

Lifetime cardiovascular risk of childhood obesity¹⁻⁴

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ABSTRACT

An increase in the incidence and an earlier onset of coronary artery disease is expected because of the increased prevalence of childhood obesity. Comorbidities of obesity, such as dyslipidemia, insulin resistance syndrome, hypertension, associated nutritional deficiencies, and a sedentary lifestyle or associated lifestyle factors such as tobacco smoke exposure, are likely to account for this increase because these are all independent risk factors for accelerated atherosclerosis. Because clinical atherosclerotic cardiovascular disease does not manifest in obese children, assessment of the subclinical markers of atherosclerosis may help in the evaluation of the progression of atherosclerosis, in further stratification of risk, and in monitoring the effects of intervention. Furthermore, because multiple risk factors with poorly understood interplay might be present in obese children, assessment of the vasculature directly, and perhaps the assignment of a “vascular age,” may be a useful method to quantify the “end organ” effect of exposure to these various risks. Obese children may show favorable changes in their behaviors that result in an improvement in clinically measurable risk factors with various clinic-based and behavior modification therapies, but the vascular benefits of such interventions need to be studied further. Broad social, cultural, legislative, and policy changes that support healthy lifestyles within families and communities need to be implemented to decrease the prevalence of childhood obesity and its cardiovascular consequences in communities. The effect of risk factor modification on the vasculature will continue to be a resource for the direction of evidence-based therapy in obese children. *Am J Clin Nutr* 2010;91(suppl):1514S–9S.

INTRODUCTION

The excessively processed, energy-dense but nutritionally deficient diet we now consume, along with a sedentary lifestyle, is likely the cause of many chronic illnesses, such as atherosclerotic cardiovascular disease, hypertension, diabetes, and certain cancers, as well as obesity, which are now so prevalent in our society (1). This changing environment, and its interaction with our “hunter-gatherer” genetic make-up that favors storage of fat, has resulted in the epidemic of obesity. The alarming increase in the prevalence of obesity in emerging and developing nations is due to the failure to adapt to these rapidly changing nutritional and lifestyle factors.

Food, shelter, energy, and health care expenditures that families incur have changed over the decades and as food prices have decreased, illness and health care expenditures have increased, which suggests that perhaps the lower-priced foods that are now available are less healthful and less nutritious. Our current diet is significantly deficient in fresh produce, fruit and

vegetables, lean protein, other essential nutrients and vitamins, good fats, and omega-3 fatty acids (**Table 1**). We no longer drink primarily water but rely on energy-dense beverages to quench our thirst and we do not exercise or venture outdoors as often.

Poor cardiovascular health is a leading cause of disease and, along with childhood-onset obesity, constitutes a pressing public health problem in the United States and many other countries, which include developing countries. This reality has dire medical and economic implications. Between the years 2003 and 2006, about one-third of 2–19-y-olds in the United States were diagnosed as overweight, with a body mass index (BMI; in kg/m²) higher than the 85th percentile for age and sex (2).

There is a strong association between childhood obesity and early-onset dyslipidemia, hypertension, and insulin resistance. These conditions, when manifested in childhood, track into and worsen in adult life because obese children are more likely to become obese adults (3, 4). Childhood-onset obesity itself and its associated comorbidities have an adverse effect on the vasculature, which results in premature onset and accelerated progression of atherosclerosis (5, 6). This could result in much higher rates of hospitalizations, interventions, disabilities, and premature deaths in the coming decades as the current cohort of obese children ages (7–9).

COMORBIDITIES OF CHILDHOOD OBESITY

Obese children may have several coexisting risk factors that are detrimental to cardiovascular health. Although the clinical effects of these cardiac risks may not be notable in childhood, their existence and persistence into adulthood are of concern. The commonly noted conditions that promote cardiovascular comorbidities in obese children include dyslipidemia, which is manifest as high triglycerides, and usually a combination of high total and LDL cholesterol, low HDL cholesterol, and high VLDL cholesterol concentrations. Many obese children are also hypertensive and have associated insulin resistance, and exposure to tobacco smoke may be prevalent in this population. A body of

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TABLE 1
The fundamentals of the hunter-gatherer diet and lifestyle¹

