

Association of Pediatric Obesity with Adult Cardiovascular Disease: A Narrative Review of Published Evidence

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Abstract

There is a global increase in the prevalence of childhood and adolescent obesity. Pediatric obesity is a strong predictor of adult obesity with its attendant health consequences, and there is now substantial evidence linking it with cardiovascular diseases (CVD) in adulthood. This review aims to discuss the pathophysiologic mechanisms involved in the development of future CVD in pediatric obesity and the findings of some published longitudinal studies which reported the relationship between the two morbidities. The pathophysiologic pathways have been established, as both abnormal cardiac remodeling and abnormal vascular remodeling are the primary outcome events arising from the 'adiposopathy' of obesity. Increased left ventricular mass (↑LVM) and increased left atrial (↑LA) size are independent risk factors for cardiovascular morbidity and mortality in adults. Premature atherosclerotic processes may result in adult cardiovascular diseases such as coronary heart disease (CHD), cerebrovascular accident (CVA), thrombo-embolism and hypertensive heart disease. Because of the complex interplay of cardio-metabolic risk confounders during the life course, there is no consensus yet on the modulating factors for disease risk from childhood to adulthood and on the best methods of measurements in children for predicting adult CVD.

Keywords: Adiposopathy; Cardio metabolic syndrome; Abnormal cardiac remodeling; Atherosclerosis; Cardiovascular diseases

Introduction

The prevalence of pediatric obesity is increasing globally because of lifestyles, which fundamentally create an imbalance that favors caloric intake over expenditure [1]. These lifestyles include sedentary habits such as addiction to computer games, internet, and television, as well as a regular intake of energy-dense fast foods [2]. Several reports reveal the health burden of childhood and adolescent obesity in both developing and developed countries [3-9]. Whereas obesity is prevalent in the lower socio-economic class in developed countries, it is more common in the upper socio-economic class in developing countries. In the latter, sedentary habits and indulgence in fast foods (nutritional transition) are regarded as signs of affluence [10]. Obesity in children and adolescents is associated with several co-morbidities and complications, like hypertension [11], obstructive sleep apnea syndrome [12], orthopedic disorders [13], insulin resistance and type 2 diabetes mellitus (T2DM) [14,15], dyslipidemia [16], and malignancies [17]. In the pediatric cardio-metabolic syndrome, genetic and environmental factors synergistically act as triggers; but obesity remains the primary etiologic factor which leads to hyperinsulinemia, and subsequently to hypertension and dyslipidemia [18]. Some authors have, however, proposed five diagnostic components for the syndrome, namely abdominal obesity (increased waist circumference), hyperglycemia (glucose intolerance), hypertriglyceridemia, low high-density lipoprotein-cholesterol (LDL-C) and hypertension [19]. More importantly, some of these diagnostic components are also putative risk factors for T2DM and adult cardiovascular diseases (CVD) such as coronary heart disease (CHD), cerebrovascular accident (CVA), heart failure, hypertensive heart disease, cardiac dysrhythmias, and thrombo-embolic disease.

There is now substantial evidence linking childhood and adolescent obesity with CVD in adults due to the high risks of hypertension and dyslipidemia [20-23]. Moreover, pediatric obesity is a strong predictor of adult obesity with its attendant health consequences [24]. Despite several cross-sectional studies on co-morbid CVD predictors [25-29] and longitudinal

studies on future CVD [30-35] in obese children and adolescents, there are still gaps in clearly understanding its evolution in these age groups [36]. For instance, the best methods of measurement in children for predicting CVD later in life and the modulating factors for disease risk during the life course remain unresolved [36]. In this review, we aim to discuss the pathophysiologic mechanisms underlying the development of future CVD in pediatric obesity and the findings of some published longitudinal studies which reported the relationship between the two morbidities.

