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Childhood obesity: increased risk for cardiometabolic disease and cancer in adulthood☆

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ABSTRACT

Prevalence of childhood obesity has worldwide more than doubled since 1980. Underlying factors are complex and are far from completely understood. Strategies to prevent childhood obesity have mainly focused on behavioral intervention; and obesity therapy was mainly based on lifestyle modification to date. However, effects for both have been quite limited so far and no country has succeeded in fighting the obesity epidemy we are facing. Normalization of body weight before onset of puberty is crucial for several reasons: First, obese children and adolescents frequently stay obese until adulthood. Second, obesity during adolescence is significantly associated with increased risk for cardiovascular and metabolic disease such as type 2 diabetes in adulthood. And third, recent data have shown a strong association between higher body mass index (BMI) during adolescence and increased risk for several malignancies such as leukemia, Hodgkin's disease, colorectal cancer, breast cancer and others in adulthood.

This review summarizes our current understanding of epidemiology, underlying factors, concomitant disease, as well as available intervention strategies and gives an overview of what has been reached so far and what measures should be undertaken to counteract the obesogenic environment.

1. Introduction and Epidemiology

More than 50% of the population of the European Union was estimated to have overweight, and one person in six was estimated to be obese in 2012 [1]. The Global Burden of Disease Study has systematically evaluated prevalence of childhood overweight and obesity since 1980 and has shown that obesity prevalence has doubled in more than 70 countries worldwide since then. In 2015, a total of 107.7 million children (and 603.7 million adults) were classified as obese, corresponding to a worldwide prevalence of childhood overweight and obesity of 23% [2–4]. Although there seems to be at least some light at the end of the tunnel as obesity prevalence is stabilizing or even decreasing in younger children, obesity prevalence as well as severity of the disease continues to increase in adolescents [5,6]. However, somatic comorbidity significantly increases with severity of obesity, and associated comorbidities include arterial hypertension, dyslipidemia, dysglycemia with disturbed glucose tolerance and hyperinsulinemia, elevated transaminases and nonalcoholic fatty liver disease (NASH), increased risk for Polycystic Ovary Syndrome (PCOS) in girls as well as psychiatric disorders such as depression or attention deficit disorder [7]. More than half of obese children and adolescents have already at least one biochemical or clinical cardio-vascular risk factor and one quarter have more than two [8]. In addition, adolescent obesity is associated with increased morbidity and mortality in midlife due to cardio-vascular or metabolic disorders [9]. There is also increasing body of evidence that childhood obesity is associated with increased cancer risk in adulthood [10,11].

2. Underlying Factors

The increase in body weight at an individual level as well as development of obesity at a population-based level is attributable to a bunch of different factors and predispositions which are far from completely understood.

On the one hand, syndromic obesity forms that might have a monogenic or oligogenic underpinning are very rare and are responsible for the development of obesity only in the absolute minority of patients. To date, only about 50 genetically based syndromes are described that share the cardinal symptom obesity (Online Mendelian Inheritance in Man ®; https://www.omim.org/).

On the other hand, as the increasing obesity prevalence is seen in both industrialized and developing countries and is affecting all age

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groups, it may not simply be attributable to income or wealth [2]. Underlying genetic and epigenetic mechanisms are complex and include the interaction between many genes and the environment. The heritability of the variance of body weight is estimated around 40–70% [12].

The predisposition of becoming obese later in life starts as early as in utero, and many factors during pregnancy are already attributable to the development of obesity during childhood. Such factors include maternal leisure-time physical inactivity [13], maternal smoking during pregnancy [14], excessive gestational weight gain and maternal obesity, gestational diabetes, high birth weight, protein content of maternal diet or short sleep duration during pregnancy [15–19]. Children born by caesarean section also seem to be at higher risk of developing obesity in childhood [20].

Factors in early infancy that have been associated with increased risk for obesity include complementary (sugar-rich) foods to infants before 4 months of age [21] or high protein diet in non-breast feed children [22]. There is also growing body of evidence that antibiotic exposure to infants younger than 2 years might be associated with increased risk for childhood overweight or obesity suggesting an influence on the microbiota [23,24]. Famine exposure during early life may increase the risk of overweight and obesity later in life especially in females [25,26]. Traffic pollution was positively associated with increase in BMI in children aged 5–11 years [27].

