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Cardiometabolic risk in obese children

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Abstract

Obesity in childhood remains a significant and prevalent public health concern. Excess adiposity in youth is a marker of increased cardiometabolic risk in adolescents and adults. Several longitudinal studies confirm the strong association of pediatric obesity with the persistence of adult obesity, and the future development of cardiovascular disease, diabetes, and increased risk of death. The economic and social impact of childhood obesity is further exacerbated by the early onset of the chronic disease burden in young adults during their peak productivity years. Furthermore, rising prevalence rates of severe obesity in youth from disadvantaged and/or minority backgrounds have prompted the creation of additional classification schemes for severe obesity to improve cardiometabolic risk stratification. Current guidelines focus on primary obesity prevention efforts, as well as screening for clustering of multiple cardiometabolic risk factors to target interventions. This review summarizes the scope of the pediatric obesity epidemic, the new severe obesity classification scheme, and examines the association of excess adiposity with cardiovascular and metabolic risk. We will also discuss potential questions for future investigation.

Keywords

obesity; pediatric; cardiovascular disease; insulin resistance; type 2 diabetes

Introduction

Childhood obesity, defined by the World Health Organization (WHO) as abnormal or excessive fat accumulation that presents a risk to health, is a global disease with potentially devastating consequences[1,2]. Youth who are overweight/obese have ~5-fold increased risk of excess adiposity in adulthood with a high risk for obesity-related comorbidities[3–7]. Obesity-associated comorbidities can be debilitating, and premature death and morbidity, primarily related to cardiometabolic disease, represents the most significant economic and social public health burden of the obesity epidemic[8,9]. In the United States, the cumulative

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Competing interests

attributable cost related to direct medical care and lost productivity from childhood obesity could exceed $250 billion[8].

Model estimates forecasting this public health impact rely on a large body of evidence linking childhood obesity to future adult cardiovascular disease. In addition to a direct effect of abnormal excess adiposity in accelerating atherosclerotic disease, the clustering of cardiometabolic risk (CMR) factors such as hypertension, insulin resistance, dyslipidemia, and type 2 diabetes compounds the cardiac disease risk. Several socio-environmental and biological factors are associated with childhood obesity and CMR. The younger age of onset for obesity, cardiovascular disease and diabetes means that the chronic disease burden will begin during the peak productivity years, further crippling the health of the community[7]. This review summarizes the magnitude of the current epidemic, provides an update on new obesity classifications schemes and their association with CMR, and highlights areas for future investigation.

Scope of the Problem

Rates of childhood obesity and overweight vary markedly by world region and income status[10]. Since the mid-1970s, the body mass index (a measure of weight relative to height as kg/m^2) in children and adolescents has steadily risen, giving way to the global recognition of childhood obesity or excess adiposity in childhood as a significant public health concern[11]. In high-income countries, such as the United States, England and Australia, rates of combined childhood overweight and obesity range between 20–35%,[12,13] with the prevalence rates of obesity alone as high as 17–20% in U.S. youth aged 2–18 years, depending on the classification scheme used. The high obesity rates observed in the U.S. are increasingly seen in countries around the globe that are undergoing epidemiological transition from communicable to non-communicable diseases[14]. For example, rates of childhood obesity are at or approaching 20% in youth residing in Polynesia, Micronesia, the Middle East, north Africa and the Caribbean[10,13]. Yet, emerging data in some high-income countries, such as the U.S. and England, suggest that the rate of increase in childhood obesity is plateauing[10,12,13].

Despite this positive trend, the global burden of excess adiposity and obesity-related comorbidities remains significant because it disproportionately affects minority racial/ethnic groups and those from disadvantaged socio-economic backgrounds[13]. Although, under-nutrition and food shortages are still the predominant form of malnutrition in many low-income countries (for example in India and Africa), rapid weight-gain and obesity are also occurring in some youth[10]. The cardiovascular impact of this dual problem of under- and over-nutrition has not been fully quantified[15].

Classification of childhood obesity

To reduce this global epidemic, accurate classification of childhood obesity and its association with disease risk is paramount for primary and secondary prevention. As childhood is a time of growth, obesity categories are commonly based on body mass index (BMI) percentiles derived from growth charts, to account for gains in weight relative to

height. Three main classification schemes are used internationally and are based on growth charts developed by the Center for Disease Control (CDC), the World Health Organization (WHO), or the International Obesity Task Force (IOTF)[16–19]. The U.S. CDC growth charts were published in 2000 and were based on smoothed data gathered from five national surveys conducted between 1963 and 1994 in the U.S[17]. According to the CDC definition, overweight classification in children over 2 years of age is defined as BMI ≥ to the 85th but less than the 95th percentile, and obesity as BMI ≥ to the 95th percentile of the reference range for age and sex[17]. Of note, the CDC growth charts do not assess height or weight in children under 2 years of age. The WHO growth charts were developed by a WHO expert committee in 2007 using the 1977 National Center for Health Statistics growth reference data from 5 to 18 years, supplemented with data from the WHO Child Growth Standards for children ages 5 years and younger[16,19]. The WHO system defines overweight as a BMI greater than 1 standard deviations (SD), and obesity as a BMI greater than 2 SD, from the mean of the WHO reference population[16,19]. In an attempt to establish an international definition of obesity, the IOTF developed a classification scheme in 2005 based on an extrapolation of the adult BMI cutoff points for overweight (25 kg/m^2) and obesity (30 kg/m^2) from large nationally representative growth data from six countries (Brazil, Great Britain, Hong Kong, the Netherlands, Singapore, and the United States)[18].

