. Female fertility is markedly improved after weight loss [154–156]. Couples with an obese male partner have a significantly higher risk of infertility than couples with normal-weight male partners and male obesity negatively affects the success of assisted reproductive technology [157, 158]. To which extent pediatric obesity is of importance for the reproductive health disturbances is unclear, but the factors involved are complex and probably long-term duration of obesity will have more detrimental effects. It is not clarified whether weight loss improves male fertility.

Oral health

The association between poor oral health and cardiometabolic disease in adults is well established [159]. Hypertension, ischemic heart disease, cerebrovascular disease, prediabetes, and T2D are all associated with periodontal disease [159, 160]. Furthermore, improved oral health may improve cardiometabolic health [161]. The local oral chronic inflammation and microbiome alterations are probably of major importance for these associations. The periodontal inflammation triggers a systemic inflammatory response partly due to periodontal pathogens entering the circulation [159].

Oral morbidity is increased in children and adolescents with obesity. Children with obesity have higher occurrence of caries in some studies [162], but the results are inconsistent [163–165]. Adolescents with obesity seems to have markedly lower saliva production compared with normal-weight adolescents, which might contribute to increased caries risk [166]. Periodontal risk markers and cytokine concentration and oral microbiota are also altered in the gingival fluid in adolescents with obesity [167–169]. There is also an association between pathological periodontal pockets and blood pressure among adolescents with obesity [170].

In conclusion, oral health is markedly disturbed among adolescents with obesity. Data from adults may indicate that this will add to the long-term cardiometabolic risk, but to what extent poor oral health among adolescents with obesity

will compromise long-term health remains to be established.

The central nervous system (CNS), cognition, neuropsychology, and psychosocial consequences

School achievement and cognition

Children and adolescents with obesity face several issues in the school environment. Children with obesity more frequently have lower school grades and reach a lower level of education compared with normal-weight peers [171, 172]. Several factors may interplay, for example, resourcefulness, parental education, intelligence, or ability to conform. Also psychosocial aspects such as stigma [173] and increased risk for anxiety and depression contribute [174]. The risk of bullying and social isolation has been shown to increase with the severity of obesity. It has been reported that more than 50% of adolescent boys with obesity and 45% of the girls experience frequent bullying [175].

However, the effects of obesity on school performance remained even when adjusted for socioeconomic status (SES) and neurodevelopmental disorders [8]. Yet, another important aspect is that childhood obesity negatively affects cognitive functions, such as memory, executive functions, and processing speed [176–178]. Animal studies confirm that obesity affects cognition [179, 180], and studies in adult females found that the effects may be reversible [181], but it has not been observed in all studies [182]. One contributing factor may be the obesity-induced downregulated GH levels discussed elsewhere in this article. GH deficiency is associated with similar reversible cognitive effects on memory, as has been found among females with obesity [183, 184].

The negative impact of childhood obesity on educational level may partly be reversed by successful obesity treatment in childhood [8], and in adults, cognitive deficits may be improved after weight loss [181, 185]. Regardless of mechanisms, it is of great importance to increase awareness of the association between obesity and school achievement.

ADHD

Neurodevelopmental disorders, such as attention deficit disorder with (ADHD) or without hyperactivity (ADD), are (at least) 2–3 times more common among children and adolescents with obesity compared to normal-weight peers. The preva-

lence of ADHD/ADD in clinical samples of pediatric obesity has been reported to be 10%–11% among females and 17%–31% among males [174, 186]. The direction of the causal associations between ADHD/ADD and obesity is not clear, even though most studies suggest ADHD/ADD to precede obesity [187, 188].

ADHD/ADD is characterized by altered executive functions, such as impulsivity and impaired ability to retain concentration, attention, as well as self-monitoring. Further, individuals with ADHD exhibit dysfunctional eating patterns to a greater extent than non-ADHD individuals and may even experience a greater reward sensitivity to food through dopaminergic activation in key brain reward areas [187]. Thus, it is likely that ADHD/ADD is a trigger for obesity development in an obesogenic environment. In addition, the psychosocial effects of ADHD/ADD on children with obesity may contribute to an increase in the obesity-related stigmatization. When ADHD/ADD remains undiagnosed among children with obesity, ADHD/ADD-related behavior will incorrectly be associated with obesity.

Depression and anxiety

The association between pediatric obesity and psychiatric problems, such as depression and anxiety, is complex since neurodevelopmental disorders and low SES are known risk factors for anxiety and depression [189, 190] and prevalent in the pediatric obesity population [174, 187, 191]. Nevertheless, there is an increasing body of literature supporting the link between obesity and depression. The results are mixed, and the link seems to be bidirectional [174, 192, 193]. Hence, obesity increases the risk for depression and vice versa. Successful obesity treatment has been associated with lower risk of depression, but not anxiety, in males but not females [174]. However, long term follow-up of adolescents after bariatric surgery indicates that, despite good short-term effects [194], the positive effects of weight loss on depression and anxiety are very limited. These results indicate that depression and anxiety, at least among adolescents with severe obesity, are associated with but not caused by obesity [195–197].