In addition, important drivers for the worldwide increase of childhood obesity are changes in the food environment, such as 24/7-availability, accessibility, and affordability of energy-dense foods and sugary drinks as well as marketing strategies of such foods, which have led to excess energy intake and weight gain, starting as early as in infancy and early childhood. On the other hand, daily physical activity has continuously decreased during the past decades, with leisure time activities of children and adolescents focusing more and more on new media and sedentary behaviors. Both factors, different eating habits and decreased physical activity are the result of urbanization [28,29]. Another factor that is increasingly gaining importance is shorter sleep duration and lower sleep efficiency, which is associated with a poorer cardiometabolic risk profile in adolescence [30]. There is strong evidence that sleep quantity and quality have major impact on cardiovascular risk profile, circadian rhythms across development (infancy to adulthood), and many other factors that may influence body weight regulation in childhood and adolescence [31].

Both, short sleep duration and poor sleep quality in children are associated with a significantly increased risk of adolescent obesity [32,33].

3. Underlying Mechanisms Leading to Disease

The pathophysiology of obesity is not fully understood; however, several mechanisms that may interplay have been identified. On a pathophysiological level, the interplay between muscle and fat tissue, gut and brain is of significant importance [34,35]. Adipose tissue, especially the tissue surrounding internal organs (visceral fat) is today regarded as an active endocrine organ that secretes a variety of pro-inflammatory adipokines, which act at both the local and systemic level [36]. Increasing adipose tissue mass leads to changes in the secretion of these adipokines as well as increased turnover of free fatty acids which facilitate insulin resistance, the harbinger of metabolic disturbances associated with obesity [37]. It is well established that visceral fat does not only play a role in the human energy metabolism, but that it also actively secretes hormones and peptides (adipocytokines), such as leptin, adiponectin, resistin, MCP-1, Retinol binding protein 4 as well as a variety of interleukins together with TNF-α, which enhance the development and/or the progression of chronic diseases, including insulin resistance and chronic inflammation [38]. There is a strong risk association between an increase in visceral fat mass and risk of developing NASH or type 2 diabetes, mediated by changes in secretion profiles of several adipokines [37–39].

4. Childhood Obesity and the Risk of Cardiovascular or Metabolic Disease in Adulthood

About 4 million deaths worldwide were attributable to overweight and obesity in 2015, and almost 70% of them were due to cardiovascular disease [2–4]. Many obese adolescents already have cardiometabolic comorbidities which often start around the onset of puberty. The incidence of arterial hypertension, dyslipidemia, non-alcoholic fatty liver disease NASH, hyperuricemia and impaired glucose tolerance/hyperinsulinemia and insulin resistance is already considerably higher in obese adolescents and young adults compared to normal weight peers [7,8,40–44].

If the onset of obesity is around 7 years of age and if BMI is further increased between that age and puberty, the risk for type 2 diabetes in midlife is significantly increased, even if body weight had been normal before the age of seven [44,45]. However, even mild reduction in body weight before the onset of puberty can significantly reduce the risk for cardiovascular and metabolic disease later in life: If increased BMI is reduced towards normalization of body weight between 7 and 13 years of age and if normal body weight is maintained into early adulthood, the risk to develop type 2 diabetes is similar to that of peers, who had normal body weight throughout their life [44]. These results were confirmed by another study with more than 6000 subjects and a follow-up period of more than 20 years: a reduction of body weight towards normal BMI-values or even a smaller reduction of body weight towards a decreased severity of obesity between childhood and adulthood has been shown to be associated with significant reduction of cardiometabolic sequalae such as arterial hypertension, dyslipidemia or type 2 diabetes in adulthood [45]. However, if obesity has started very early in life and persisted from early childhood until adolescence, the risk of coronary heart disease in midlife was significantly increased [46,47].

Childhood obesity is not only associated with considerably increased risk for cardiovascular disease later in life but apparently also with increased risk for disturbed glucose tolerance and type 2 diabetes that may start as early as during adolescence. Prospective cohort studies could show that the duration of obesity is independently associated with increased risk for type 2 diabetes later in life. Moreover, each 2-year increment in the duration of obesity increases the risk of type 2 diabetes by as much as 14% [48,49].