Among the three classification schemes is heterogeneity in prevalence assessments for overweight and obesity[20–22]. The prevalence estimates of overweight and obesity are often highest when using the WHO classification systems, intermediate with the CDC definition, and lowest when using the IOTF definition[20,21]. At present, therefore, there is no international gold-standard definition for overweight and obesity in childhood, yet governments and non-governmental research organizations strive to ensure consistency and transparency in the classification schemes used to enact policy changes related to childhood obesity. In the U.S., for example, CDC growth charts are used for youths ≥2 years old, while WHO charts are used during the first 2 years of life[23]. Notably, long-term data are also required for evaluating the classification scheme that best correlates obesity and cardiometabolic disease in adulthood.

Over the last two decades, there has been a marked rise in prevalence of extreme obesity, i.e. youth with a BMI ≥ to the 99th percentile on the CDC growth charts[13]. With increasing prevalence of marked adiposity, further classification schemes for extreme obesity in childhood have been proposed that utilize BMI Z-scores or additional growth percentiles[24–26]. However, BMI Z-scores poorly correlate with degree of body fatness in youth with severe obesity[24]. Alternatively, Flegal *et al.* used smoothing models to derive additional growth percentiles for children with severe obesity to improve tracking of clinical progress and assessment of associated health risks[25,26]. Additional proposed obesity subcategories are: Class I (BMI 95th percentile to 120% of the 95th percentile), Class II (BMI 120% to 140% of the 95th percentile), and Class III (BMI >140% of the 95th percentile)[27]. Recognizing the need for standardized definitions and for describing the clinical picture associated with patients presenting with large volumes of adipose tissue, the American Heart Association and the Obesity Society published a scientific statement in 2013 recommending that severe obesity in children 2 years of age and older be defined as a BMI ≥120% of the 95th percentile or an absolute BMI ≥35 kg/m^2, [26]. Including an absolute

BMI threshold was proposed to align the pediatric definition of obesity with the high-risk category of class II obesity in adults. These subcategories were incorporated into new growth charts for severely obese children for improved tracking of clinical progress and assessment of associated health risks[25,26].

BMI as screening tool for cardiometabolic risk

Traditional BMI categories are widely accepted risk screening tools because of their simplicity, cost-effectiveness, and strong correlation with CMR[28,29]. Additional risk stratification, using the 3 subcategories of obesity (Class I, II, and III) mentioned above, have been recently recommended by the American Heart Association and the Endocrine Society Guidelines on Childhood Obesity[26,30]. Using data for 3- to 19-year old children from the 1999–2012 National Health and Nutrition Examination Survey (NHANES), Skinner et al. demonstrated that compared to youth with Class I obesity, youth with Class III had a >2-fold increased risk of hyperglycemia and hypertension[31]. Similarly, in a larger group of youth aged 6–19 years, the odds for hypertension, hypercholesterolemia and fasting hyperglycemia progressively doubled with every increase in BMI category from normal to overweight to Class I, II, and III obesity, respectively[32]. Therefore, these obesity subcategories help to identify youth who may benefit from more intensive treatment strategies, such as pharmacotherapy, supervised lower-calorie diets, or bariatric surgery (assuming patients meet specific criteria).

Though BMI classification of overweight and obesity is a universally accepted screening tool, it is not without limitations. BMI measures weight relative to height (kg/m^2) and approximates total adiposity with relatively high specificity[33]. However, BMI may have low sensitivity in specific populations; it can overestimate adiposity in youth with a high percent lean body mass and underestimate adiposity in very lean youth[33]. Importantly, BMI suboptimally predicts CMR among certain racial/ethnic groups with low, normal or high-normal BMI[34]. In these individuals, high CMR despite lower BMI categories may be related to socio-environmental factors, for example, low socio-economic status, failure to thrive, or early childhood adverse events such as intrauterine growth retardation, child maltreatment and parental incarceration[35–38]. The influence of childhood adversity on heart disease, T2DM, and stroke later in life is underscored in the recently published Scientific Statement on Childhood and Adolescent Adversity and Cardiometabolic Outcomes from the American Heart Association[39]. The conceptual model posits that childhood adverse events are related to 3 inter-related mechanisms: (1) health behaviors such as physical inactivity, poor-quality diet, poor sleep, and smoking, (2) physiologic mechanisms including inflammation and hypercortisolemia, and (3) substance abuse and mental health disorders[39]. Each of these mechanisms in isolation or combined is strongly related to increased CMR. Although strong, the existing evidence has been associative and future studies to elucidate mechanisms and resiliency are needed, especially in children with normal weight and BMI.

One key reason why BMI percentiles may not accurately capture degree of adiposity, is the limited specificity of BMI to identify ectopic fat depots such as visceral and hepatic compartments[40]. It is well established by multiple epidemiologic and clinical studies in adults and children, that CMR varies with location and distribution of fat accumulation. In

recognition of the variation in the relationship of adiposity with CMR among individuals of Asian descent[41], the American Diabetes Association (ADA) recently updated their overweight screening recommendations to include a lower BMI cut-point of ≥ 23kg/m^2 for defining overweight status in adult Asian Americans. This lower BMI cut-point for Asian Americans has subsequently been shown to improve sensitivity for detecting prediabetes and diabetes[42]. Currently there are no racial/ethnic thresholds for children in the United States or around the world, despite the knowledge that population-specific reference BMI percentiles are superior for assessing patterns of adiposity[43].

Childhood obesity and cardiovascular disease

Regardless of measurement method, excess adiposity in children has been shown to be strongly associated with the development of atherosclerosis and hypertension. The strongest data confirming the independent and interdependent association of childhood obesity and its comorbidities with cardiovascular disease is derived from post-mortem and several well-designed prospective studies (Table 1).

