Childhood obesity, cardiovascular and liver health: a growing epidemic with age

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REVIEW ARTICLE

Childhood obesity, cardiovascular and liver health: a growing epidemic with age

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Abstract

Background The frequency of childhood obesity has increased over the last 3 decades, and the trend constitutes a worrisome epidemic worldwide. With the raising obesity risk, key aspects to consider are accurate body mass index classification, as well as metabolic and cardiovascular, and hepatic consequences.

Data sources The authors performed a systematic literature search in PubMed and EMBASE, using selected key words (obesity, childhood, cardiovascular, liver health). In particular, they focused their search on papers evaluating the impact of obesity on cardiovascular and liver health.

Results We evaluated the current literature dealing with the impact of excessive body fat accumulation in childhood and across adulthood, as a predisposing factor to cardiovascular and hepatic alterations. We also evaluated the impact of physical and dietary behaviors starting from childhood on cardio-metabolic consequences.

Conclusions The epidemic of obesity and obesity-related comorbidities worldwide raises concerns about the impact of early abnormalities during childhood and adolescence. Two key abnormalities in this context include cardiovascular diseases, and non-alcoholic fatty liver disease. Appropriate metabolic screenings and associated comorbidities should start as early as possible in obese children and adolescents. Nevertheless, improving dietary intake and increasing physical activity performance are to date the best therapeutic tools in children to weaken the onset of obesity, cardiovascular diseases, and diabetes risk during adulthood.

Keywords Cardiovascular · Childhood · Liver health · Obesity

Introduction

Obesity in children and adolescents has emerged as one of the most serious health problems, condition which threatens future health and longevity. Over the past 30 years, childhood obesity rate has doubled and, in some cases, even tripled in developed countries [1].

According to the Global Health Observatory Data 2017 by World Health Organization (WHO), there are over 340 million obese children and adolescents aged 5–19.

The aim of this thematic review is to provide current data about the impact of excessive body fat accumulation in infancy across adulthood, as a sound predisposing factor of cardiovascular and hepatic consequences. We also discuss the impact of physical and dietary behaviors starting from childhood on obesity-related comorbidities.

Epidemiologic burden and consequences of obesity

The rate of increase in obesity is faster in children than in adults [2]. Countries with a rapid development, as China, are displaying a remarkable increase in childhood obesity,

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with the number of overweight and obese Chinese children aged 7–18 years increasing by 28 times from 1985 to 2000 [3]. In the United States, the prevalence of obesity in the pediatric population reaches 18.5%, affecting almost 14 million of children and adolescents [4]. In Italy, about 21% of children are overweight and 10% are obese, with obesity trends expected to increase further [5]. A similar trend emerged in a previous ultrasonographic study in children and adolescents in southern Italy [6]. Obese children have a fivefold increased risk to stay obese during adulthood, as compared to normal-weight children [7, 8]. Infancy and childhood are critical moments in which key metabolic changes occur with health effects later in life. Both the children born large for gestational age or small for gestational age have the risk to develop obesity and metabolic consequences (Fig. 1). Genetic factors play only a minor role whilst social, economic, and environmental factors drive the increase of the obesity prevalence. The role of epigenetic factors at an early age is also important in determining adulthood metabolic abnormalities [9–13]. Table 1 depicts the potential weight-related comorbidities in obese children. Obese children are more susceptible to cardiovascular diseases (CVD) [14–17], metabolic alterations [18, 19], orthopedic complications, and psychosocial disorders, such as low self-esteem, anxiety, social isolation, and poor academic performance [20]. In addition, obese children may show abnormalities in the liver, reproductive system, brain, as well as increased blood pressure, impaired gluco-lipid metabolism, and sleep apnea. Thus, the priority

Table 1 Potential weight-related comorbidities in obese children

Hypertension
Nonalcoholic fatty liver disease
Dyslipidemia
Cardiovascular disease, early atherosclerosis
Insulin resistance, type 2 diabetes mellitus
Sleep apnea
Orthopedic disease
Precocious puberty
Polycystic ovary syndrome
Pseudotumor cerebri

Adapted from [14–17].

is to design preventive measures to halt the number of obese children becoming unhealthy during adulthood [21].