Taken together, there is strong evidence by large cohort studies that childhood obesity is associated with markedly increased risk for concomitant cardiovascular or metabolic disease in adulthood. Thus, every effort towards normalization of BMI – ideally before onset of puberty – should be made, as already small steps are beneficial: Already mild overweight during adolescence is associated with increased cardiovascular risk in midlife, as shown by a large cohort study with data sets from 2.3 million adolescents between 1967 and 2010. A BMI between 50 and 74th percentiles during adolescence (which would still be regarded as normal weight) was already associated with significantly increased risk for cardiovascular disease and death from coronary heart disease compared to those with BMI values between the 5th and 24th percentile during 40 years of follow-up [50]. The lowest rates of cardiovascular deaths were observed in the group with BMI-values between 25th and 49th percentile during adolescence [50].

However, also normalization of body weight or "decreasing severity if obesity" between childhood and adulthood is associated with significantly reduced risk for metabolic syndrome, including type 2 diabetes, arterial hypertension or dyslipidemia, in adulthood [45]. The duration of obesity is independently associated with an increased risk of type 2 diabetes, and each-year increment in the duration of obesity (already starting during adolescence) increases the risk of diabetes by as much as 14%. Increased BMI at 7 years of age seems already to be markedly associated with significantly higher risk for mortality from cardiovascular disease in adulthood [44]. However, a distinct BMI threshold that is associated with increased cardiometabolic risk remains to be determined [50].

5. Childhood Obesity and Cancer Risk in Adulthood

Excess body fat is associated with predominantly twelve cancer sites – mouth/pharynx and larynx, esophagus (adenocarcinoma), stomach (cardia), bowel, liver, gall bladder, pancreas, postmenopausal breast, endometrium, ovary, kidney, prostate and womb [51]. Four to 38% of these cancers (depending on site and gender) can be attributed to overweight or obesity in adulthood [52]. Moreover, there is sufficient evidence to date in humans that avoiding overweight or obesity may markedly reduce the risk of cancers of the colorectum, endometrium, kidney (renal cell), esophagus (adenocarcinoma) and postmenopausal breast cancer [53].

Meta-analyses of prospective cohort studies as well as large observational studies have confirmed these associations, and could, in addition, show a positive association between BMI and some other malignancies, including thyroid cancer, leukemia, malignant melanoma, multiple myeloma and Non-Hodgkin lymphoma [53] as well as gastric cardia cancer [54]. A recent meta-analysis including seven large prospective studies could demonstrate an increased relative risk to develop acute myeloid leukemia (AML) in both, obese man and obese women. A linear increase of 3.8% in AML incidence was found per kg/m^2 BMI [55].

Taken together, available observational studies provide evidence that most of the risk increases are in the range of 10–30% for an increase in BMI of 5 kg/m^2. The risk of obese subjects to develop any of these cancers discussed before is estimated to be 1.5–3.5-fold [52,53]. In Germany, incidence of newly diagnosed malignancies is due to overweight and obesity in more than 30,000 cases per year (7%) [56]. Thus, there is strong evidence about a positive association between obesity or excess body weight and cancer risk, and maintaining a normal, healthy weight is regarded as one of the key players to reduce cancer risk throughout the life [57].

To date, there is conflicting evidence on childhood obesity and cancer risk in adulthood [58]. First evidence was suggested about 10 years ago that the risk for adult cancer is increased if the individuum had been obese during childhood. This has been especially shown for smoking-related cancers [59] and for colorectal and kidney cancer [60].

The most recent and most comprehensive data set to answer that questions is provided by a large multiethnic cohort study involving about 2.3 million male and female adolescents aged 16–19 years who underwent medical examinations for the compulsory military service in Israel. For the first time, possible associations between being obese during adolescence and the risk of developing different types of cancer later in life were investigated. The follow-up period was 45 years. An association could be shown for increased BMI during adolescence and higher risk for leukemia [11], Non-Hodgkin lymphoma [61], pancreatic cancer [62, gastroesophageal adenocarcinoma [63], colorectal cancer [64], renal cell carcinoma [65], and acute myeloid leukemia [66] in adulthood. Higher BMI in (late) adolescence was found to be associated with increased cancer risk, irrespective of country of origin and after correction for potential confounding factors [11,61–66].

