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Childhood Obesity and Cardiovascular Disease Risk

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Abstract

Purpose of Review The global epidemic of youth-onset obesity is tightly linked to the rising burden of cardiometabolic disease across the lifespan. While the link between childhood obesity and cardiovascular disease is established, this contemporary review summarizes recent and novel advances in this field that elucidate the mechanisms and impact of this public health issue.

Recent Findings The review highlights the emerging data supporting the relationship between childhood adverse events, social determinants of health, and systemic and institutional systems as etiological factors. We also provide updates on new screening and treatment approaches including updated nutrition and dietary guidelines and benchmarks for pediatric obesity screening, novel pharmacological agents for pediatric obesity and type 2 diabetes such as glucagon-like 1 peptide receptor agonists, and we discuss the long-term safety and efficacy data on surgical management of pediatric obesity.

Summary The global burden of pediatric obesity continues to rise and is associated with accelerated and early vascular aging especially in youth with obesity and type 2 diabetes. Socio-ecological determinants of risk mediate and moderate the relationship of childhood obesity with cardiometabolic disease. Recognizing the importance of neighborhood level influences as etiological factors in the development of cardiovascular disease is critical for designing effective policies and interventions. Novel surgical and pharmacological interventions are effective pediatric weight-loss interventions, but future research is needed to assess whether these agents, within a socio-ecological framework, will be associated with abatement of the pediatric obesity epidemic and related increased cardiovascular disease risk.

Keywords Pediatric · Overweight · Obesity · Cardiometabolic · Obesity · Cardiovascular disease

Introduction

Childhood obesity and its comorbidities are risk factors for many chronic conditions, including three of the major non-communicable diseases worldwide: type 2 diabetes, cardiovascular disease, and cancer [1]. Globally, the prevalence of childhood obesity has increased dramatically in the last 2–3 decades across all world regions, with the most devastating impact in low- to middle-income countries that have the dual burden of undernutrition and obesity [2–5]. Despite international recognition of this public health emergency, no region in the world has successfully stemmed the rise in pediatric obesity. In the USA, contemporary simulation models project continued increases in obesity prevalence and three times higher risk for obesity in adults over the next 5–10 years [6]. While multiple publications address the scope of the problem and propose interventions to mitigate and prevent this chronic disease [1, 7], pediatric obesity remains a top World Health Organization (WHO) initiative with an expansive impact that worsened during the COVID-19 pandemic [8].

Prior to the COVID-19 pandemic, studies indicated that public health efforts implemented in high-income countries, such as the USA and UK, stabilized the rapid rises in childhood obesity prevalence [3, 9]. However, the COVID-19 pandemic upended this short-term reprieve. During the COVID-19 pandemic era, epidemiologic studies report consistent and steep rises in the trajectory of weight gain among many countries across all ages and BMI categories [10–17].

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Childhood overweight and obesity afflicts up to one-third of children in European and American regions [3, 5, 10]. Among low-income countries and small island developing states, the rates of rise childhood obesity are 30% higher than in developed nations [4, 5, 18]. Two additional considerations are noteworthy: (1) the co-occurrence of excess adiposity and nutritional stunting in youth from middle and low-income countries [2] and (2) the continued steep trajectory of weight gain among youth with severe obesity [10]. Nutritional stunting with obesity portends a multitude of complications among populations with limited resources and requires aggressive targeted interventions in those at highest risk. In contrast, in high-income countries, the rate of weight gain during the COVID-19 pandemic was highest in youth with severe obesity [10], a group already at greatest risk for obesity-related complications [19]. Therefore, the burden of childhood obesity across the globe is differentially impacted by risks related to stunting and severity of obesity that—individually and together—accelerate the development of atherosclerotic disease.

This contemporary review discusses recent advances in understanding the pathophysiology of cardiovascular disease in youth with overweight and obesity, and critically analyzes the role of social determinants of health and socio-ecological factors that compound and hinder current obesity prevention efforts. We also provide an update on the latest advances in nutrition science and behavioral interventions and highlight areas of future research that could support pragmatic and innovative solutions to address the double burden of childhood malnutrition and obesity, and the high risk for cardiometabolic disease.