Adiposopathy of Obesity and CVD

The pathways involved in the development of obesity-driven CVD are well documented in a recent review [36]. Obesity is associated with 'adiposopathy,' which triggers major metabolic diseases (dyslipidemia, hypertension, and T2DM), resulting in two significant sequelae: abnormal vascular remodeling and abnormal cardiac remodeling (Figure 1). 'Adiposopathy' refers to the anatomic and pathophysiologic consequences of pathogenic adipose tissue (from the patient's perspective; the so-called 'sick fat') [37,38]. It is a disorder characterized by pathogenic adipose tissue that is sustained by positive caloric balance and sedentary lifestyle in individuals with a genetic and environmental predisposition [37]. Anatomic manifestations of obesity such as adipose hypertrophy and visceral adiposity physiologically result in endocrine and immune sequelae which eventuate in metabolic disease [39]. Thus, genetics and metabolic milieu determine when the positive caloric balance will result in adipose hypertrophy and visceral adiposity; which constitute the pathogenic precursors for the major metabolic diseases. Furthermore, the pathogenic potential of adipose tissue is also determined by its signaling exchanges with contiguous adipocytes and interactions with other body organs [37]. Finally, the functional integrity of these non-adipose organs determines the extent of the contributory role of adipose tissue to metabolic disease. Besides its frequent association with metabolic diseases like T2DM, hypertension, dyslipidemia, and cardio-metabolic syndrome, adiposopathy may also be a direct contributor to CVD, especially atherosclerosis (abnormal vascular remodeling) [40]. In summary, the pathogenic mechanisms involved in the development of these metabolic diseases include defective adipogenesis, visceral adiposity, increased net release of free fatty acids (FFA), endocrine and inflammatory responses of 'deranged' adipose tissue, as well as the altered signaling exchanges among adipocytes and the altered interactions with non-adipose tissue [37].

Abnormal Vascular Remodeling: The Pathogenic Pathways

Apart from its energy-conserving property, adipose tissue also produces several pro-inflammatory, vasoactive, and metabolic active hormones and cytokines, which are collectively referred to as adipocytokines (adipokines) [41]. These substances play a role in insulin resistance and are believed to be contributory to the evolution of atherosclerosis, T2DM, and hypertension: which could subsequently result in CVD [42]. Despite the focus on leptin, resistin, adiponectin, and interleukin-6 (IL-6), some studies linking these adipocytokines to CVD have given conflicting results [43-45]. In fact, a more recent study observed that neither adiponectin nor

leptin was independently associated with CVD; thus, disputing their role in CVD [46]. Interestingly, the authors instead found that C-reactive protein (CRP) - used as IL-6 surrogate - was significantly linked with an increased risk of CVD, and also substantially reduced the CVD risk related to body mass index (BMI); they, therefore, suggested that IL-6-linked pathways may play a role in mediating obesity-related CVD [46].

Nevertheless, it is now well established that preclinical or asymptomatic atherosclerosis (abnormal vascular remodeling) commences naturally in early childhood and may be influenced over the life course by obesity [47]. Obesity-related cardiovascular risk factors may also alter the initial steps in atherosclerosis (i.e. endothelial function, arterial stiffness, adhesion molecule expression, foam cell formation, and smooth muscle proliferation) and the subsequent changes (i.e. atherosclerotic plaque rupture and thrombosis) [36]. Endothelial dysfunction is a crucial initial step in the development of CVD. It may be modulated by the duration and severity of obesity, as well as the interaction of obesity with other cardiovascular/metabolic risk factors [36]. Abnormal vascular remodeling occurs from the following complex pathophysiologic mechanisms. First, insulin resistance (the link between obesity and T2DM) may contribute to these cardiovascular sequelae via diabetes-induced endothelial dysfunction. Visceral adiposity and ectopic adipose tissue are associated explicitly with insulin resistance [48]. Other obesity-related factors that are correlated with insulin resistance also include elevated serum resistin levels [49-51], as well as the so-called 'silent inflammation' triggered by excess adipocytes [52]. In the latter, adipose tissue produces arachidonic acid which is metabolized into pro-inflammatory eicosanoids leading to the formation of new inflammatory mediators like tumor necrosis factor- α (TNF- α) and IL-6 [52]. A chemotactic eicosanoid, called LTB₄, has been suggested as the 'molecular link' between obesity and T2DM, as it binds to receptors of contiguous macrophages and activates them, resulting in 'silent inflammation' and subsequent insulin resistance [52]. Also, excessive TNF- α has earlier been noted to contribute to insulin resistance, given its ability to inhibit lipogenesis, promote lipolysis (\uparrow FFA), and disrupt insulin signaling [53]. Second, dyslipidemia from the 'adiposopathy' of obesity (\uparrow triglycerides and \uparrow LDL-C) is also known to initiate the early development of atherosclerosis by the formation and deposition of atherosclerotic plaque: one of the late stages in endothelial dysfunction (Figure 2). Third, physiologic levels of adiponectin has several anti-atherosclerotic activities such as the inhibition of monocyte adhesion to aortic endothelial cells and downregulation of the expression of adhesion molecules on these cells [54], the suppression of aortic smooth muscle cell proliferation and migration [55], the inhibition of macrophage foam-cell transformation [56], as well as the increased production of tissue metalloproteinase inhibitor-1 (TIMP-1): a modulator of atherosclerotic plaque rupture [57]. In 'adiposopathy,' adiponectin levels are reduced and thus promote the development of atherosclerosis. Low adiponectin levels have been reported to be associated with endothelial dysfunction in childhood and adulthood [58], as well as with higher evolution of coronary artery calcification (arterial stiffness) and thicker carotid intima-media