In conclusion, obesity in childhood affects the likelihood to reach the same level of education as that for their normal-weighted peers. Despite that,

the full mechanisms of the mediating factors for this are yet to be determined and the association seems to be partly reversible by weight reduction. Further, it is important to identify children with altered executive functions since ADHD/ADD is common in the obesity population. An attention deficit disorder can worsen the obesity-related psychosocial consequences and increase the risk for stigmatization. Further, depression is prevalent in the pediatric obesity population and needs to be addressed to enable realistic conditions for obesity treatment.

Pseudotumor cerebri

Pseudotumor cerebri, also called idiopathic intracranial hypertension or benign intracranial hypertension, is a neurologic syndrome consisting of headache caused by elevated intracranial pressure. Severe cases may also have signs of vision loss and cranial nerve symptoms, which can be permanent [198, 199]. When it occurs, it is often present together with obesity, but the underlying mechanisms remain unknown. The diagnosis is often delayed as the initial symptom, headache, occurs frequently among individuals with obesity. A substantial weight loss—10% or more—is an effective treatment [200].

Cancer

It is well established that increased BMI in adults is associated with several types of cancer, including the upper intestinal tract, stomach, lower intestinal tract, and parenchymal and endocrine organs [201]. A study from the UK showed that obesity is responsible for nearly 5% of all cancer types, and thereby the second largest modifiable cancer risk factor after smoking that accounts for 17% of the cancer incidents [202]. In a viewpoint review, they found 13 cancer types associated with severe obesity with relative risks that varied from 7.1 for corpus uteri cancer down to 1.1 for thyroid cancer. For eleven other cancer types, the evidence was limited or inadequate [201].

Adolescence cancers

In a large study on 2.3 million Israeli adolescents who were followed for almost 30 million person-years, obesity in adolescence increased the incidence of several cancers [203]. Compared with normal weight, the hazard ratios for overall cancer were 1.26 in males with obesity and 1.27 for females when cervix and breast can-

cer were excluded. However, when including all cancer types, female adolescent obesity was not associated with future cancer. In addition, cancer was diagnosed at an earlier age and with a higher mortality rate for both males and females who had obesity in adolescence [203].

Childhood cancers

Children who gain more in weight than average have an increased risk of several cancers [204, 205]. The duration of obesity, and whether the weight gain is in childhood or adulthood, may affect the risk of cancer. However, it is difficult to distinguish as childhood and adolescent obesity often remains till adulthood. BMI in childhood and during puberty has been positively associated with risks of bladder, colon, endometrial, kidney, liver, esophageal, ovarian, pancreatic, prostate, and thyroid cancer in adulthood, whereas there seems to be an inverse association between breast cancer before menopause and BMI [204]. The associations become stronger with the child's age; for example, the hazard ratios for overall cancer ranges from 1.05 to 1.68 per BMI Z-score at ages 7 and 13 years. Further, childhood BMI is directly associated with the risk of some adult hematologic malignancies, such as non-Hodgkin's lymphoma and diffuse large B-cell lymphoma [205].

A recent study, pooling data from seven international longitudinal cohorts, found that high childhood BMI was associated with subsequent overall cancer mortality, independent of other examined childhood risk factors and more importantly, independent of adult BMI [206]. Further, in individuals who had obesity in childhood, cancer seems to be the most common endogenous cause of death in young adulthood [3]. Thus, childhood and adolescence, periods essential for determining exposures over the life-course, may be an optimal period to intervene to lower subsequent cancer risk.

There is evidence suggesting that high BMI in childhood followed by an increase in BMI during puberty increase the risk for colon cancer [207, 208]. Yet, another study shows that overweight in childhood that persists into early adulthood is associated with an increased risk of colon cancer whereas overweight that disappears before early adulthood or is developed after childhood is not [209]. Two studies found no association between childhood BMI and later rectal cancer, suggesting different etiologies of colon and rectal cancer [207, 208].

Table 1. Risk reduction of future disease depends on when weight loss is achieved

	Cardiovascular	Type II diabetes	Cancers	Autoimmune disease
Prepubertal children	↓↓↓	↓↓↓	↓↓	Unknown
Adolescents	↓↓	↓↓	↓	Unknown
Adults	↓	↓↓	↓	Unknown

Note: Schematic summary of available evidence of risk reductions associated with weight loss. Note that other factors contribute to the development of these diseases, such as genetic and environmental factors. ↓↓↓, total or almost total risk elimination; ↓↓, marked risk reduction; ↓, modest risk reduction.

There are several mechanisms involved in the association between childhood obesity and cancer [210]. The research is complicated as there may go several decades between the effects of the obesity-associated cancerogenic factors on the organs and the development of the cancer. The chronic inflammation, as discussed above, the altered endocrine pattern and alterations in the growth factor secretion, and the metabolic derangements resulting in oxidative stress are most likely contributory factors. Also, the gut microbiome may contribute [211]. More detailed longitudinal long-term studies are required to disentangle the specific factors and their interaction with genetic and epigenetic factors for the development of the different cancer forms.