Early evidence that increased adiposity in childhood is associated with atherosclerotic lesions was derived from two landmark studies. The Bogalusa Heart Study was a post-mortem evaluation of 204 young persons, aged 2–38 years, who died from primarily traumatic causes[44]. Among the 93 youth/young adults with ante-mortem risk factor data, the presence of fatty streaks and fibrous plaques in otherwise healthy children confirmed the early-onset and progressive nature of coronary heart disease. In a larger multi-center study of 2876 autopsied young persons aged 15–34 years, The Pathobiological Determinants of Atherosclerosis in Youth (PDAY), obesity was an independent and a prominent risk factor for fatty streaks[45]. Notably, the extent of atherosclerotic lesions was mediated by the number of CMR factors present (i.e. obesity, hypertension, dyslipidemia and smoking), irrespective of age. Several cross-sectional[46–51] and prospective studies[44,52–59] have subsequently established the association of childhood obesity with surrogate markers of atherosclerosis – carotid intima media thickness (CIMT), arterial stiffness and coronary artery calcification during adulthood (Table 1). Obesity in adolescence increases the risk for incident stroke[60] and premature death from coronary heart disease and stroke, by 2–4 fold[61].

Discerning the independent contribution of childhood obesity to cardiovascular disease and diabetes is challenging because obesity co-segregates with other CMR factors such as hypertension, dyslipidemia, and insulin resistance. Most, but not all, studies[62,63] that have rigorously tracked risk factors from childhood to adulthood and accounted for known adult-onset mediators such as adult BMI and systolic blood pressure, support childhood obesity as a primary mediator of risk[57,58,64]. Even in studies in which the magnitude of the relationship between childhood BMI and CIMT was small, the strong tracking of BMI from childhood to adulthood suggest that childhood obesity remains a primary driver of adult CMR[57].

The International Childhood Cardiovascular Cohort (i3c) consortium was created in 2009 to facilitate collaborations and provide insight into the interdependent contributions of obesity and CMR factors to cardiovascular disease[65,66]. The consortium initially comprised of 4 large comprehensive prospective cohorts: The Bogalusa Heart Study, The Muscatine Study,

PDAY, and The Childhood Determinants of Health Study and has since expanded to include smaller studies such as the Princeton Follow-up Study, two Minneapolis studies and the National Heart Lung and Blood Institute Growth and Health Study [65,66]. Collectively, consortium data have demonstrated that childhood obesity is a strong independent risk factor for arterial vascular abnormalities, even after adjusting for risk factor status in adulthood (e.g. adult hypertension and obesity)[67]. Importantly, data from this consortium has also helped to determine that 9 years is the optimal age for using childhood BMI as an independent risk predictor[68].

Pathophysiology

A direct pathological association of obesity with cardiovascular disease may be mediated by increased preload and vascular damage[51]. When combined with ectopic fat accumulation in the myocardium, increased ventricular stiffness leads to vascular dysfunction, hypertension and left ventricular hypertrophy[69]. Independently, obesity-associated insulin and leptin resistance also promote inflammation and endothelial dysfunction which increases arterial stiffness, susceptibility to plaque formation and accelerated atherosclerosis[51]. Furthermore, the tracking of elevated blood pressure in youth to adulthood and the increased strain placed on the ventricles significantly increases CMR early in life[70].

Notably, the increased ventricular strain induced by childhood obesity may be reversible; children with obesity who transitioned to normal weight status as adults had a risk comparable to persons who were never obese[71,72]. In keeping with these findings, the Childhood Determinants of Adult Health sub-study demonstrated that obesity was associated with increased ventricular mass in childhood but this was not related to poor ventricular diastolic function as an adult[73]. Rather, differences in risk for heart failure were closely correlated with current adult weight. Interestingly, childhood BMI was strongly associated with insulin resistance and hyperglycemia as an adult, while BMI gain from childhood to adulthood was the most important determinant of adult hypertension and hyperlipidemia and stroke[7475].

Childhood obesity, insulin resistance and type 2 diabetes

Childhood obesity strongly correlates with insulin resistance and type 2 diabetes[76]. Moreover, severe obesity occurs in a majority of diabetic youth,[77] and the emergence of prediabetes and type 2 diabetes in children closely correlated in time with the childhood obesity epidemic. Progressive glucose intolerance towards type 2 diabetes is precipitated by rapid weight gain, the physiologic decline in insulin sensitivity of puberty, and a relative decline in insulin secretion unable to compensate for the increased demand[78–81]. The prevalence of prediabetes in youth with obesity is variable but this may be related to differences in the definitions used for prediabetes. Using a HbA1c thresholds ≥ 5.7%, and fasting glucose ≥ 100mg/dl, rates of prediabetes in adolescents aged 12–19 years were 5%, and 15% respectively[82]. However, if a 2-hour glucose threshold of ≥140mg/dl is used, up to 21% of obese youth could be classified as having prediabetes[83].

Once glucose intolerance develops, prediabetes progresses to diabetes ~10–15% per year, with the highest rates in African-American youth with severe obesity[84]. The childhood

obesity epidemic is associated with a 3-fold increase in prevalence rates of type 2 diabetes rates in youth over the last 3 decades. Youth in the lowest socio-economic bracket and from ethnic minorities (African-American, Hispanic, Asian or Pacific Islanders and Native American youth) have the highest prevalence rates[85,86]. High cardiovascular risk in these youth is related to both the comorbidities of type 2 diabetes (dyslipidemia, hypertension, non-alcoholic steatosis) and the hyperglycemic effect on the vasculature. Increased risk of disability from microvascular disease and death from cardiovascular disease occurs just 10–15 years after disease onset[87,88]. This rapid nature of type 2 diabetes in youth further accelerates the progression of micro and macrovascular complications, and unfortunately short-term improvement in glycemia did not decrease the prevalence of CMR markers[89]. In fact, despite over 2 years of treatment with metformin, rosiglitazone or diet and lifestyle modification in the TODAY study (see below for details), dyslipidemia and chronic inflammation (measured by high sensitive C-reactive protein) worsened with time[89]. Further research is urgently needed to identify targeted therapies to help reduce the risk of future cardiovascular disease in these high-risk youths.