thickness (IMT) in adolescents [59,60]. Although there is higher IMT in obese children and adolescents in comparison with their non-obese counterparts [27,61,62], some investigators did not report any difference despite changes in endothelial function and arterial stiffness [63,64]. Nevertheless, aortic IMT and carotid IMT are regarded as surrogate markers of atherosclerosis as well as indirect evidence of disease progression [65].

Abnormal Cardiac Remodeling: The Pathogenic Mechanisms

The cardiac chambers are affected by obesity-related hemodynamic changes, which can occur both in children and adults [66,67]. There is now enough evidence to suggest that the influence of childhood obesity on cardiac structure persists into adult life and may worsen the cardiac effects of obesity in adulthood [36]. Childhood and adolescent adiposity exert significant influences on cardiac structure and function, particularly on the left ventricle [68]. Notably, left ventricular muscle thickness, quantitatively measured as left ventricular mass (LVM), is a stand-alone risk factor for cardiovascular morbidity and mortality [69]. Several studies have shown that LVM is increased in obese children and adolescents when compared with their normal-weight counterparts [22,70,71], and also has a linear relationship with childhood BMI [72]. However, central adiposity (excess visceral adiposity) appears to have a better correlation with LVM in children [73], given its link with CVD [74]. Similarly, left atrial (LA) size is directly related to BMI in children [75], with a larger LA size observed more frequently in obese than in non-obese children [76]. Also, LA size has been noted

to be an independent risk factor for atrial fibrillation, cardiac failure and CVA in adulthood [77].

The mechanisms behind the abnormal cardiac remodeling are based on the hemodynamic effects of adiposopathy. Systemic and pulmonary hypertension (related to adiposopathy) directly affects cardiac remodeling leading to abnormalities like increased LA size (↑LA size) and LVM (↑LVM) (Figure 1). The pathogenic trajectory comprises the increased sympathetic activity from adiposopathy, which leads to an increase in circulating blood volume, increased stroke volume, and increased heart rate. This hemodynamics may directly influence the left atrial and ventricular functions leading to chamber strains: with the consequent ↑LA size and ↑LVM. However, assessment of atrial phasic function with atrial strain has not been reported in childhood obesity [36], as some authors thus advance the hypothesis that obesity-related ↑LA size may be linked to abnormalities in ventricular mechanics (especially diastolic dysfunction) seen in childhood obesity [78], and adult obesity [79]. In a nutshell, obesity affects cardiac muscle through several mechanisms [80]. It can singularly cause chronic volume overload and associated higher cardiac output [81]. Both hemodynamic and metabolic factors linked to obesity can cause structure-function changes of the myocardium leading to ↑LVM. Also, obesity-related hypertension increases the work of the heart and stimulates cardiac growth while obesity-associated oxidative stress, inflammation, and activation of the renin-angiotensin system (RAS) can trigger cardiac remodeling with increased cardiac myocyte and connective-tissue matrix accumulation [82-84].