Childhood Obesity and its Relationship with Cardiometabolic Risk and Early Vascular Aging

As childhood is a time of growth and pubertal development, pediatric overweight and obesity must be defined in relative terms, standardized for sex and age. For a detailed review of the definition, classification, and pathophysiology of childhood obesity, as well as its comorbidities, we refer the readers to our prior publication [20]. Childhood obesity is an established risk marker for atherosclerotic cardiovascular disease (ASCVD), a progressive vascular disease that begins in childhood [21–23]. Comprehensive historical reviews on the association of childhood obesity, including seminal autopsy (e.g., Bogalusa Heart Study, Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study,) and epidemiological studies (Childhood Determinants of Adult Health study, Cardiovascular Risk in Young Finns study, Atherosclerosis Risk in Young Adults study, International Childhood Cardiovascular Cohort Consortium) linking excess adiposity to ASCVD, have been published [20, 24–32]. Overall, it is well recognized that ASCVD begins in childhood and that ASCVD risk and subsequent mortality is significantly increased by childhood obesity and the clustering of metabolic risk factors, such as high triglycerides, low HDL-cholesterol, high blood pressure, and dysglycemia [33, 34•, 35, 36]. Childhood obesity is associated with at least twofold increased odds of dyslipidemia, hypertension, type 2 diabetes, and metabolic diseases (such as non-alcoholic steatohepatitis and polycystic ovarian syndrome) [37–39]. In addition to metabolic risk factor clustering in childhood and adolescence, the cumulative ASCVD risk is compounded in young adulthood because youth with pediatric obesity have a high prospective risk for obesity and type 2 diabetes as adults [34•, 40]. Among adolescents (median age 14 years), severe class II/III obesity in adulthood occurred in ~ 50% of children with obesity and 80% of youth who had severe obesity [33].

Since our previous review publication [20], there has been increasing recognition of the prognostic ability of cardiovascular risk factors in childhood and the degree to which cardiometabolic risk is elevated across different phenotypes and body compositions in youth. In one of the largest pediatric cohort studies to evaluate cardiovascular risk, the International Childhood Cardiovascular Cohort (i3C) Consortium evaluated the predictive potential of five traditional risk factors (body mass index, systolic blood pressure, total cholesterol, total triglyceride, and youth smoking) for fatal and non-fatal cardiovascular events in 38,589 participants after mean follow-up of 35 years [41]. This seminal and comprehensive analysis demonstrated strong associations of childhood risk factors—independently and in combination—with major cardiovascular events. Studies have also demonstrated that all adiposity is not the same. Metabolically unhealthy excess weight is characterized by increased visceral fat, decreased subcutaneous fat, adipocyte hypertrophy, increased secretion of inflammatory factors, and ectopic fat deposition [42]. Youth with excess visceral adiposity have marked elevations in atherogenic lipoproteins and increased incidence of dysglycemia [43–46].

Our understanding of the prevalence and progression of cardiovascular risk markers and subclinical ASCVD in youth with obesity and type 2 diabetes has also improved [47]. Approximately 1 in 4 youth with type 2 diabetes have a microvascular complication or hypertension at diagnosis and the cumulative prevalence rises to over 60% in 10–12 years [48]. In addition, although age remains one of the strongest drivers for the development of ASCVD [49], the extent to which childhood obesity and its metabolic complications accelerate the progression through the four stages of atherosclerosis (endothelial dysfunction, lipid accumulation, plaque formation, plaque rupture) is still emerging [50]. Both cross-sectional and longitudinal

youth cohort studies have suggested an accelerated tempo in vascular aging—the deterioration of vascular structure and function—among youth and emerging adults with obesity with and without type 2 diabetes [51, 52••, 53–57]. Both obesity and type 2 diabetes were identified as major risk factors for accelerated vascular aging, measured as carotid-femoral pulse wave velocity (PWV) or augmentation index [52••, 53]. Childhood obesity is independently associated with increased carotid intima-media thickness (cIMT) with the cumulative effects likely moderated by the association with dyslipidemia and insulin resistance [20, 56, 58, 59]. Furthermore, cumulative exposure to insulin resistance and dysglycemia was shown to adversely impact left ventricular remodeling and function in middle aged adults [60]. These findings support accelerated vascular aging in youth-onset obesity and type 2 diabetes accelerate and emphasize the need to identify the modifiable mechanistic drivers of disease progression to effectively target early intervention efforts.