In summary, epidemiological studies have shown a strong association between obesity in childhood and adolescence and increased risk for several malignancies in adulthood. The underlying mechanisms are not completely understood, but several adipocytokines and inflammatory markers seem to be key players in this process. Normalization of body weight before the onset of puberty seems to reduce the risk for cancer later in life.

Conclusion

It is well established that childhood obesity is associated with long-term risks to develop cardiometabolic diseases and colon cancer, leading to markedly reduced life expectancy [212, 213]. However, the effects of early childhood obesity on immunological processes and the development of autoimmune diseases and several other cancers have been clarified relatively recently and our understanding of mechanisms and how to prevent these diseases are still limited.

The effect of weight loss on future disease risk seems to be disease and age dependent and early

normalization of weight appears to be required for cancers and probably also for autoimmune diseases (Table 1). However, it has to be emphasized that the associations between weight loss and long-term comorbidities have to be handled cautiously. There are decades between the weight loss and some of the comorbidities studied, and the obesity treatment offered 20–40 years ago was of limited efficiency and often nonexistent. During such conditions, genetic and social factors contributed considerably to weight loss, factors that may also affect later comorbidity risks. Thus, the associations between specific diseases and the timing of weight loss have to be confirmed in studies performed when effective weight-loss treatment methods are available.

The societal costs for childhood obesity are obvious, but difficult to estimate. Many diseases associated with childhood obesity may first become apparent in adulthood and costs associated with these diseases, such as health care utilization, productivity loss, disability retirement, and premature mortality, are possible to identify first after several decades [3, 214–216]. Consequently, the estimated costs vary considerably. In Sweden, the extra lifetime costs for a 4-year-old child with obesity have been estimated to be approximately 75,000 Euro [217, 218] but lower estimations have been published from other countries and with other methods [214].

The efficacy of childhood obesity treatment is still rather limited [60, 219]. A reduction in calorie intake is always the goal, but this is difficult to achieve in our society. Intensive lifestyle support with frequent visits every other week is required to obtain a consistent effect [220], but this is rarely an option for families or health care systems. However, digital supported interaction between family and health care staff may markedly reduce the need for frequent physical

Table 2. Treatment options for childhood obesity

Type of treatment	Age group	Average treatment outcome (body-mass index Z-score)	Adverse effects	Comments	Reference
Lifestyle modification support, 4–6 h/year	4–18 years	–0.13 to –0.15	None	Limited effect for adolescents	60, 219
Intensive lifestyle support, 26–52 h/year	4–18 years	–0.17 to –0.30	None	Low adherence ^a Time consuming	220, 225, 226
Parental group sessions, parenting training	4–6 years	–0.30	None	Low adherence ^a Limited experience	227
Digital support for lifestyle modification	4–18 years	–0.30	None	Limited experience	221
Liraglutide	12–18 years	–0.22	Primarily gastrointestinal	For adolescents with insufficient effect of lifestyle support	223
Orlistat	12–16 years	–0.10 ^b	Frequent steatorrheas	Low adherence ^a	228
Gastric bypass surgery	14–18 years	–1.6	Several ^c	Only for adolescents with severe obesity	229

Note: This table provides an overview of treatment options with key references without any ambition to provide a complete list of treatments and supporting references. The outcomes presented are after a treatment period of at least 12 months; for surgery it is 5 years post surgery.

^aIncludes both unwillingness to participate and/or high dropout rate.

^bCalculated from average body-mass index and age provided in the article.

^cAbdominal surgery for intestinal obstruction and gallstones, nutrition problems, gastrointestinal problems, and more.

visits and thereby increase the feasibility, effectiveness, and cost effectiveness of lifestyle support [221, 222].

A new generation of pharmacological treatments are currently being tested in children also, and the first of them, liraglutide, a GLP-1 agonist, is approved from 12 years of age both in Europe and the United States. Despite a good effect on adolescents [223], liraglutide is not yet reimbursed in Europe. The second generation of GLP-1 agonists, semaglutide, which requires weekly injections instead of daily, is currently being tested in adolescents, and tirzepatide, a combined GLP-1 and GIP agonist with marked weight-loss effects, has recently

been approved by the FDA for the treatment of T2D.

Also, bariatric surgery is an option for adolescents with severe obesity. Gastric bypass has been shown to be effective with a marked reduction of cardiometabolic risk markers [61] but one concern is that the long-term outcome is limited for up to 25% of individuals after surgery [224]. Given the life-long perspective, the long-term outcome must be improved for adolescents after bariatric surgery, most probably via intensified post-surgical lifestyle support and pharmacological treatment. Nevertheless, as summarized in Table 2, the pediatric obesity treatment toolbox is far better equipped today than only 5 years ago.

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Conflict of interest

No conflict of interest was declared.

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