Assessment of childhood overweight and obesity

Obesity results from excessive fat accumulation in the body, usually assessed by body mass index (BMI), i.e., body weight (kg) divided by the square of height (m^2). According to the International Classification by the WHO, adults are considered overweight when BMI $\geq$ 25 kg/m^2 and obese if BMI $\geq$ 30 kg/m^2. Incorrect evaluation of BMI as indicator of body adiposity can occur when muscle
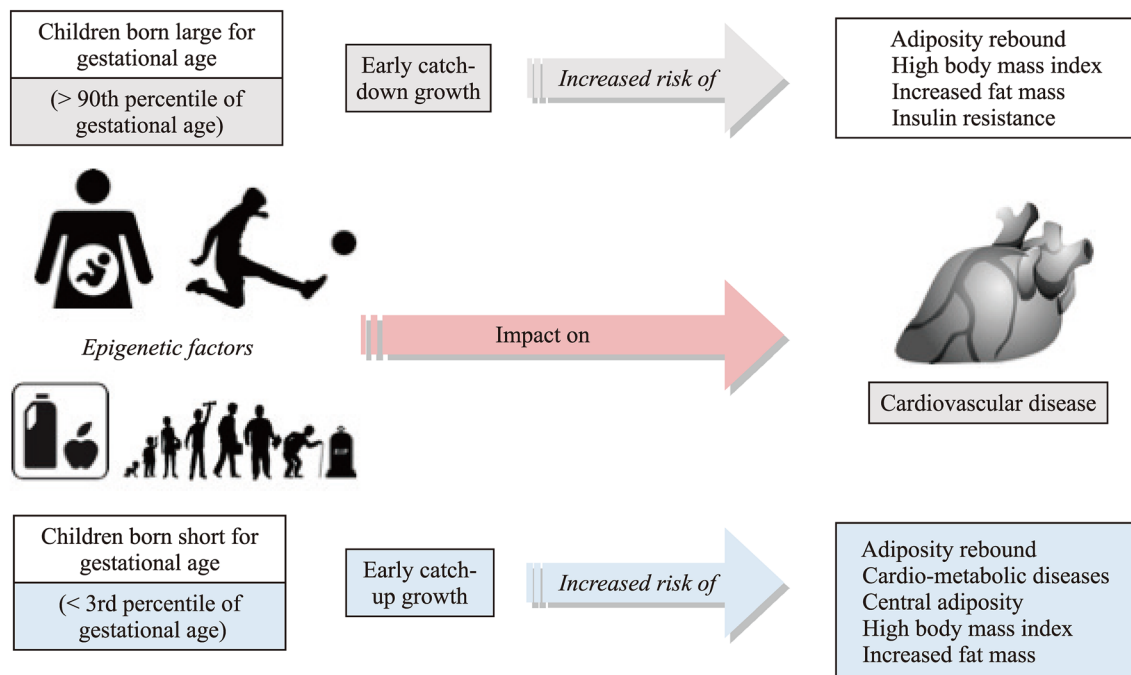

Fig. 1 Factors influencing obesity and its comorbidities

mass is increased or reduced in people engaged to frequent physical activity and to sedentary life, respectively.

In children up to 2 years, the diagnosis of overweight and obesity relies on the weight/length ratio using the WHO 2006 reference curves. For children over 2 years, the diagnosis is based on the use of BMI using the WHO 2006 reference curves up to 5 years, and the WHO 2007 reference curves thereafter. The diagnosis of overweight is made for BMI values ≥ 85th percentile and < 95th percentile, while obesity is defined by BMI values ≥ 95th percentile [22, 23]. The 99th percentile is the cut-off used to define severe obesity since this value corresponds to a higher prevalence of cardio-metabolic risk factors and persistence of obesity later in life, as compared with lower percentiles [14]. However, the WHO terminology used to define severe obesity differs from younger (up to 5 years of age) compared to older children and adolescents. Indeed, the 99th percentile identifies obesity in the former group, and severe obesity in the latter. The different cut-off used to define these conditions is justified by the differences in growth process at different ages [24, 25].

The recommendation to use the WHO reference curves relies on their higher sensibility in identifying overweight and obese children. Indeed, the Italian BMI thresholds [26] underestimated the prevalence, likely due to the curves based on dates collected in a time when the increase in obesity had already occurred [27].