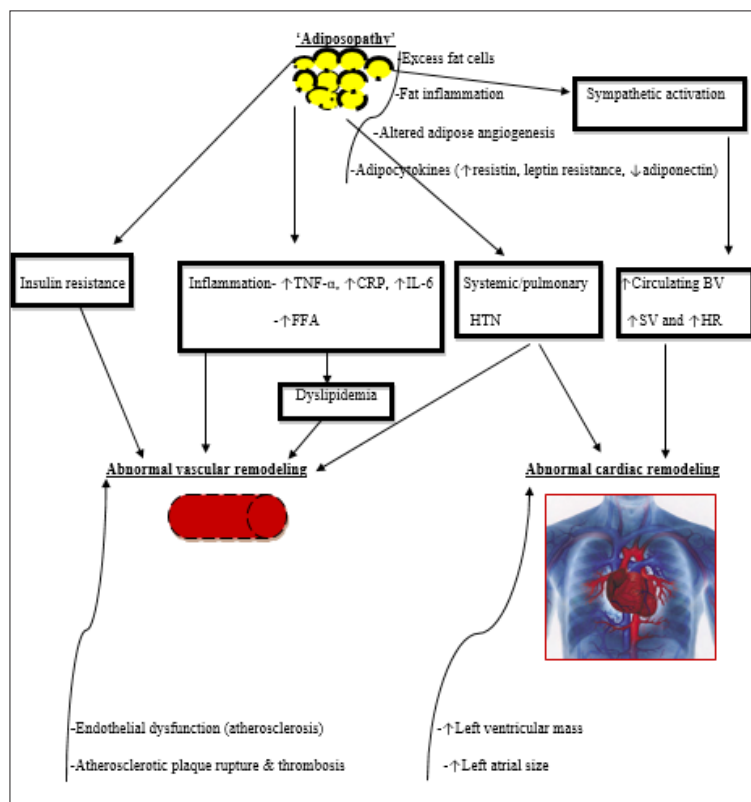


Figure 1: The pathophysiological mechanisms of cardiovascular disease in obesity [34]. TNF-α, tumor necrosis factor-alpha CRP, C-reactive protein IL-6, interleukin-6 FFA, free fatty acids HTN, hypertension BV, blood volume SV, stroke volume HR, heart rate.

Pediatric Obesity Versus Adult CVD: Some Longitudinal Studies

In a population-based, multi-center, prospective cohort study in Finland, Raitakari et al. [30] investigated the cardiovascular risk factors of 2229 Caucasian male and female subjects: first in early childhood and adolescence (age 3 to 18 years) and 21 years later in adulthood (age 24 to 39 years). The authors aimed to study the association of cardiovascular risk-factor profiles assessed in childhood and adolescence with carotid artery intima-media thickness (cIMT) measured in adulthood as a surrogate marker of preclinical atherosclerosis. Specifically, there was a statistically significant association of cIMT in adulthood with LDL-C levels, systolic blood pressure, and BMI in childhood, as well as with adult systolic blood pressure. More importantly, the cardiovascular risk-factor profiles (high levels of LDL-C, systolic blood pressure, BMI and cigarette smoking) measured at adolescence (age 12 to 18 years) were directly related to cIMT measured in adulthood (age 33 to 39 years) in both sexes (Table 1). These findings confirm the previous observations about the utility of ultrasonographic measurement of cIMT as a marker of preclinical atherosclerosis because of its known correlation with cardiovascular risk factors [85], its relationship with the severity and degree of CHD [86], and its predictive ability for possible cardiovascular events [87,88].

Elsewhere in the United States, the community-based Bogalusa Heart Study was conducted among biracial (Caucasian and Negroid) subjects by Li et al. [32]. Their study objective was to examine the effect of putative CV risk factors measured from childhood to adulthood on LVM measured in young adults. Multiple

observations were made during childhood (age 4 to 17 years) and young adulthood (age 18 to 38 years), which enabled an assessment of the cumulative burden of CV risk-factor variables commencing in childhood. A total of 1420 subjects were studied. A 2D M-mode echocardiography examination was performed on 467 subjects in adulthood. Other assessments conducted from childhood to adulthood were BMI, systolic and diastolic blood pressure, high-density lipoprotein-cholesterol (HDL-C) and triglycerides (TG), and cholesterol levels. Using multiple regression analyses, the authors found that adiposity (measured as BMI) in childhood, adiposity and systolic blood pressure in adulthood, and the cumulative burden of adiposity and systolic blood pressure from childhood to adulthood were significant predictors of LVM index in young adults [32] (Table 1). Their findings buttress the fact that the cumulative burden of risk factor profiles in childhood was more likely to result in ↑LVM in adulthood than increased adiposity and hypertension which were previously identified as the two major factors leading to excessive cardiac growth in children [89], and adults [90]. In another longitudinal study, Bjørge et al. [33] in Norway evaluated the long-term effects of adolescent obesity on cause-specific mortality. The authors studied 227,000 adolescents (aged 14 to 19 years) and compared the cause-specific mortality among subjects whose baseline BMI was below the 25th percentile, between the 75th and 84th percentiles, and above the 85th percentile in a US reference population with that of subjects whose BMI was between the 25th and 75th percentiles. In a 22-year old follow-up, relative risks of death from ischemic heart disease and other mortalities were observed for both males and females in the highest BMI percentile category (Table 1).