Eat whole, natural, fresh foods; avoid highly processed and high-glycemic-load foods.
 Consume a diet high in fruit, vegetables, nuts, and berries and low in refined grains and sugars. Nutrient-dense, low-glycemic-load fruit and vegetables such as berries, plums, citrus, apples, cantaloupe, spinach, tomatoes, broccoli, cauliflower, and avocados are best.
 Increase consumption of omega-3 fatty acids from fish, fish oil, and plant sources.
 Avoid *trans* fats entirely and limit intake of saturated fats. This means the elimination of fried foods, hard margarine, commercial baked goods, and most packaged and processed snack foods. Substitute monounsaturated and polyunsaturated fats for saturated fats.
 Increase consumption of lean protein, such as skinless poultry, fish, game meats, and lean cuts of red meat. Cuts with the words “round” or “loin” in the name are usually lean. Avoid high-fat dairy and fatty, salty processed meats such as bacon, sausage, and deli meats.
 Incorporate olive oil and/or non-*trans* fatty acid canola oil into the diet.
 Drink water.
 Participate in daily exercise from various activities (and incorporate aerobic, strength-training, and stretching exercises). Outdoor activities are ideal.

¹ Reproduced with permission from reference 1.

evidence is being accumulated that links obesity and cardiovascular risk to low concentrations of vitamin D (10–15).

CHILDHOOD OBESITY AND ITS EFFECTS IN ADULTHOOD

Considerable evidence supports increased morbidity and mortality in adults with a history of childhood obesity. In a cohort of children born in Denmark and followed for >5 million person-years, a higher BMI in childhood was associated with increased risk of coronary artery disease in adulthood (16). A 55-y follow-up of the Harvard Growth Study of 1922–1935 showed that being overweight in adolescence resulted in more than a 2-fold higher relative risk of coronary artery disease mortality, independent of adult weight (17). A British study that involved a 57-y follow-up of a cohort also confirmed that all-cause and cardiovascular mortality were increased when childhood BMI was higher than even the 75th percentile (18). Thus, it is likely that there is a direct relation between BMI and cardiovascular disease and that adverse outcome may manifest even at BMI percentiles that do not qualify as overweight. The current epidemic of childhood obesity has been projected to further increase rates of coronary artery disease in young and middle-aged adults, and it is estimated that the prevalence of coronary artery disease may increase by 5–16% by the year 2035 (19).

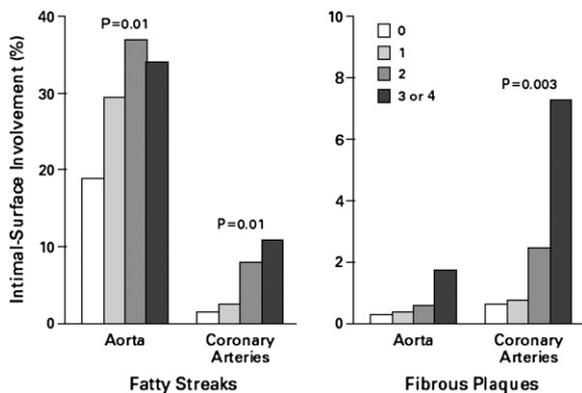


FIGURE 1. Effect of multiple risk factors on the extent of atherosclerosis in the aorta and coronary arteries in children and young adults. Reproduced with permission from reference 6.

EVIDENCE THAT SUPPORTS THE LONG-TERM VASCULAR EFFECT OF CARDIOVASCULAR RISK FACTORS NOTED IN CHILDHOOD

Pediatric epidemiologic studies have shown that high total cholesterol (20), high BMI, and high LDL cholesterol in childhood (21) are associated with an increased carotid artery intima-media thickness (CIMT), a marker of atherosclerosis and heart disease, in adulthood. The Bogalusa Study, which involved a long-term follow-up of a racially diverse population sample showed that the atherosclerotic lesions in the coronary arteries were increased in youth with multiple atherosclerosis-promoting risk factors (6) (Figure 1). These investigators also showed that childhood obesity that tracked into obesity in adult life resulted in a further increase in CIMT, which suggests that the adverse vascular effects of childhood-onset obesity persist (5) (Figure 2).