Body composition can change among different ethnicities. For example, within the same BMI, non-Hispanic black children and adolescents show lower percentages of fat mass than non-Hispanic white or Mexican Americans. This condition explains why they are less prone to become obese [28]. Singapore Chinese adolescents, on the other hand, tend to have higher fat mass than Dutch Caucasian adolescents [29], and they are more predisposed to develop obesity-related consequences; hence, the cut-off to define overweight and obesity in Asian children and adolescents is lower [30]. Notably, in a recent meta-analysis, the number of genomic loci associated with height and BMI was disproportionately increased compared to previously published genome-wide-associated studies [31]. The authors suggest that the discovery of new loci will increase prediction accuracy and provide further data to explain complex trait biology.

The impact of childhood and adolescence obesity on CVD

CVDs are the most frequent cause of morbidity and mortality globally. Atherosclerosis is one of the main contributing factors for CVD. This process begins already during childhood mostly under the influence of environmental factors. Some studies suggest that maternal weight gain in early pregnancy may be a critical period for an adverse childhood cardiovascular risk profile [32].

Other studies found an association between BMI in childhood and increased risk of adulthood CVD and mortality. Twig et al. examined BMI in a cohort of 2,300,000 Israeli aged 16 and 19 years, in the search for a correlation between death and CVD later in life. In the 40-year follow-up, a correlation existed between increased risk of cardiovascular events and all-cause mortality in adults whose BMI increased during adolescence [33]. Baker et al. found similar results in a cohort of 276,853 Danish children. In particular, the increase of 1 unit in BMI Z score in 13-year-old children almost doubled the risk of adulthood CVD [34]. Bjorge et al. found a correlation of obesity with premature death, even if the critical age range associated with such increased risk remained uncertain [35]. Concerning the critical BMI threshold, Aune et al. conducted a meta-analysis of the available studies investigating the correlations of BMI with all-cause mortality. The nadir existed at BMI 23–24 kg/m^2 among non-smokers, 22–23 kg/m^2 among healthy non-smokers, and 20–22 kg/m^2 when the analysis was limited to studies with longer durations of follow-up [36].

Due to the strong correlation between childhood obesity and the CVD risk during adulthood, several studies aimed to identify early markers of CVD. McGill et al. demonstrated the presence of early atherosclerotic lesions [37], which appear first in the distal aorta and then in the carotid arteries. Carotid intima–media thickness (cIMT) is considered a valid marker of pre-clinical atherosclerosis, and several studies support its role as independent predictor of CVD even in asymptomatic subjects [38]. In addition, cIMT may be a good marker of cardiovascular alterations in children, although studies show some discrepancies [39]. Freedman et al. analyzed a cohort of 513 subjects and detected a positive correlation between BMI measured throughout life and cIMT at age of 35 years. These associations, however, were restricted to adults who continued to be obese. In particular, they found the BMI-CVD correlation to be weak before the age of 11 years, but it progressively increased with age, reaching the strongest correlation among adolescents aged 15–18 years [40]. Juonala et al. found no significant association between BMI measured at 3, 6, 9 or 15 years and cIMT 21 years later, even though a positive correlation existed with BMI at ages 12 and 18 [41]. In a longer follow-up, Wright et al. did not find any significant correlations between childhood BMI and cIMT at the age of 50 [42].

The impact of childhood and adolescence obesity on liver health

The raising prevalence of obesity, metabolic syndrome together with insulin resistance [43], worldwide is associated with liver abnormalities encompassing the clinical spectrum