Pathophysiology

Insulin resistance—Obesity associated accumulation of high circulating levels of free fatty acids and pro-inflammatory factors causes peripheral and hepatic insulin resistance[90]. Increased ectopic fat deposition (liver and visceral compartments) are strong predictors of glucose intolerance and type 2 diabetes. Many, but not all studies[91,92], indicate that ectopic fat accumulation in visceral and hepatic compartments is a more significant determinant of cardiometabolic health than overall BMI in adolescents[93,94] and adults[95] with obesity. Visceral and intra-peritoneal adipose depots may increase hepatic insulin resistance through the release of localized inflammatory mediators or as a direct substrate for the release of free fatty acids[90]. In addition, increased abdominal subcutaneous fat may also play a role and was found to be a stronger predictor of insulin sensitivity and dyslipidemia in children compared to adults[91].

Type 2 diabetes—As in adults, the pathogenesis of type 2 diabetes in youth is characterized by two main pathophysiological features: insulin resistance and declining insulin secretion[96]. However, the natural history of type 2 diabetes in youth is characterized by a more rapid decline in β-cell function and faster progression to diabetes-related complications in youth compared to adult-onset disease[97,98]. In the only randomized treatment trial for type 2 diabetes in youth, The Treatment Options in Type 2 Diabetes in Youth (TODAY) study, severe metabolic decompensation, requiring insulin therapy, was evident in ~50% of youth within 3 years of diabetes onset[98]. Treatment failure occurred regardless of treatment with metformin, metformin plus rosiglitazone or metformin plus lifestyle modification and was accompanied by a 20–35% decline in pancreatic β-cell function per year [99]. In contrast, only 20–30% of adults treated with metformin experience treatment failure within 5 years and β-cell function declines at 7–11% per year as illustrated by the ADOPT and UKPDS studies[100,101]. Additionally, severe hepatic insulin resistance and fasting hyperglycemia secondary to increased gluconeogenesis is a prominent early pathophysiologic feature in youth with type 2 diabetes[102]. This phenotype of severe hepatic

resistance contrasts with the more gradual development of increased hepatic glucose production that occurs in adults later in the disease course[103].

The etiology of reduced β-cell functional reserve and severe hepatic insulin resistance in these youth is not yet fully understood but may be secondary to environmental susceptibility and cross-generational transmission of genetic and epigenetic factors. Maternal obesity during pregnancy is associated with a 3-fold increased odds of having a child who is overweight[104]. Moreover, ~50% of 632 children with type 2 diabetes in the TODAY trial were born to mothers with a history of diabetes during or within 2 weeks of delivery[105]. The mechanism of transfer of an “obesity” or “diabetes” trait could be secondary to inherited genetic variants passed from parent to child or differences in genetic expression related to varying methylation patterns (epigenetics). Genome-wide association studies have uncovered >80 genes and multiple gene variants linked with type 2 diabetes but which explain only a small fraction of heritability of type 2 diabetes[106].

Aside from shared genetic risk, intrauterine and postnatal risk factors are closely correlated with increased cardiometabolic risk (Table 2)[107,108]. New research on the intergenerational transmission of childhood obesity and type 2 diabetes indicates that post-translational modifications, including environmentally-induced variations in methylation patterns, may be a primary causal mechanism[109]. Siblings born to mothers before and after weight-loss from bariatric surgery exhibited different CpG methylation patterns in genes known to regulate inflammatory pathways and type 2 diabetes signaling[110]. Epigenetic modification in the offspring of mothers with obesity could be a consequence of an obese maternal intrauterine environment which alters developmental β-cell programming, decreases β-cell functional reserve and increases susceptibility to type 2 diabetes pathways across the lifecourse[111,112]. More research is needed to help understand how the intrauterine environment might induce epigenetic changes and determine if these relationships are causally linked.

Preterm birth and post-natal growth are both important independent risk factors of future cardiometabolic disease[113]. However, the independent contribution of intrauterine growth retardation vs. post-natal growth is still unclear. Intrauterine growth retardation increased risk for increased abdominal and total fat accumulation associated with markers of insulin resistance[113]. Alternatively, regardless of birth weight or preterm birth, rapid weight gain in infancy was associated with reduced insulin sensitivity and visceral fat accumulation in childhood and young adults[114–116]. Further, rapid weight gain in infancy and childhood is linked to cardiovascular risk markers (e.g. pulse wave velocity)[117] and hypertension in longitudinal birth cohorts[118,119]. Although the exact mechanism and timing of weight gain that confers the greatest disease risk remains to be determined, the magnitude and rate of post-natal weight gain have been identified as important modifiable risk factors and current guidelines have focused on weight monitoring and targeted interventions for infants less than 1 year of age[120,121].