The association between obesity and cancer risk seems to be regardless of timing of obesity for some malignancies: Obesity in early life seems to be associated as strongly as obesity in the years immediately prior to diagnosis in acute myeloid leukemia or myelodysplastic syndrome, and the strongest associations were observed in individuals with class II/III obesity (≥35 kg/m^2). Although a threshold weight for increased risk could not be defined, most subjects gained >10 kg between adolescence and adulthood [67].

6. Prevention of Childhood Obesity - What Has Been Reached So Far?

Much emphasis has been given towards preventive strategies during the past decades, which should start as early as possible. Preventive interventions were classified into behavior-oriented (individual-based) and community-based or environment-oriented (context-related) [68]. Most obesity prevention programs for children and adolescents have focused on the behavioral approach to date. However, effects on reducing children's BMI in the long term have been only marginal so far [69,70]. We know that current prevention strategies for childhood overweight and obesity are insufficient in terms of reducing body weight in the long term and inadequate in daily life or clinical practice in most countries of the world. As available data are very heterogeneous in terms of type, duration and intensity of the intervention as well as long-term follow-up, it is not possible to draw final conclusions at this point [70].

Community-based/environment-oriented prevention strategies have to be implemented to stop the global obesity epidemic we are facing. Such strategies are based on the recommendations of the Association for the prevention and control of noncommunicable diseases of the WHO [71]. In order to fight the obesity epidemy in the long term, public health approaches are mandatory. Such approaches should include measures by municipalities such as parks and playgrounds within walking distance of residential areas, save bike lanes, promoting save footways to kindergardens and school as well as approaches by federal governments such as improving quality of school meals by development of binding quality standards for the catering offers in kindergartens and schools, implementation of a sugar – or fat tax to reduce consumption of unhealthy foods, increase in daily physical activity by offering more physical activity/sports in schools and kindergartens and a ban on unhealthy food advertisement to children [71,72].

Some countries have already started to implement some of these measures or policies, and results in terms of long-term outcome are desperately awaited [73].

7. Treatment Options for Childhood and Adolescent Obesity

As far as therapeutic options of childhood obesity are concerned, the most important approach for the majority of patients is **lifestyle modification** including behavioral treatment, a balanced diet with reduction in energy-dense, sugar- and fat-rich produces and increase in physical activity. These are the cornerstones for treatment of pediatric obesity [74]. However, effect sizes achievable over 12–24 months, measured in BMI-SDS (standard deviation score of body mass index) units are rather small and are ranging between 0.05 and 0.42 BMD-SDS units. Success rates clearly correlate with age with younger kids having significantly better outcome, sex (girls perform better), socioeconomic status (success rates are better in participants from families with higher SES), migration background, ethnicity, and many other factors [74–76]. Thus, there is considerable interest in combining lifestyle modification with additional strategies, including pharmacotherapy, to ameliorate pediatric obesity. However, with regard to **pharmacotherapy**, there are no currently approved drugs for childhood obesity except Metformin, an oral antihyperglycemic agent approved by the US Food and Drug Administration to treat type 2 diabetes in children aged >10 years. Its safety profile led to enthusiasm for use in the pediatric population, and Metformin has been proven to be of therapeutic value in its application. Although evidence regarding the effects of metformin in pediatric obesity is scarce to date, a reduction in BMI after metformin therapy (1000–2000 mg/d) compared with the effects of lifestyle interventions alone after 6 to 12 months has been shown in obese children and adolescents in several studies [77–82]. In addition, Metformin improved cardiovascular risk profile and inflammatory biomarkers in obese children and adolescents [79–81].

Although there are some promising results regarding the effects of Metformin in obese children and adolescents with type 2 diabetes, puberty might act as a potential modifier on the effect of metformin in childhood: The decrease in body mass index and inflammatory and cardiovascular-related obesity parameters seems to be greater in prepubertal children compared to pubertal children [83].