of nonalcoholic fatty liver disease (NAFLD). NAFLD occurs in the absence of other triggering factors such as hepatitis C, alcohol consumption, parenteral nutrition, or steatogenic drugs. Whereas nonalcoholic fatty liver (NAFL)—a relatively benign condition [44]—implies more than 5% of fatty hepatocytes without hepatocellular injury, the term nonalcoholic steatohepatitis (NASH) is associated with fatty liver and hepatocellular injury revealed by the histological findings of hepatocyte ballooning, with or without fibrosis [45]. A third category is NASH cirrhosis, showing current or previous evidence of histologic NASH or NAFL. Ethnicity, age, metabolic syndrome, insulin resistance [46, 47], dyslipidemia [48], high intake of dietary fructose [49–51], all influence the development of NAFLD [52], with males showing higher risk than females [53]. In children, NAFLD is now the most common cause of liver disease [54–56], and this trend is somewhat worrisome because even in children NASH may evolve to fibrosis, cirrhosis (as early as 8 years) [57, 58], and even liver failure [59–61]. This correlation NAFLD/NASH, however, seems weaker in children than adults, suggesting a milder phenotype of NAFLD [62]. Since adults with NAFLD have high risk to die from cardiovascular disease, clinicians and the public should be aware that children with NAFLD must receive a full evaluation to detect or prevent important comorbidities listed in Table 1, and including type 2 diabetes mellitus, and cardiovascular disease. Based on elevated serum aminotransferases, imaging or liver biopsy, the prevalence of NAFLD in children and adolescents and in obese children ranges between 6 and 38%, depending on the context, the population studied, and the ethnicity (Table 2).

As reported in adults, also children with NAFLD remain mostly asymptomatic [8] or describe mild symptoms such

as pain in the right upper quadrant or nonspecific symptoms, including fatigue and abdominal discomfort [63, 64], or symptoms due to obesity-associated comorbidities (i.e., gallstones, gastroesophageal reflux disease, etc.) [65]. Thus, physical examination should look for comorbidities, splenomegaly, and end-stage liver disease (cirrhosis). Serum abnormalities include elevated liver transaminases, alkaline phosphatase, and gamma-glutamyl transpeptidase [8, 56, 58, 66, 67] which tend to improve upon adoption of healthy lifestyles (see below) [66, 68]. Notably, even in children with NASH the levels of aminotransferases may remain normal [69], and this possibility is intrinsic to the limited sensitivity and specificity of serum aminotransferase levels for clinically significant NAFLD. Due to the high and further raising prevalence of obesity and metabolic syndrome in children, recent guidelines recommend the screening of obese children as the primary screening for NAFLD. Steps vary according to the existence of concomitant comorbidities and levels of serum transaminases (i.e., normal, moderate, and > 2 upper normal limit persistent elevation) [15]. At least in children, imaging techniques for the screening diagnosis of NAFLD are not routinely recommended [15, 70], due to poor sensitivity and specificity (ultrasonography) [71, 72], poor correlation with steatohepatitis, fibrosis (magnetic resonance) [73–75], or detection of only advanced fibrosis, costs, lack of definitive cut-off values and need validation (magnetic resonance elastography) [76]. The role of liver biopsy (which ultimately confirms the diagnosis of NAFLD and determines the severity of the fatty liver disease with the presence and extent of inflammation and fibrosis [15, 56]) needs to be discussed on a case-by-case basis. Cases should include forms of more progressive NAFLD, possibility of

Table 2 Studies relating diagnosis of nonalcoholic fatty liver disease with prevalence of nonalcoholic fatty liver disease in children/adolescents

Diagnosis	Country	Populations	Prevalence of NAFLD	References
Aminotransferase elevations[a]	USA	2450 children (12–18 y) NHANES III	6% in all 10% in obese	[67]
	USA	12,714 children (12–19 y)	11% in all	[68]
	USA	Meta-analysis on 23 studies (1–19 y)	7% in all 13.7% in obese	[59]
Ultrasound	USA	Meta-analysis on 44 studies (1–19 y)	7.6% in all 41.3% in obese	[59]
Liver histology	USA	Autopsy 742 children/adolescents (San Diego County)	Whole 9.6% (NASH 3% of all, 23% of NAFL) 38% in obese Hispanics > White > Black	[69]
	USA	Liver specimens within 48 h death 582 subjects (2–19 y) 50% Black, 33% Hispanic, 12% White, 3% Asian, and 2% other; 36% had a body mass index > 85%	4.5% NAFLD (1.7% NASH) White 8.3%, Hispanics 7.9%[b], Black 1%	[70]

NHANES National Health and Nutrition Examination Surveys, *NASH* nonalcoholic steatohepatitis, *NAFLD* Nonalcoholic fatty liver disease

[a]Limited sensitivity and specificity for clinically significant NAFLD [71, 72], [b]Large proportion of Caribbean Hispanics (protective against NAFLD)

other liver diseases, and morbidly obese scheduled for bariatric surgery.