Early childhood and behavioral risk factors—Multiple early childhood and behavioral risk factors, are associated with increased childhood obesity (Table 2)[120]. The central role of changes in our food and built environment concomitant with a transition to a sedentary culture that have contributed to the pediatric obesity epidemic childhood obesity

are well documented[11]. Specific factors such as poor sleep hygiene, a sedentary lifestyle with increased screen time, coupled with high intake of nutrient dense foods, and sugar-sweetened beverages are primary targets for obesity intervention programs[120]. These risk factors not only predispose youth to excessive weight gain but may also be independently linked to increased CMR[122,123]. For example, numerous studies have linked poor sleep quality and duration with excess weight gain in childhood[122,123]. Yet, the underlying pathophysiological mechanism is still unclear. Short sleep duration is strongly associated with increased energy intake (unhealthy dietary patterns) and reduced energy expenditure (longer sedentary periods), which could cause excess adiposity over time[123]. Reduced sleep duration is also linked to insulin resistance and could be a primary mediator of CMR, irrespective of childhood obesity status[123]. Additional research is needed to evaluate whether the relationship between sleep hygiene and CMR in pediatric obesity is causal.

Childhood obesity-related comorbidities and increased cardiometabolic risk

Childhood obesity is strongly associated with multiple comorbidities with high CMR (Table 2). In this section, we will discuss the cumulative CMR risk of obesity with each of the following conditions: metabolic syndrome, polycystic ovarian syndrome, dyslipidemia, non-alcoholic steatohepatitis, and obstructive sleep apnea.

Cardiometabolic risk clustering and metabolic syndrome—Cardiometabolic risk is highest with clustering of risk factors such as abdominal obesity, abnormal cholesterol, hypertriglyceridemia, hypertension, and smoking, in youth and adults. Moreover, the combined risk level for coronary heart disease and greater CIMT in adults is strongly linked to CMR clustering in childhood[59]. This co-existence of risk variables, associated with increased risk for type 2 diabetes and cardiovascular disease, has been defined as the metabolic syndrome[124,125]. The prevalence of risk factor clustering markedly increases with greater severity of adiposity, and underscores the importance using the new severe obesity classification schemes[126].

Since CMR clustering in children is associated with higher prevalence of metabolic syndrome in adults[127], multiple definitions have been used to delineate and risk stratify metabolic syndrome in children[128,129]. However, metabolic syndrome is difficult to define in children because of physiologic variations in thresholds with age and pubertal change (e.g. systolic blood pressure, waist circumference) and risk stratification with the various definitions are not well characterized in children. Given the lack of consensus over the optimal diagnostic criteria for the pediatric metabolic syndrome, efforts have shifted from defining metabolic syndrome towards identifying youth with CMR factor clustering, who are at increased cumulative CMR[130].

Polycystic ovarian syndrome—Polycystic ovarian syndrome (PCOS) is a disorder characterized by hyperandrogenism, chronic anovulation, and insulin resistance. Obesity is a common, but not universal, feature of PCOS, although reliable nationally representative prevalence data are lacking[131]. In a retrospective analysis of electronic data records, the odds of PCOS were 14-fold higher in youth with severe obesity compared to normal weight youth[132]. Women with PCOS have increased surrogate markers of atherosclerotic disease

and diabetes risk. However, the association of PCOS in adolescence with future CMR is not well defined and is complicated by the lack of a standardized definition for PCOS in young girls. Cross-sectional studies confirm an association of PCOS with insulin resistance in youth, and other CMR markers (including obesity, hypertension and dyslipidemia) are often present soon after diagnosis [133]. However, there is conflicting data on the contribution of obesity versus PCOS for mediating atherosclerotic risk[134]. Increased CIMT, arterial stiffness, and a more atherogenic lipid profile have been observed in young girls with PCOS and obesity compared to weight-matched controls[135] but the relationship to future cardiovascular mortality and morbidity remains to be determined.

Dyslipidemia—Prospective cohort studies have established the strong tracking of dyslipidemia from childhood to adolescence and adulthood[136] and its association with surrogate markers of atherosclerosis[52,59,137]. This relationship of abnormal lipoprotein levels in childhood with adult dyslipidemia is strongest in children with obesity[59,138]. The combined dyslipidemia of insulin resistance is a principal component of pediatric obesity and is characterized by elevated triglycerides, decreased HDL, and elevated small, dense LDL particles. A recent systematic review examined the magnitude of the association between BMI and risk parameters for cardiovascular disease in children, including serum lipids[29]. Triglyceride concentrations were more likely to be elevated and HDL cholesterol lower in youth with obesity compared to normal weight school-aged youth. Increased atherosclerotic risk is related to high levels of triglyceride-rich lipoprotein particles secreted by the liver and subsequent processing into small, dense LDL and less large HDL particles[139]. Small LDL particles are pro-atherogenic as they are trapped into the sub-endothelium and contribute to increased carotid intimal thickness and features of subclinical atherosclerosis[140].

Non-alcoholic fatty liver disease—Non-alcoholic fatty liver disease (NAFLD) describes a spectrum of disorders associated with excess liver fat accumulation (>5% liver weight) that is not secondary to alcohol consumption or other liver pathologies[141,142]. When ectopic fat infiltration (hepatic steatosis) is associated with hepatocellular inflammation and injury (steatohepatitis), fibrosis can eventually lead to cirrhosis[141]. Pediatric obesity significantly increases the risk of hepatic steatosis and steatohepatitis, such that NAFLD occurs in ~34% of youth with obesity[143]. Furthermore in adults, NAFLD is an independent predictor of subclinical cardiovascular disease, after adjusting for age, smoking, body mass index, alcoholic consumption, dyslipidemia and metabolic syndrome[144]. The role of NAFLD as a primary contributor to early atherosclerotic disease risk in children and whether this is independent or interdependent of pediatric obesity is still uncertain. A few small cross-sectional studies in youth (n = 78–131) associate hepatic fat with increased or no difference in CIMT[145–147] in youth with obesity in the presence or absences of NAFLD. NAFLD was also associated with worse endothelial function and lower hepatic, adipose tissue, and peripheral insulin sensitivity suggesting that subclinical atherosclerosis with NAFLD may be mediated by insulin resistance[148].