In recent years, attention has also shifted to translating these research findings into the clinical arena. Metrics used to evaluate early vascular aging include measures of vascular structure (common, bulb, and internal cIMT) and arterial stiffness (carotid-femoral PWV and augmentation index). Efforts have focused on publishing normative data for PWV and cIMT percentiles in youth that may be used for risk stratification [56, 59]. However, cIMT can be difficult to obtain in the general pediatric population because reproducibility and reliability are limited by intra-individual variability in ultrasound techniques [61]. Alternatively, carotid-femoral PWV is less reliant on user skill but the translation of this technique in clinical settings has been slow in pediatric and youth populations [62]. International efforts are underway to evaluate these methods, with additional studies needed to standardize and validate vascular aging assessment techniques [63, 64].

Social Determinants of Health, Childhood Obesity, and Cardiovascular Disease

The causative factors and pathways in the development of to ASCVD are multi-factorial across socio-ecological levels. Within the socio-ecological framework—a paradigm describing the inter-relationships between individual, family, and communities—social determinants of health (SDOH) may mediate and moderate the development of childhood obesity and cardiometabolic disease risk (Fig. 1). SDOH propagate non-communicable diseases and directly influence the success of childhood obesity programs [65]. SDOH are structural and environmental, and include factors such as neighborhood and built environment, education access, and social and community relationships. Specifically, low socioeconomic status, limited access to healthcare, early childhood adversity, food insecurity, and social isolation may directly increase chronic stress and allostasis or indirectly promote risky and adverse lifestyle behaviors [66, 67]. Still, many research studies on childhood obesity prevention do not focus on socio-ecological determinants but instead target individualistic determinants and solutions. Recognizing the importance of these systems-level influences on childhood obesity and risk for cardiometabolic disease is a major step towards designing effective policies and interventions. Yet, such new policies and interventions have been hindered by a wide range of socio-ecological factors, including economic slowdowns and downturns, political agendas, and ingrained structural racism and cultural norms [2].

Two institutional level factors were recently highlighted as important mediators of cardiovascular disease risk: food insecurity and adverse childhood experiences [68, 69]. Food insecurity and malnutrition have reached a critical stage worldwide, according to the WHO 2021 report and are associated with the development of childhood obesity and cardiometabolic disease in adults [70–73]. However,

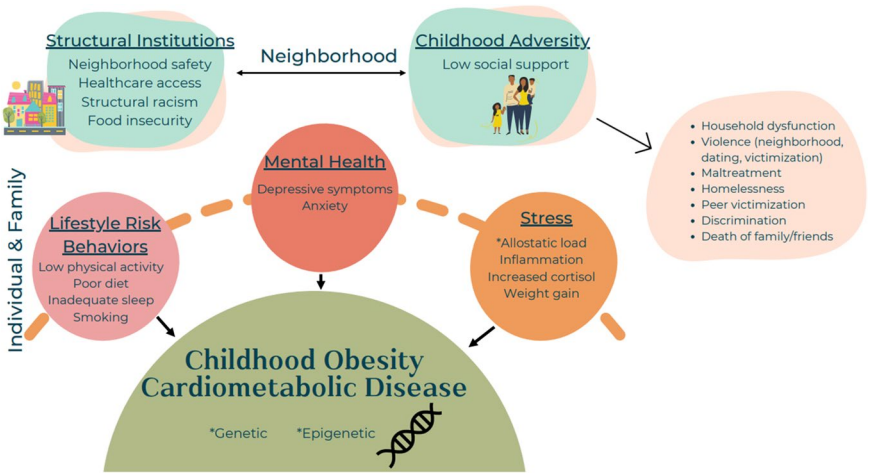

Fig. 1 Conceptual model of socio-ecological determinants of cardiometabolic disease in childhood obesity [68] (Adapted from: Suglia, SF, et al. Circulation, 2018;137:e15–e28; with permission from Wolters Kluwer Health, Inc.)

the relationship between food insecurity and cardiovascular disease risk in youth with obesity is inconsistent. Some studies indicate a moderate association of food insecurity with dyslipidemia and fasting glucose in childhood [73, 74] {Lee, 2019 #10,064}. In contrast, other studies fail to show an independent association of cardiovascular risk markers with food insecurity among youth at risk [72, 75]. A contemporary analysis from the National Human and Nutrition Examination Survey 2007–2012 (NHANES) in adolescents at or below 300% of the poverty line did not find a relationship between food insecurity and childhood cardiometabolic risk factors [75]. In the NHANES analyses, outcomes were adjusted for both institutional and neighborhood level variables (income and parental education) as well as individual level socio-ecological factors (physical activity, sedentary time, and smoking status). These findings suggest that socio-ecological factors may be interdependent mediators of cardiovascular disease risk in youth. Large medical organizations, including the American Academy of Pediatrics and the American Heart Association, emphasize the complex inter-relationship of food insecurity and lifetime cardiometabolic risk [68, 76]. In the USA, ~ 10% of households were food insecure, prompting governmental officials to acknowledge the disproportionate impact on children, and fueling new policies and strategies that promote nutrition and target obesity and cardiovascular diseases [77]. Compared to the general US population, youth and young adults with type 1 and type 2 diabetes report nearly twice the prevalence of food insecurity [78]. Among youth with diabetes in the USA, predictors of household food insecurity include youth without insurance or receiving Medicaid or Medicare, level of parental education, and lower household income [78].