NATURAL AND UNNATURAL EVOLUTION OF ATHEROSCLEROSIS

Atherosclerosis is a degenerative disease process that is noted in all humans beginning in childhood but its progression to

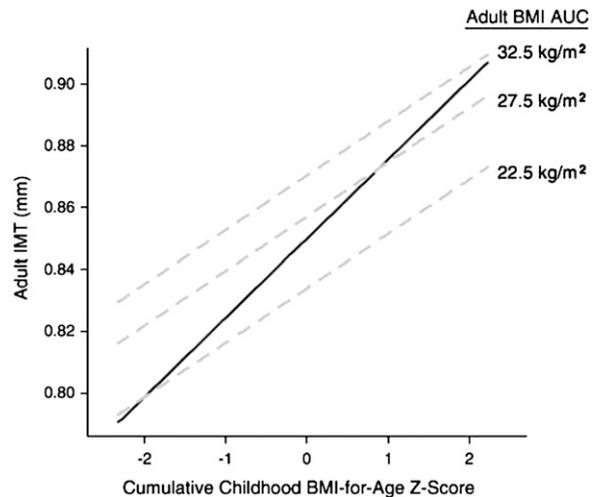


FIGURE 2. Relation of cumulative levels of the BMI z score during childhood to adult carotid artery intima-media thickness (IMT) as estimated in regression analyses (solid black line), controlled for race, sex, and age. The effects of further adjustment for adult BMI are shown by the dashed gray lines. The estimated difference in carotid artery IMT by adult BMI (at a constant childhood BMI-for-age) is represented by the vertical distance between the dashed lines. AUC, area under the curve. Reproduced with permission from reference 5.

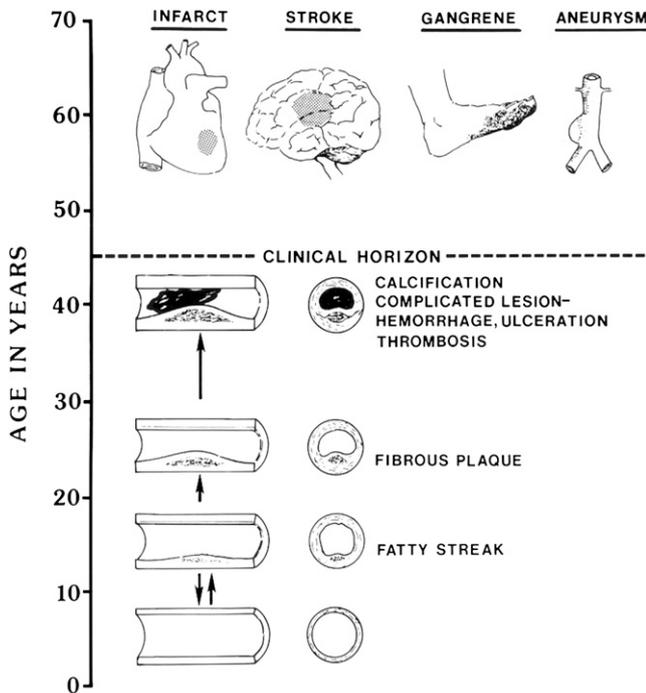


FIGURE 3. The natural history of atherosclerosis. Reproduced with permission from the author, Henry McGill, Southwest Foundation for Biomedical Research, San Antonio, TX.

clinically manifest disease spans over years (**Figure 3**). The disease evolution is premature in onset and accelerated in the presence of several immutable and mutable atherosclerosis-promoting risk factors, such as advancing age, male sex, family history of premature coronary artery disease/stroke and peripheral vascular disease, dyslipidemia, hypertension, insulin resistance, obesity, tobacco smoke exposure, and other risks (**Table 2**).

Historical and autopsy data have attested to the childhood origins of this disease and its long, presymptomatic, “silent” period. Among young, apparently healthy, victims of the Korean and Vietnam wars who were autopsied, there was a 45–77% prevalence of atherosclerosis of the coronary arteries, which suggested its childhood origins (22, 23). These observations were made >50 y ago when the prevalence of childhood obesity was

TABLE 2
Immutable and mutable risk factors for atherosclerosis

Immutable risks	
Age	
Male sex	
Family history	
Genetic markers	
Mutable risks	
Obesity (especially abdominal adiposity)	
Hypertension	
Exposure to tobacco smoke	
Insulin resistance	
High total and LDL cholesterol	
Low HDL cholesterol	
High triglycerides	
High VLDL cholesterol	
Novel risk factors: low vitamin D, other less-understood risks	

lower than it is at present. In the 1990s, investigators from the Pathobiological Determinants of Atherosclerosis in Youth research group reported the link between atherosclerosis and risk factors such as dyslipidemia, tobacco smoke exposure, hypertension, diabetes, and age (24), and in a follow-up study suggested a link between abdominal obesity and coronary artery lesions in youth (25).