Obstructive sleep apnea—Obstructive sleep apnea (OSA) is a common obesity comorbidity characterized by recurrent hypoxic episodes during sleep and daytime

somnolence. In childhood, OSA is associated with insulin resistance, a more atherogenic lipid profile, PCOS, and hypertension[149–152]. However, the independent contribution of OSA to increased CMR, irrespective of excess adiposity status, is still unclear. Retrospective and case-control studies have identified positive associations of markers of insulin resistance (fasting insulin and HOMA-IR) with moderate and severe OSA in youth[150,151]. In contrast, a large cohort analysis of over 500 children with OSA, showed that insulin resistance and dyslipidemia were strongly associated with increased BMI and were not related to the presence or absences of OSA[152]. Longitudinal data is also lacking but the limited analysis from the Bogalusa Heart Study, found that overweight status in youth was a prominent risk factor for OSA in middle-aged adults[153]. Although, there is insufficient evidence to determine causality, the data support the strong association between increased CMR, OSA and obesity and highlight the need for well-designed randomized OSA intervention trials in youth with and without obesity and increased CMR.

Congenital heart disease and CMR

When considering childhood obesity, children with severe congenital heart disease are a group of emerging concern[154,155]. Thanks to incremental advances in the surgical management of congenital heart disease, many children with previously fatal congenital heart defects are surviving and thriving into adolescence and young adulthood[156,157]. Pediatric obesity is increasingly being observed in these children, and is a strong predictor of future adiposity even in adult survivors with the most complex single ventricle morphology[158]. In fact, the prevalence of obesity in adults with congenital heart disease is comparable to the general population[159].

Increased risk for obesity may be secondary to dietary and lifestyle factors unique to children with severe congenital heart disease[159]. Infants with complex congenital heart disease often receive nutritional supplementation to support their growth. Rapid weight gain during infancy coupled with reduced physical activity and exercise capacity could contribute to the increased risk for obesity in these vulnerable patients[160,161]. Increased adiposity may exacerbate an already high risk for cardiovascular disease, depending on the intrinsic morphological defect[162–164]. Adults with severe congenital heart disease are at increased risk for coronary heart disease, hypertension and/or cardiac failure, as well as non-cardiac disorders such as metabolic syndrome, insulin resistance, and type 2 diabetes[156,162,165–167]. The extent to which pediatric obesity modifies the increased cardiometabolic risk in adulthood remains to be elucidated. In a retrospective cohort analysis of childhood and adult survivors with Fontan circulation, obesity was associated with normal height velocity and reduced heart failure rates implying improved function[158]. Prospective studies are needed to investigate the predictors of both obesity and CMR and determine the degree to which they may be related. Recommendations for minimizing cardiovascular risk in youth and adults with congenital heart disease include nutritional and physical activity guidelines that promote a balanced diet with goal-setting and regular bouts of moderate-vigorous physical activity[168,169]. Longitudinal studies are also needed to evaluate the long-term effect of these guidelines on morbidity and mortality in individuals with severe congenital heart disease.

Cardiovascular risk reduction

Screening for cardiometabolic risk

The multitude of studies linking pediatric obesity to high CMR have underscored the importance of primary prevention of cardiovascular disease and T2DM in childhood by promoting early identification and treatment of childhood obesity[120]. Obesity screening practices are already well-accepted components of the childhood pediatrician visit[170]—length and weight are standard metrics in the well-child evaluation. Tracking of weight for length during infancy helps to reduce rapid weight gain in the first 2 years of life[30] and routine BMI screening for overweight/obesity is recommended beginning at 2 years of age[30,120,171]. Once identified, a structured behavioral family-centered lifestyle program should be recommended and weight goals individualized by age and pubertal stage[172]. Importantly, small changes in BMI (a decrease of ≥ 0.5 SDS) may result in marked improvements in CMR[49].

Screening for CMR risk factors (hypertension, dyslipidemia, diabetes) should be undertaken in all children with obesity. The NHLBI Expert Panel guidelines recommend lipid profile screening to all children ≥ 2 years with BMI ≥ to the 85th percentile[120]. The American Diabetes Association recommends screening for type 2 diabetes in youth with overweight/obesity and who have at least 2 additional risk factors (Table 3)[173]. Specific coronary risk scores, such as the Framingham risk score, are well-established for clinical risk stratification in adults, however no similar risk stratification tools are available in children. A risk score developed from the PDAY study has been used in pediatric research to predict CIMT[174] but further studies are needed to confirm the utility of this risk score in the clinical setting.

Treatment of childhood obesity and primary prevention of cardiometabolic disease

A comprehensive approach to the management of childhood obesity and primary cardiometabolic disease prevention is broadly outlined in the World Health Organization 2016 Interim Report of the Commission on Ending Childhood Obesity and will be summarized in this review[11]. This report proposed a multi-faceted approach to obesity prevention and management by detailing targeted strategies for socio-environmental, political, economic and behavioral determinants of obesity. Key stake holders included healthcare and research communities, governmental and non-governmental organizations and the private sector. This societal qualitative conceptual model to obesity management is as important, if not more so, than individualized or community treatment plans[175].