In spite of the emerging epidemics of pediatric NAFLD worldwide, there is no established treatment so far, even when considering metformin (for improving insulin sensitivity), vitamin E (for reducing inflammatory changes in the liver), cysteamine bitartrate (as antioxidant agent), and ursodeoxycholic acid (for reducing the bile acid hepatotoxic effect) [15]. As a matter of fact, aggressive treatment of comorbidities and lifestyle intervention (diet, exercise, weight management, counseling) remain the mainstay of treatment even in pediatric NAFLD [77, 78].

Impact of lifestyles starting from childhood

Physical inactivity affects a vast majority of children and adolescents who become prone to high obesity rates and related diseases, including CVD and NAFLD. Promotion of programs involving physical activity has, therefore, become a relevant topic in health policy. Messing et al. conclude that "multi-component interventions in childcare facilities and schools stand out prominently" [79]. Molina–Molina et al. have recently discussed several mechanisms for which physical inactivity might affect CVD [80]. Between ages 5–6 and 8–9, there are similar increases in physical inactivity for both boys and girls, as reflected in a British cohort of 57 primary schools [81]. Already during adolescence, physical activity starts to decrease, contrarily to body weight [82]. A series of factors such as dietary intake and sedentary behaviors contribute to childhood obesity [83]. The phenotype of obesity could differ depending on the children's age, gender, and family characteristics. Studies on television viewing and total recreational screen time in youth might be associated with adverse CVD risk factors, such as adiposity, increased triglycerides, and metabolic syndrome [84]. Other authors have linked sedentary time with diabetes and high blood pressure in obese and overweight adolescents [85, 86]. Several hours of television viewing by adolescents doubles the odds for metabolic syndrome later in adulthood, as observed in a study by Wennberg et al. [87]. Not only sedentary behaviors, but above 10 hours of night time sleep in primary school children from Germany was also associated with obesity [88].

Poor dietary habits in children also increase the risk of obesity. Among children, parents and caretakers have the greatest influence on their eating habits [89]. According to a study by Lipowska et al., children's eating patterns are influenced by the parent–child interaction, shaping the nutritional status, which ultimately contributes to their health [90]. Nutritional status of children can also have direct effect on growth, development, and nutrition related-health problems [91].

The portion size of food consumed each day depends on age, sex, stage of growth, body weight and size, and level of physical activity [92]. Children who consume large portion sizes, hyper-caloric and high-energy-dense foods gain excess weight and body fat, while CVD risk increases [93]. Reduced consumption of fats, carbohydrates, and added sugars and more intakes of vegetables and fruits could decrease obesity in children and risk to CVD [94].

Both an optimal nutrition and regular physical activity increase the chances of healthy maturation during childhood [95]. According to Elmaogullari et al., age and BMI are the most important factors to be considered in childhood obesity [96]. Overall, changing dietary patterns seems the best treatment against obesity, CVD, diabetes, and NAFLD.

Conclusions and future perspectives

The epidemic of obesity and obesity-related comorbidities worldwide raises concerns about the impact of early abnormalities during childhood and adolescence. Exact evaluation of body composition parameters is required at an early age, to classify correctly the metabolic abnormalities, and to decrease the chances of further dysmetabolic changes at a later age.

Two key abnormalities in this context include cardiovascular diseases, and nonalcoholic fatty liver disease, a wide spectrum of conditions ranging from simple liver steatosis, steatohepatitis, and (metabolic) cirrhosis. Notably, nonalcoholic fatty liver is associated with increased risk of mortality in the adults. This means that appropriate metabolic screenings and associated comorbidities should start as early as possible in obese children and adolescents. Nevertheless, improving dietary intake and increasing physical activity performance are to date the best therapeutic tools in children to weaken the onset of obesity, CVD, and diabetes risk during adulthood.

Compliance with ethical standards

Ethical approval This article does not contain any studies with human participants, but refers to previously published papers/studies that were in accordance with the ethical standards of the institutional and/

or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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