These data provide the rationale for treatment initiation in those affected with premature atherosclerosis at an early age and even in childhood, because the atherosclerotic process is end stage by mid-adulthood. The aim for intervention in children is to prevent the premature onset of and to contain atherosclerosis rather than to prevent clinical disease events. Thus, the vasculature in children serves as a surrogate endpoint in the absence of clinical endpoints and therefore, monitoring the vasculature with a noninvasive imaging modality over time may be of value.

PATHOLOGY OF ATHEROSCLEROSIS

The earliest manifestation of atherosclerosis is a fatty streak, an accumulation of lipid-filled macrophages within the arterial intima. Progressive lipid accumulation over time results in macrophage and smooth muscle proliferation and development of

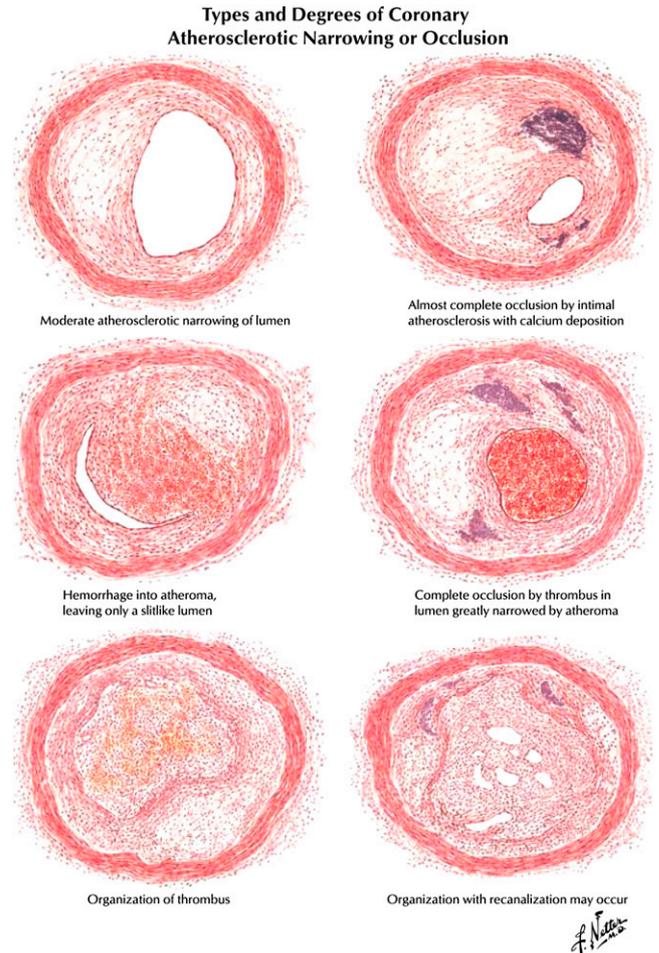


FIGURE 4. The evolution of atherosclerosis as seen in the cross-section of the artery. Reproduced from Netter Illustration with the permission of Elsevier Inc. All rights reserved.

a fibrous plaque. As this plaque increases in size over the years, there may be necrosis or bleeding within the plaque or the plaque can rupture. Prooxidative and proinflammatory states facilitate some of these changes in the vascular intima. Enlarging plaques lead to progressive luminal narrowing, which leads to either a slow occlusion of the vessel or sudden occlusion of a distal vessel because of plaque embolization (26–28) (**Figure 4**).

ASSESSMENT OF SUBCLINICAL MARKERS OF ATHEROSCLEROSIS BY THE MEASUREMENT OF CIMT

One method to examine coronary artery health is to obtain an ultrasound of the carotid arteries and to measure CIMT, a measure of carotid atherosclerosis. Assessment of CIMT is non-invasive, technically easy, relatively inexpensive, and devoid of radiation or side effects, and so can be repeated to track changes over time. Changes in the CIMT and carotid atherosclerosis are known to parallel the atherosclerotic changes seen in the coronary arteries (29, 30). Increased CIMT in adults has been associated with cardiovascular risk factors (31), coronary artery disease, stroke (32–34), and progression of coronary atherosclerosis (28, 29, 31, 34, 35). Because clinical cardiovascular events do not typically occur in childhood, the effect of the risk factors on the CIMT may help in understanding the progression of the structural disease processes in at-risk children and in monitoring the effectiveness of interventions. Frequently, obese children also have multiple coexisting atherosclerosis-promoting risk factors and their sum effects on the vasculature may vary based on the length of exposure to the various risks, risk factor interactions, and genetic predisposition, and perhaps the presence of other unknown and undocumented risks. Thus, CIMT measures can be considered one “end organ effect” of all the known and unknown

