Published in final edited form as:

Curr Pediatr Rev. 2017 ; 13(4): 255–259. doi:10.2174/1573396314666180117092010.

Pediatric Markers of Adult Cardiovascular Disease

Micah Olson, MD^{1,2}, Melissa Chambers, DO¹, and Gabe Shaibi, PhD^{1,2}

¹Division of Endocrinology and Diabetes, Phoenix Children's Hospital, Phoenix, AZ

²Center for Health Promotion and Disease Prevention, College of Nursing and Health Innovation, Arizona State University, Phoenix, AZ

Keywords

atherosclerosis; cardiovascular disease; dyslipidemia; childhood obesity; metabolic syndrome

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality in the United States [1]. Atherosclerotic CV events do not occur until adulthood, except in the context of rare genetic disorders such as homozygous familial hypercholesterolemia. However, the atherogenic process that leads to CVD begins in childhood and progresses throughout the lifespan [2]. The degree of atherosclerosis early in life is associated with established risk factors for CVD (e.g. family history, obesity, dyslipidemia), indicating that the development and progression of atherosclerosis in childhood is driven by genetic as well as environmental factors. Therefore, although CV events do not occur in childhood, establishing heart healthy behaviors and managing CV risk factors in childhood may prevent or delay the development of atherosclerosis and, in turn, reduce the risk of CVD later in life.

The purpose of this review is to 1) outline the evidence that atherosclerosis begins in childhood, 2) identify the risk factors associated with childhood atherosclerosis, and 3) identify the risk factors present in childhood that are associated with adult CVD. The information presented in this review will lay the foundation for the pediatric origins of CVD and conceptually support primordial and primary prevention strategies to reduce the overall burden of CVD.

Autopsy Studies

Atherosclerosis begins as fatty streaks in the intima of large muscular arteries [2]. As lipid accumulates it is covered by a fibromuscular cap to form a raised lesion, also called a fibrous plaque. In some individuals, the fibrous plaque increases in size and eventually impinges upon the lumen of the artery. When a plaque ruptures, a thrombus forms and further occludes the lumen which results in ischemia of the involved organ.

Autopsy studies of children and young adults who deceased from accidental causes demonstrate the presence of early atherosclerotic lesions [3]. The first widely documented report of atherosclerosis in the young came from American soldiers who were killed in the Korean War [4]. Autopsy examination of these American soldiers (average age 22 years) revealed the presence of advanced coronary artery lesions.

Another early report of atherosclerosis present in the young came from The Bogalusa Heart Study [5], a longitudinal population-based study in a semirural black and white community in Louisiana. It started in 1972 as an epidemiology study of cardiovascular risk factors in children and adolescents with the goal of investigating childhood antecedents of adult CVD [6]. In this cohort, 66 autopsy subjects who had died between the age of 3 and 31 years had previously measured risk factor levels, including cholesterol panel, systolic and diastolic blood pressure (BP), and body size [5]. Coronary artery fatty streaks found in the autopsy specimens were associated with elevated low density lipoprotein (LDL), very low density lipoprotein (VLDL), and systolic BP.

The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study is a multicenter study of the relation of the risk factors in teenagers and young adults to atherosclerosis [7]. The investigators collected approximately 3,000 sets of coronary arteries and aortas from accident, homicide, and suicide victims who were autopsied in forensic laboratories. Postmortem serum was analyzed for CV risk factors. Specimen collection was from 1987 to 1994, and patients were 15–34 years of age. In this cohort, non-HDL cholesterol was associated positively, and HDL cholesterol negatively, with raised lesions in the right coronary artery [8]. Elevated Hemoglobin A1c (defined as an A1c $\geq 8\%$) [9] and hypertension (defined by measuring the thickness of the intima of the small renal arteries) [10] were associated with more raised lesions in the right coronary artery. Increased body mass index (BMI) was associated with more extensive coronary artery raised lesions in men but not in women [9].