Adverse childhood experiences (ACEs) are also closely associated with poor cardiovascular outcomes with or without underlying food insecurity [68, 79••]. Notably, the cardiometabolic consequences of ACEs are increasingly observed in youth and emerging adults but may not manifest until later in adulthood [68]. The conceptual model describing the socio-ecological relationship of ACEs with ASCVD includes a framework of three main mediating factors: (1) unhealthy behaviors such as physical inactivity, poor-quality diet, poor quality and duration of sleep, and smoking; (2) adverse physiologic mechanisms including inflammation and hypercortisolemia; and (3) substance abuse and mental health disorders (Fig. 1) [68]. Neighborhood and community level influences may mediate shifts in healthy lifestyle behaviors, promote mental health disorders, and/or induce physiological stress and dysregulation (Fig. 1). These effects are compounded in individuals who have genetic predisposition for ASCVD and its risk determinants [80]. Although there is a strong link between ACEs and ASCVD, evidence to date is associative and observational. Future studies to elucidate the mechanisms and biomarkers of physiologic stress and resiliency factors and their relationships with risky and unhealthy behaviors are needed in youth. For example, while the impact of poor sleep quality and sedentary time on ASCVD risk in adults is strong [81–83], additional evidence is needed to determine the dose–response relationship between these unhealthy behaviors in childhood and the future risk for ASCVD.

Accumulating evidence also demonstrates that mental health conditions such as depression and anxiety are important and potentially modifiable comorbidities of pediatric obesity. Depression is prevalent in youth with pediatric obesity and adolescent girls are at increased odds for symptoms [84–86]. However, these data are mainly derived from epidemiologic studies and a direct association of markers of vascular aging with depression in adolescence and adulthood is elusive [87]. Alternatively, a strong relationship exists between allostatic load and stress with increased risk for ASCVD and major cardiovascular events [66]. What remains to be seen, however, is how this relationship is modified by pediatric obesity and whether it is the duration of obesity, the rapidity of weight gain, or the presence of adult obesity that are major determinants of ASCVD.

Updates to Treatment of Childhood Obesity and Mitigation of ASCVD Risk

Lifestyle interventions alone or with concomitant pharmacotherapy as indicated remain a cornerstone of treatment across all risk levels and are underscored by multiple clinical practice guidelines [88–90]. Although lifestyle modifications, including healthful dietary intake, daily physical activity, avoidance of smoking and alcohol, stress management, social support, and sufficient high-quality sleep, are recognized as first-line approaches for preventing and managing childhood obesity and related disease risks, individual lifestyle interventions may be unsuccessful in isolation [91, 92]. Furthermore, lifestyle interventions without additional treatment approaches are less effective in youth from underserved and minority groups [93]. Lifestyle behavior interventions that yield the greatest accessibility and efficacy in preventing harmful weight gain in adolescent populations remain a limited area of research [94]. Youth from underserved communities have the lowest accrual, retention, and completion rates for behavioral and activity interventions [93].

Diet

Nutritional management targets reduction of cardiometabolic risk factors and comorbidities without adverse effects on growth and development, while supporting a healthy relationship with food and activities. Broad recommendations

include a balanced diet with age-specific nutritional and energy intake values, limiting excess consumption of energy-dense, nutrient-poor foods (e.g., sugar-sweetened beverages, highly processed items, red meats, and high-sodium foods) while encouraging the consumption of whole fruit, vegetables, whole grains, nuts, seeds, legumes, and other sources of lean proteins [95]. In collaboration with patient preferences and readiness, medical nutrition therapy provided by a registered dietitian and reinforced by all members of an interdisciplinary care team emphasizes nutritionally adequate heart-healthy dietary patterns.