Nevertheless, individual behavior modification remains a cornerstone of healthcare-directed pediatric obesity management, as highlighted in the recently published Pediatric Obesity Clinical Practice Guidelines endorsed by The Endocrine Society, Pediatric Endocrine Society and European Society of Endocrinology[30]. In summary, this statement emphasizes that one of the key goals of obesity treatment in childhood is to prevent cardiometabolic disease and includes increased surveillance for and treatment of obesity-related co-morbidities. The working committee outlined 3 main treatment approaches for pediatric obesity: diet and lifestyle modification, pharmacological interventions and surgical management.

Comprehensive diet and lifestyle modification is the backbone of obesity management[30]. However, the implementation and efficacy of these approaches varies with geographical region and cultural context[176]. Diet and lifestyle plans should be tailored in a population-specific manner, accounting for access to resources (such as sports equipment, or lack thereof) and to cultural variations in meal preparation and ingredients[176]. At its core, promoting interventions aimed at achieving a healthy weight and regular physical activity have been successful in a variety of contexts[177]. In a recent systematic review of interventions to prevent global childhood overweight and obesity, school-based programs that combined diet and physical activity with a home element had the greatest effectiveness[177]. Specific recommendations include a balanced diet with age-specific nutritional and caloric intake values, avoiding the consumption of calorie-dense nutrient-poor foods (e.g. sugar-sweetened beverages, sports drinks, high-fat or high-sodium processed foods) and encouraging the consumption of whole fruits and vegetables. Dietary changes should be coupled with increased physical activity that gradually increases in intensity to a recommended goal of 20–60 minutes, with a goal of 60 minutes, of moderate to vigorous physical activity daily. Moreover, behavioral intervention programs have the greatest efficacy in youth with severe obesity in younger age groups, before the teenage years[178]. Forty-four percent of 643 children between 6–9 years achieved clinically significant reduction in BMI-SD score of 0.5 units or more compared to 20% of children age 10–13 years and 8% of adolescent youth[178]. Therefore, age at treatment initiation and degree of obesity are important predictors for weight loss. Behavioral modification programs that target these youth prior to the adolescent years are poised to have the greatest programmatic and individual successes.

Acknowledging the independent contribution of sedentary time, the Endocrine Society committee recommended limiting non-academic screen time to 1–2 hours per day and using cognitive behavioral therapy to promote compliance with lifestyle modification[17]. Specific treatment options for monogenic disorders and hypothalamic obesity may be complex and include a combination of behavioral modifications[179–181] (details are beyond the scope of this review).

The positive effect of incremental weight loss on improving cardiometabolic risk factors has been demonstrated in several randomized controlled trials[182,183]. For example, a ~1kg/m^2 decrease in BMI with an intensive behavior modification regimen, reduced 2-hour glucose in 42% of youth vs. 7% after standard of care[184]. In keeping with the findings of the landmark study in adults, The Diabetes Prevention Program, a recent systematic review of 133 randomized controlled trials in youth, highlighted that modest weight loss (5–7% of initial body weight) was sufficient to improve the lipid profile, and systolic blood pressure and may help to prevent or delay the onset of future adult cardiovascular disease[183,185]. It is notable that a small change in weight and/or BMI, that did not result in changes in obesity category, improved the cardiometabolic risk profile. This data posits the theory that weight stabilization in childhood, coupled with increased physical activity, could be a more important driver of improved metabolic health than an absolute change in total adiposity. However, this notion is based on short-term improvements in markers of metabolic health. Since increased CMR occurs along a continuum and is not segregated to BMI classifications, incremental changes in weight loss improve CMR risk factors[182]. However,

there are no longitudinal randomized trials that have assessed the independent contributions of degree of weight change versus physical activity in childhood to hard outcomes in adulthood (cardiovascular disease morbidity and mortality). Therefore, current obesity treatment recommendations in youth, focus on improving overall nutritional intake and lifestyle and not at reducing BMI categories as a treatment benchmark[30]. Future research should explore the dose-response relationship for diet and physical activity induced weight-loss in youth for predicting cardiometabolic outcomes in adults.

There are relatively few therapeutic alternatives to diet and lifestyle that have been extensively investigated or employed in youth[186,187]. In addition to the limited data on pharmacological and surgical options in youth, these interventions are not widely available in many middle and low-income countries. Moreover, although there is medium term (up to 8 year outcomes data in youth post-bariatric surgery), there is no long-term data on safety, efficacy for reducing cardiometabolic disease in childhood or adults[188].

The 2017 Endocrine Society Clinical Practice Guidelines recommend pharmacotherapy for children or adolescents after a formal program of intensive lifestyle modification has failed to limit weight gain or to ameliorate comorbidities[30]. Orlistat, a lipase inhibitor, is the only FDA (US Food and Drug Administration) approved weight-loss medication for use in children ≥ 12 years who are overweight/obese. Orlistat is associated with 1–2 kg weight loss in adolescents, but its use is limited by its unpleasant side effects (bloating and greasy loose stools)[189]. Orlistat has been associated with modest improvement in diastolic blood pressure and a marker of endothelial function (flow-mediated dilation), but its cumulative effect on reducing cardiometabolic disease remains to be elucidated[190,191].

Next to orlistat, metformin is the most common agent evaluated for the treatment of obesity in children[187]. Metformin, is a widely used anti-diabetic agent, that is FDA approved to treat type 2 diabetes in adults and children. Randomized trials of metformin have demonstrated modest weight loss (2–4 kg) in youth with marked improvement in markers of insulin resistance[187]. However, similar to studies conducted for orlistat, most metformin trials are ≤ 1 year duration and the durable effect of these pharmacological agents on weight-loss or cardiometabolic risk reduction requires further investigation. Other weight-loss medications approved for long-term use in adults, but not in children, are liraglutide, phentermine plus topiramate, buproprion plus naltrexone, and lorcaserin. The frequency of off-label use of these agents is unclear and their efficacy for CMR reduction unknown[30].