Table 1: Summary of findings from some longitudinal studies on childhood and adolescent obesity versus adult cardiovascular disease. †Age range at first investigation, ††Age range at second investigation, ‡Assessed by ultrasound, §Assessed by 2D M-mode echocardiography LDL-C, low-density lipoprotein cholesterol HDL-C, high-density lipoprotein cholesterol TG, triglycerides BP, blood pressure BMI, body mass index cIMT, common carotid artery intima-media thickness LVM, left ventricular mass, CVD, cardiovascular disease CHD, coronary heart disease CVA, cerebrovascular accident.

Authors (year)/ Country	Type of Study	Study population	Outcome Measures in Childhood and Adolescence	Outcome Measures in Adulthood	Major Study Findings
Raitakari et al. [30] (2003)/Finland	A population-based, multi-center, prospective cohort study	2229 Caucasian subjects	-LDL-C	-LDL-C	-Cardiovascular risk-factor profiles measured at 12 to 18 years were better predictors of adult cIMT
		-aged 3 to 18 years [†]	-HDL-C & TG	-HDL-C & TG	
		-aged 24 to 39 years ^{††}	-LDL-C/HDL-C ratio	-LDL-C/HDL-C ratio	
			-Systolic & Diastolic BP	-Systolic & Diastolic BP	
			-BMI & Smoking	-BMI & Smoking	
				-cIMT [‡]	

Juonala et al. [31] (2010)/Finland	-Multi-center, prospective cohort study*	4380 subjects	-Cardiovascular risk factor data (total Cholesterol, TG, BP & BMI)	-cIMT	-Cardiovascular risk factor measurements obtained at or after 9 years of age in childhood and adolescence were significantly predictive of cIMT in adulthood
		-3 to 18 years [†]			
		-20 to 45 years ^{††}			
Li et al. [32] - The Bogalusa Heart Study (2004)/United States	Community-based, cross-sectional surveys and longitudinal study	1420 Caucasian and Negroid subjects	-BMI	-BMI	-Adiposity (measured as BMI) in childhood, adiposity and systolic BP in adulthood, and the cumulative burden of adiposity and systolic BP from childhood to adulthood were significant predictors of LVM index in young adults
		-aged 4 to 17 years [†]	-Systolic & Diastolic BP	-Systolic & Diastolic BP	
		-aged 18 to 38 years ^{††}	-HDL-C & TG	-HDL-C & TG	
			-Cholesterol	-Cholesterol	
				-LVM [§]	
Bjørge et al. [33] (2008)/Norway	Population-based longitudinal study	227000 subjects	-BMI (values compared with different BMI percentile categories)	-The relative risk of death from endocrine, nutritional & metabolic diseases, and CVD	-Relative risks of death from ischemic heart disease and other mortalities noted for both sexes in the highest BMI category
		-aged 14-19 years [†]			
		-aged 36-41 years ^{††}			
Twig et al. [34] (2016)/Israel	Population-based longitudinal study	2,298,130 male Jewish subjects	-BMI (according to age- and sex-specific percentiles from the U.S. Centers for Disease Control and Prevention)	-The number of deaths attributed to CHD, CVA, sudden death from an unknown cause, or a combination of all three categories (total cardiovascular causes)	-A BMI in the 50th to 74th percentiles, within the accepted normal range, during adolescence was associated with increased cardiovascular and all-cause mortality during 40 years of follow-up
		-16 to 19 years [†]			
		-56 to 59 years ^{††}			