Guidance is provided on the age-appropriate total calories consumed while emphasizing diet quality, independent of caloric intake, as important mediators of weight and metabolic cardiovascular risk [96, 97]. Evidence for lower disease risk in adolescents by implementing dietary interventions is derived from adult and multi-level pediatric interventional studies [98–102]. Several studies support the conclusion that consuming a plant-centered, nutrient-rich diet in youth and young adulthood has a positive effect on cardiovascular risk reduction later in life [103–108]. In the Coronary Artery Risk Development in Young Adults (CARDIA) cohort study, greater plant-centered diet quality at a younger age was associated with lower subsequent risks of ASCVD [104], type 2 diabetes, and excess weight gain [103]. However, the evidence supporting one dietary intervention over others, and their safety in youth, has yet to be elucidated.

The Dietary Guidelines for Americans, Academy of Nutrition and Dietetics, American College of Cardiology, and American Heart Association outline whole food, plant-rich patterns, including Dietary Approaches to Stop Hypertension, the Mediterranean diet, vegetarian and vegan diets, and a Healthy US-style diet for risk reduction [89, 109]. A 2022 National Lipid Association clinical perspective on nutrition interventions for youth with dyslipidemia reinforced components of these dietary patterns, highlighting the effects of food sources of saturated and unsaturated fatty acids, dietary fiber, added sugars and refined carbohydrates, and phytosterols on lipid metabolism. Incorporation of a variety of lean protein foods, including plant-based sources [110], and reduction of ultra-processed foods [111–113] are among other emphasized recommendations with opportunities for future research. Additional interconnected mechanisms may relate to (1) nutritional effects on hepatic LDL receptor activity [114], (2) satiety-promoting low energy dense foods within a greater food volume, (3) reduced intake of inflammatory diet factors, (4) fiber-mediated effects on glucose absorption, gut-microbial short-chain fatty acid (SCFA) synthesis, and (5) and cholesterol synthesis through binding and excretion of bile acids [115–119].

Emerging data supports associative links between metabolically unhealthy obesity shifts in the gut microbiota composition, though whether the relationship is bi-directional or causative is unclear [120]. Plant-based diet patterns high in dietary fiber further maintain a key role in beneficially shifting gut microbial composition—increasingly implicated in CVD risk and excess adiposity—potentially through mitigating production and activity of compounds including reduction of trimethylamine-n-oxide (TMAO) and increasing SCFAs [119, 121, 122]. TMAO is a metabolite derived from gut microbiota that is associated with poor cardiometabolic outcomes with evidence of direct activity in the pathogenesis of atherosclerosis [123–125]. Synthesis of TMAO depends on production of trimethylamine (TMA) by gut microbiota from nutrient precursors, including choline, phosphatidylcholine, carnitine, and betaine, which are concentrated in animal foods such as red meat, eggs, fish, and dairy [126, 127]. While accumulating evidence linking nutrition, obesity, and microbial activity implicates TMAO in the pathogenesis of ASCVD in adults, scarce research exists in youth and young adults. Limited studies suggest mixed associations of TMAO compared to TMAO precursors as appropriate indicators of CVD risk at younger ages [128–130]. Further interventional and longitudinal studies are warranted to examine the impact and usefulness of TMAO and precursor biomarkers in risk assessment and management of obesity and CVD in childhood [131]. Another major class of gut microbial metabolites, SCFAs—primarily acetate, butyrate, and propionate—are produced by bacterial fermentation of non-digestible carbohydrates and exert widespread physiological effects relevant to development of obesity and CVD [131]. In contrast to TMAO, these signaling molecules are broadly connected to positively influencing health status through multiple processes, including appetite regulation, gut hormone production, anti-inflammatory and anti-neoplastic properties, glucose homeostasis, and lipid metabolism, in several target tissues [131]. For both TMAO and SCFAs as well as other bacterially produced compounds, additional research is needed to elucidate mechanistic features, ideal microbial composition for reducing chronic disease risk, and potential differences in biomarkers of risk in both healthy and at-risk for disease youth and young adults compared to adults and elderly populations.