In pubertal or post-pubertal youth who have not responded to lifestyle modification and/or pharmacotherapy, surgical weight loss intervention may be a viable option. Eligible candidates are those with either BMI of >40 kg/m^2 or BMI of >35 kg/m^2 as well as significant, extreme comorbidities, such as moderate to severe obstructive sleep apnea, type 2 diabetes, benign intracranial hypertension, or non-alcoholic steatohepatitis[192]. Youth should be Tanner 4–5 in pubertal development and have achieved at least near final height [17]. The most common procedures used in children and associated with significant weight loss and improvement in metabolic control are: Roux-en-Y gastric bypass, sleeve gastrectomy, or laparoscopic adjustable gastric banding[188,193–195]. Post-surgical weight loss is often variable but usually ranges between 20–50% of initial body weight.

Bariatric surgery significantly improves short- and medium term CMR risk factors such as non-HDL cholesterol and glycemia at 3 and 8 years post-surgery[196]. The durable weight loss at 5–12 years post-operative is associated with persistent improvements in metabolic control (decreased prevalence of hypertension, type 2 diabetes and dyslipidemia)[188,197]. Remarkably, up to 94% of youth with dysglycemia experience remission of their T2DM or prediabetes at 1 year with sustained glycemic control up to 8 years post-operatively[188,197]. While these metabolic effects are encouraging, bariatric surgery should be reserved for appropriate candidates as the procedure can be associated with multiple peri- and post-operative complications. Early complications include anastomotic strictures, bowel perforation, wound infections and re-intervention related to the surgical procedure[197,198]. In addition, nutritional and vitamin deficiencies are among the most common late complications, requiring close monitoring. Lastly, the long-term effects on CMR and cardiovascular mortality are still under investigation.

Conclusion

Pediatric obesity is associated with high CMR, and evidence of subclinical atherosclerosis, type 2 diabetes and insulin resistance that begins in childhood. The cumulative burden and severity of childhood obesity are primary mediators of worse cardiovascular and metabolic outcomes. Good evidence demonstrates that decreasing the severity of obesity positively impacts markers of cardiovascular risk and delays or prevents onset of future cardiometabolic disease. Optimal risk reduction strategies should target risk factor clustering for the treatment of individual cardiometabolic abnormalities as indicated, and the early implementation of a multi-faceted behavioral lifestyle treatment program.

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Table 1

Prospective Studies Associating Childhood Obesity with Subclinical Atherosclerosis in Adulthood

Study	Country	Design	Study Size (n)	Mean follow-up (years)	Participant characteristics at baseline	Outcome	Other CHD risk variables studied	Reference
Bogalusa Heart Study	United States	Population based cohort	254	16–17	12–17 years 44% male 30% African-American	Carotid IMT (B-mode ultrasound)	LDL, HDL, BP, smoking	Li et al.[52]
Muscatine Heart Study	United States	Population based cohort	384	12 and 18	15 years 51% male	Coronary artery calcification (CT)	LDL, TG, BP, Apolipoprotein A1 and B, homocysteine	Mahoney et al.[54]
Muscatine Heart Study	United States	Population based cohort	725	8–18	18–25years 48% male	Carotid IMT	LDL, HDL, BP, TG	Davis et al.[53]
Cardiovascular Risk in Young Finns Study	Finland	Population based cohort	1171	21	12, 15 &18years 45% male	Carotid IMT	LDL, HDL, BP, smoking	Raitakari et al.[58]
Childhood Determinants of Adult Health Study	Australia	Population based cohort	286	20	12 and 15 years 50% male	Carotid IMT	LDL, HDL, BP, smoking	Magnussen et al.[59]
Kaunas Cardiovascular Risk Cohort Study	Eastern Europe	Cohort	380	36–37	12–13 years 44% male	Carotid IMT and pulse wave velocity	LDL, HDL, BP, smoking, socio-economic status	Petkeviciene et al.[74]

IMT: intimal media thickness; CT: computed tomography

Table 2

Cardiometabolic risk factors associated with pediatric overweight/obesity status

Socio-environmental	Biological
Caloric dense, nutrient poor diet	History of maternal obesity in pregnancy
Sedentary lifestyle	History of gestational diabetes
Excessive screen time	Family history of obesity and/or CVD
Tobacco exposure	Intra-uterine growth restriction
Poor sleep quality and short duration	Hypertension
	Diabetes mellitus and insulin resistance
	Dyslipidemia
	Hepatic steatosis
	Polycystic ovarian syndrome
	Obstructive sleep apnea

Table 3

Screening for diabetes and pre-diabetes in asymptomatic youth ≤ 18 years

Overweight/Obese defined as: • BMI ≥85th percentile for age and sex, or • Weight for height ≥85th percentile, or • Weight ≥120% of ideal for height
Plus any two of the following risk factors:
• Family history of type 2 diabetes in first- or second-degree relative
• Race/ethnicity (Native American, African-American, Latino, Asian American, Pacific Islander)
• Maternal history of diabetes or gestational diabetes during the child's gestation
• Signs of insulin resistance or conditions associated with insulin resistance - Acanthosis nigricans - Hypertension - Dyslipidemia - Polycystic ovary syndrome - Small-for-gestational age birth weight

Screening should be initiated at 10 years or at age of onset of puberty, if puberty occurs at a younger age.

Frequency of screening: every 3 years.

Adapted from American Diabetes Association: Classification and Diagnosis of Diabetes. Diabetes care. 2017;40(Suppl 1):S11-S24