The Finnish prospective cohort study by Juonala et al. [31] employed data for 4380 subjects of 4 prospective cohorts-Cardiovascular Risk in Young Finns Study (Finland), Childhood Determinants of Adult Health Study (Australia), Bogalusa Heart Study (United States), and Muscatine Study (United States)-which have gathered cardiovascular risk factor profiles from childhood (age 3 to 18 years) and subsequently performed cIMT estimations in adulthood (age 20 to 45 years) [31]. Interestingly, the authors found that the number of childhood risk factors (namely high total cholesterol, TG, blood pressure, and BMI) was significantly predictive of increased cIMT based on risk factors estimated at the ages of 9 years, 12 years, 15 years, and 18 years (Table 1). On the other hand, the associations with risk factors estimated at ages three years and six years were found to be nonsignificant: making the authors conclude that risk factor profiles obtained at or after nine years of age were predictive of preclinical atherosclerosis in adulthood [31]. These observations are not surprising given that atherosclerotic processes which begin in early childhood progress over the life course and are worsened by obesity and other cardio-metabolic factors (Figure 2). Finally, the study by Twig et al. [34] was based on a national database of 2.3 million Israeli male

adolescents in whom the BMI was estimated for over 40 years. The investigators evaluated the relationship between the BMI in late adolescence and mortality from CHD, CVA, and sudden death in adulthood. During 42,297,007 person-years of follow-up, 2918 of 32,127 deaths (9.1%) were from cardiovascular causes, including 1497 from CHD, 528 from CVA, and 893 from sudden death. A BMI in the 50th to 74th percentiles (within the accepted normal range) during adolescence was associated with increased cardiovascular and all-cause mortality during the 40 years of follow-up (Table 1). These findings are in tandem with those of other studies which suggest that a BMI within the upper-normal range in adolescence is associated with an increased risk of death from cardiovascular causes [34,91,92]. Two pathways by which adolescent BMI probably determine cardiovascular outcomes in adulthood have been highlighted [35]. The first is the obesity-linked cardiovascular and metabolic abnormalities (previously stated) such as abnormal plasma lipid or lipoprotein levels, hypertension, impaired glucose metabolism, and insulin resistance [20,93], cardiac remodeling [94], as well as the formation of coronary and aortic atherosclerotic plaques.

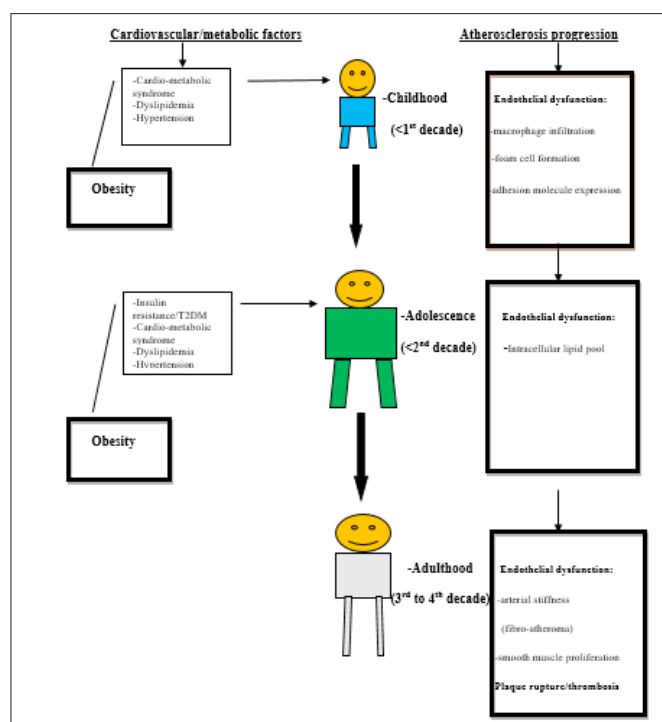


Figure 2: Effects of obesity versus stages of endothelial dysfunction in atherosclerosis over the life course

N/B: Obesity causes premature development of atherosclerosis over the life course through ‘adiposopathy.’

Conclusion

Obesity in childhood and adolescence is associated with an increased risk of cardiovascular diseases in adulthood. The pathophysiologic pathways have been established, as abnormal cardiac remodeling and vascular remodeling remains the main outcome events. Abnormalities of cardiac remodeling like \uparrow LVM and \uparrow LA are independent risk factors for cardiovascular morbidity and mortality in adults, whereas abnormal vascular remodeling like atherosclerotic processes (which if symptomatic in the late stages) may lead to adult cardiovascular diseases such as CHD, CVA, thrombo-embolism and hypertensive heart disease. Because of the complex interplay of cardio-metabolic risk confounders during the life course, there is no consensus yet on the modulating factors for disease risk from childhood to adulthood and on the best methods of measurements in children for predicting adult CVD.

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