Other prominent dietary trends for treating or mitigating ASCVD in adults with obesity include intermittent fasting or time limited eating by which foods are consumed within a defined window. Intermittent fasting is not currently recommended in children or adolescents due to lack of evidence, conflicting data in adults [132], and potential adverse effects on eating disorder risk. Small pilot [133] and case series [134] implementing versions of intermittent fasting in pediatric populations suggest flexible approaches may yield benefits on weight outcomes. Additional data would be needed to determine the safety of intermittent fasting time windows and the effects on ASCVD risk reduction. In addition to personalized

nutrition counseling, multi-level innovative approaches for supporting lifestyle changes that may be promising include culinary medicine and teaching kitchen interventions [135–140] and produce prescription programs, medically tailored meals or groceries, and mobile health applications [141].

Pharmacological and Surgical Treatment

The last 10 years have been monumental in therapeutic and surgical advancements for the treatment of pediatric obesity and type 2 diabetes [142]. In December 2020, liraglutide became the first pediatric anti-obesity drug to be approved by the Federal Drug Administration (FDA) in over 2 decades. Liraglutide's weight-loss potential is modest (~ 3–5% of body weight) for youth compared to adults, but it is associated with an improved glycemic and cardiometabolic profile. A second combination drug, phentermine/topiramate, was approved in June 2022 for the management of chronic obesity in youth based on clinical trials demonstrating 4–8% reduction in BMI over 54 weeks. Alternative agents, such as semaglutide and naltrexone, are approved for chronic weight management in adults, but clinical trial data is just beginning to emerge in youth [143, 144]. Recent clinical trial results of semaglutide in adolescents were promising; semaglutide for 68 weeks resulted in a mean change in BMI of − 16.1% compared to 0.6% with placebo [144]. However, it remains to be determined whether these medications will have durable long-term weight loss effects and lead to overall ASCVD risk reduction.

Bariatric surgery, on other the hand, is the only available therapy that results in sustained weight loss with demonstrated long-term safety up to 10 years post-surgery [142, 145]. Furthermore, the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study showed improvement of multiple cardiovascular risk factors after bariatric surgery [146]. Vertical sleeve gastrectomy (VSG) is currently the most common bariatric surgery recommended and performed in adolescents in the USA [147]. In 2018, the American Society for Metabolic and Bariatric Surgery outlined pediatric severe weight management guidelines [148] and surgical options for chronic weight management of severe obesity in youth were endorsed by the American Academy of Pediatrics in 2019 [149, 150].

Research Gaps and Areas for Future Research

The last decade has seen significant advances in our understanding of the severity and burden of pediatric obesity as well as therapeutic advances to address this global problem. However, gaps in knowledge still exist. We are just beginning to understand how metabolic risk factor clustering in childhood predicts hard cardiovascular outcomes in young to middle adulthood. Longitudinal studies with systematic and comprehensive data collection are still needed, especially among youth with obesity and diabetes, to inform the timing of mitigation strategies in the highest risk youth and young adults. For example, current pediatric dyslipidemia guidelines were largely based on adult ASCVD outcome trials, and there are no data supporting whether treatment of modest dyslipidemia in youth with obesity and diabetes will reduce ASCVD-related morbidity or mortality. Similarly, ideal target values for LDL and total cholesterol concentrations are based on adult data. However, lipid guidelines in adults now include a risk-based approach with statin and cholesterol lowering medication recommendations derived from randomized controlled analyses of major cardiovascular events. There are no parallel data in youth and the ideal cutoff or targets for statin therapy are based on expert advice rather than empirical data. There is also a need to investigate the most reliable and reproducible markers for early stage ASCVD and vascular aging, with a focus on which socio-ecological factors should be considered primary drivers of ASCVD risk in youth. Lastly, the link between childhood obesity, cardiovascular disease risk, and gut microbial dysbiosis with associated TMAO metabolites is intriguing but the evidence is preliminary and many questions remain as to whether these pathways are causal or associative.

Conclusion

Childhood obesity, its complications, and comorbidities persist as significant ASCVD risk factors. The COVID-19 pandemic served to exacerbate pediatric obesity rates, as well as many of its associated SDOH. Studies show post-pandemic increases in psychosocial stress as well as depression and anxiety among youth [151, 152]. While progress has been made in our understanding of the increased cardiovascular disease risk associated with pediatric obesity, much is yet to be determined. The pathophysiologic mechanisms behind the relationships between SDOH and increased obesity-related cardiometabolic risk need to be clarified if we are to make true progress in identifying youth at greatest risk for ASCVD. Once identified, innovative treatment modalities will need to be implemented at the optimal time to stem the tide of youth-onset obesity and its cardiovascular complications.

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Declarations

Conflict of Interest The authors have no conflicts of interest to disclose.

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