Medications under development that might have therapeutic value in the pediatric population include *Incretin hormones* such as glucagon-like peptide 1 (GLP-1). It enhances glucose-stimulated insulin secretion, exert central anorectic effects and has several peripheral actions.

Exenatide and *liraglutide* (GLP-1 analogs) are approved by FDA so far for adults with type 2 diabetes mellitus [84]. Preliminary studies in (extremely) obese children and adolescents are promising: A significantly higher weight loss can be achieved from exenatide compared to lifestyle modification alone [85]. However, studies on the long-term safety, tolerability, and efficacy of GLP-1 analogs in children and adolescents are needed before further recommendations regarding the use of this drug in pediatric obesity can be made.

Bariatric surgery is a treatment option only for a minority of patients with morbid (extreme) obesity and concomitant disease, if conservative treatment approaches have failed [86]. Two large trials (Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS study) and Treatment Options of Type 2 Diabetes in Adolescents and Youth (TODAY study) have compared glycemic control in severely obese adolescents with type 2 diabetes following medical treatment or surgical intervention. In the TODAY study, participants were randomized to receive metformin therapy alone or in combination with rosiglitazone (or insulin therapy in cases of progression of disease) or an intensive lifestyle intervention. Teen-LABS participants underwent a primary bariatric surgical procedure. After 2 years, body mass index and mean hemoglobin A1c concentration significantly decreased in participants of the Teen-LABS study, but not in those of the TODAY study. These data provide evidence that surgical treatment of severely obese adolescents with type 2 diabetes may improve glycemic control significantly more than medical treatment or lifestyle intervention [86]. However, data on long-term outcome of surgical therapy in terms of weight reduction or side effects on the growing organism are still limited. At present, bariatric surgery is not recommended as treatment option for the majority of obese adolescents, but only for a minority of patients with severe obesity, significant morbidity and if conservative treatment options have failed [86].

In summary, lifestyle modification is the cornerstone intervention for both preventive and therapeutic approaches for childhood and adolescent obesity so far, but achievable effect sizes have been rather small to date. Pharmacotherapy of bariatric surgery is a therapeutic option only for a minority of obese pediatric patients with defined criteria such as type 2 diabetes or other concomitant disease.

8. Discussion and Outreach

Obesity prevalence has dramatically increased worldwide and increase in childhood obesity was as high as 8- to 8.7-fold since 1975 [67]. Overweight and obesity in adolescence account for as much as 20–25% of cardiovascular deaths in adulthood [50]. Already modest increase of BMI between 7 and 13 years of age is associated with a significantly higher risk to develop type 2 diabetes or cardiovascular disease later in life [43,50]. As pointed out in the Global Burden of Disease 2015 study, obesity has emerged to be one of the leading health risks and is associated with significant morbidity and increased mortality in adulthood [2,3].This is – at least in part – also contributable to the fact that childhood obesity is linked to markedly increased risk for metabolic and cardiovascular disease as well as several malignancies in adulthood [50,51].

No country worldwide has developed a successful strategy so far that could stop the high prevalence of childhood or adolescent obesity and that could fight the obesity epidemy. Although effective interventions for prevention and therapy of childhood and adolescent obesity are available as shown in systematic reviews of the Cochrane database, the effect sizes achievable in terms of long-term weight loss are rather small [68].

There is increasing body of evidence that normalization of body weight in obese children should be achieved before onset of puberty, as already moderate increase of BMI, starting between 7 and 13 years of age, is associated with a significantly higher risk for type 2 diabetes and cardiovascular disease in midlife [43,44]. Obesity during childhood and adolescence also seems to be associated with significantly increased cancer risk later in life. Many of these associations have been demonstrated for the first time in a large prospective cohort study with 2.3 million Israeli adolescents [11,61–66]. Underlying mechanisms are far from completely understood, however, it is postulated that an increase in body weight and development of obesity that occur during the critical period of puberty may play a central role in the development of type 2 diabetes later in life: Puberty is a period that is associated with marked decrease in insulin sensitivity [87]. Thus, it may be biologically plausible that excess body weight during childhood and adolescence leads to the development of type 2 diabetes through the early onset of insulin resistance [87]. Additional metabolic alterations associated with obesity and excess body weight include increased circulating levels of inflammatory markers and increased levels of estrogens and other hormonal factors [57]. These factors may – in addition to cardiometabolic disease – also contribute to the development of cancer: An energy-dense, fat- and sugar-rich diet with low intake of dietary fibers, fruits and vegetables as well as high consumption of red meat [88] as well as physical inactivity [89] are both directly associated to cancer risk. The change of diet towards a diet rich of fibers, fruits and vegetables may significantly reduce the individual cancer risk by reduction of adipose tissue, circulating insulin and inflammatory markers as well as by decreasing sex steroids and growth factors [88]. On the other hand, physical activity may prevent cancer by decreasing fat depots and insulin resistance, but also by reducing inflammatory markers, sex hormones and growth factors as well as by minimizing oxidative stress and DNA-damage [89].