risk factors that may be prevalent in children. Pediatric epidemiologic studies have shown that high total cholesterol (20), a high BMI, and high LDL cholesterol in childhood (21) are associated with an increased CIMT in adulthood. Furthermore, several case-control and observational studies in children have confirmed increased CIMT in childhood in the presence of atherosclerosis-promoting risk factors such as hypertension, dyslipidemia, diabetes mellitus, and obesity (36–39).

VASCULAR AGE ESTIMATION IN COMPARISON WITH CHRONOLOGIC AGE

“A man is as old as his arteries,” said Thomas Sydenham, a 16th-century physician. An assessment of “vascular age” compared with chronologic age may be a useful concept in children with multiple risk factors because this may predict atherosclerotic burden more accurately than risk factor assessments alone. In adults, estimation of vascular age and reclassification of “Framingham 10 year cardiovascular event probability risk” based on vascular age has been shown to be reliable (40). Vascular age can be estimated through the performance of a carotid artery ultrasound and measurement of CIMT (**Figure 5**). However, the paucity of normative data for CIMT in children at this time dictates that their CIMT be compared against that of sex- and race-matched adult normative CIMT data.

Vascular age estimations in our clinic population have confirmed an advanced vascular age (CIMT comparable to that of a race- and sex-matched 45-y-old) in the majority of obese teenagers with multiple atherosclerosis-promoting risk factors (41). This evidence further supports the need for atherosclerosis-halting efforts to begin in childhood.



FIGURE 5. Ultrasound images of the right common carotid artery (CCA), the bifurcation, and the external and internal carotid arteries. The 10-mm-wide box contains the region of interest where the carotid artery intima-media thickness (IMT) is measured, with the reading depicted on the right.

EFFECTS OF LIFESTYLE ALTERATION AND PHARMACOTHERAPY ON VASCULATURE IN OBESE CHILDREN

Weight reduction, aerobic and strength training, or gastric bypass surgery in obese children is associated with improvements in clinically measurable risk factors such as LDL cholesterol, triglycerides, insulin concentrations, and blood pressures and an improvement in HDL cholesterol (42–46). The efficacy and relative safety of statin therapy as a lipid-modifying drug in children with familial dyslipidemia has also been established (47). An intriguing question is whether the premature aging of the vasculature can be slowed or is in fact reversible with lifestyle alterations or with pharmacologic therapy of the risk factors.

Improvements in CIMT have been reported with interventions in adults (46). A few pediatric reports on obese children and children with familial dyslipidemia have also described short-term, favorable changes in vascular function (47–49) and CIMT measures (38, 49), respectively, with lifestyle alterations such as diet modification, daily moderate-to-vigorous physical activity, or lipid-modifying therapy such as statin therapy. However, long-term follow-up on the comparative effectiveness of various pharmacologic and nonpharmacologic therapies on the vasculature in obese children needs to be pursued.

CONCLUSIONS

Several risk factors that facilitate premature acceleration of atherosclerosis are present in obese children and these risk factors frequently track into adulthood, which imposes an unusual burden as these children become young adults. Obese children with multiple atherosclerosis-promoting risk factors may have accelerated progression of atherosclerosis and hence should be screened for these associated risk factors. In addition, childhood obesity itself, which tracks into adulthood, creates a cumulative burden on cardiovascular health. The use of carotid artery ultrasound and CIMT measurement may help further stratify children who are at higher risk of development of premature coronary artery disease. These children with an advanced vascular age may need intensive management, which includes pharmacotherapy for risk factor modification, with the goal of halting the progression of atherosclerosis. Such interventions may alter the lifetime risk of excess morbidity and mortality due to atherosclerosis.

Broad social and cultural changes that support healthy lifestyles within families, communities, and workplaces need to be implemented to halt the epidemic of childhood obesity and its cardiovascular consequences in communities. Although these population-based strategies are of the utmost importance in the curtailment of the effects of childhood obesity on the cardiovascular system, a small number of obese children with the most serious atherosclerosis-promoting risk factor abnormalities may need clinic-based behavioral modification or pharmacologic therapies.

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