Adipose tissue is meanwhile recognized as a metabolically active organ. More than 400 adipose-tissue-derived hormones and cytokines (adipokines) are produced or secreted by adipose tissue. Metabolic alterations in adipose tissue and other organs of obese individuals include increased levels of insulin or steroid hormones or changes in the bioavailability of insulin-like-growth factor I (IGF-I). These alterations have been implicated to have major influence in the development of cardiovascular and metabolic diseases associated with obesity as well as the development of cancer [57,90].

In vitro and in vivo studies in animals have shown that insulin may stimulate the proliferation of tumor cells in colon, breast, prostate, and bladder [91]. Indirect evidence for a potential impact of insulin in cancer development in humans is provided by epidemiological studies: Patients with type 2 diabetes mellitus and hyperinsulinemia have an increased risk for developing different types of malignancies as could be shown in a large meta-analysis of randomized controlled trials, cohort studies and case-control studies. Subjects with type 2 diabetes who used metformin had a reduced risk to develop cancer compared to patients who received sulfonylurea, a medication to stimulate insulin secretion. The latter had an increased in all-cancer risk [92].

Several adipokines which are secreted in adipose tissue have been suggested as key players in the pathogenesis of cancer: Leptin promotes the production of inflammatory markers, and several oncogenes have been linked to inflammation and cancer development via different pathways: on the one hand, some types of tumors need an inflammatory environment before a malignant change occurs; on the other hand, other types of tumors induce an oncogenic change via an inflammatory microenvironment that promotes the development of the tumor. In addition, an inflammatory environment promotes the proliferation and survival of malignant cells as well as angiogenesis [93].

It remains unclear to date if there is a threshold BMI for the switch from metabolic health to metabolic disease and how this switch may over time change cardiovascular disease risk. The Nurses' Health Study (NHS) followed up more than ninety thousand women between 1980 and 2010 for incident of cardiovascular disease or metabolic health, defined as absence of diabetes, arterial hypertension and hypercholesterolaemia. The alarming news were that women who maintained metabolically healthy obesity during follow-up were still at a higher cardiovascular disease risk compared with women with stable healthy normal weight, suggesting that obesity remains a significant risk factor for metabolic and cardiovascular disease, even when metabolic health is maintained during long periods of time [94].

In summary, normalization of body weight before puberty is the goal for slowing down the progression of risk for type 2 diabetes and cardiometabolic disease as well as cancer risk in adulthood. To achieve this innovative action is needed on individual, environmental and policy levels [95].

9. Conclusions

Obesity during childhood and adolescence has emerged to be a global health burden. Many obese adolescents stay obese until adulthood, which leads to markedly increased morbidity and mortality later in life.

Obesity induces major changes in the cytokine and hormone status of the growing organism in childhood and adolescence, which are involved in the pathogenesis of type 2 diabetes, cardiometabolic disease and different types of cancer. Thus, normalization of body weight before the onset of puberty is desirable, as this is a crucial period of time for the development of hyperinsulinemia and insulin resistance. Hyperinsulinemia and subclinical inflammation are suggested to be key players for the development of concomitant disease of obesity.

As no country worldwide has succeeded in developing a successful strategy to prevent (or treat) childhood and adolescent obesity, we need to rethink which measures and strategies have to be implemented in the future. There needs to be a shift towards public health approaches including measures by municipalities as well as approaches by politicians and federal governments. We need to get the ball rolling in order to stop the obesity epidemy that is already seen in most countries of the world.

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