Childhood Risk Factors and Adult Cardiovascular Events and Mortality

Although atherosclerosis develops at an early age, the actual occurrence of a CV event is typically still decades away. This time gap makes the investigation of childhood risk factors for adult CVD challenging, as few studies encompass the time duration necessary to associate data in childhood with actual CV events later in life. A limited number of such studies exist, however, and provide valuable insight into the presence and strength of correlations between childhood risk factors and adult CVD.

A longitudinal Israeli population study included 2.3 million adolescents who, in the time period from 1967 to 2010, had BMI measured at 16 to 19 years of age (prior to mandatory military service). The study examined associations between childhood BMI and death from coronary heart disease, stroke, and sudden death from unknown cause, or a combination of all three categories [11]. BMI percentiles were grouped according to percentiles for age and sex established by the U.S. Centers for Disease Control and Prevention. There was an increased risk of death from CV causes that started in individuals who had a childhood BMI in the 50th to 74th percentile, and the risk of death worsened with increasing BMI categories

(Figure 1). When compared with the reference group (BMI 5th to 24th percentile), the obese group (BMI ≥ 95th percentile) had a hazard ratio of 3.5 (95% CI, 2.9 to 4.1) for death from total CV causes. The 85th to 94th percentile BMI group had a hazard ratio of 2.3 (95% CI, 2.0–2.6) for total CV deaths. Even the 50th to 74th percentile BMI group and the 75th to 84th percentile BMI group, both of which are generally thought to be healthy BMIs, had hazard ratios of 1.3 (95% CI, 1.2–1.5), and 1.8 (95% CI, 1.5–2.0), respectively, for total CV deaths compared to the reference group.

A longitudinal Danish study examined the association between BMI in childhood and coronary heart disease in adulthood [12]. The study included 276,835 schoolchildren who were born from 1930 through 1976 and who had BMI measured between 7 to 13 years old through a mandatory annual health exam. Higher childhood BMI values increased the risk for having a coronary heart disease event in adulthood. The association between childhood BMI and adult coronary heart disease became stronger with increasing age. Other smaller longitudinal cohort studies have examined associations between childhood BMI and adult CVD, with most showing significant associations [13, 14], although one showed no association [15].

The information needed to calculate BMI (height and weight) is relatively convenient to obtain, and this convenience has allowed for a robust analysis of associations between childhood BMI and adult CVD disease in the above-referenced population studies. Although limited, longitudinal studies that correlate childhood risk factors other than BMI with adult CVD do exist. The Princeton Follow-Up Study (PFS) examined relationships between lipid and non-lipid risk factors to subsequent CVD [16]. Eight hundred and eighteen children were followed from a mean age of 12 years at baseline to 38.5 years at follow-up, with 19 individuals experiencing at least 1 CV event. Increased BMI and triglyceride level were predictive of a CV event in young adulthood, whereas LDL cholesterol was not. It is noteworthy that hypertriglyceridemia is often seen in association with obesity, insulin resistance, hypertension, and the metabolic syndrome, and there remains controversy whether hypertriglyceridemia alone or the associated risk factors (obesity, hyperglycemia, hypertension, and insulin resistance) drive CVD [17].

In a follow-up study of the PFS cohort [18], high triglyceride level, as defined by a triglyceride level ≥ 110 mg/dL, predicted adult CVD with an odds ratio of 5.85 (95% CI of 2.33–14.7). High BMI (≥ 85th percentile), predicted adult CVD with an odds ratio of 3.03 (95% CI of 1.18–7.73), and high BP (≥ 90th age/height-specific percentile) predicted adult CVD with an odds ratio of 3.02 (95% CI of 0.92–9.89). A high triglyceride level (≥ 110 mg/dL) had a 7% positive predictive value for adult CVD (mean age of follow-up 39.5 years old), which is to say that 7% of participants who had a childhood triglyceride level ≥ 110 mg/dL had a CV event by an average age of 39.5 years old. The positive predictive values of adult CVD for a BP ≥ 90th age/height-specific percentile, and a BMI ≥ 85th percentile, were 6% and 5%, respectively.

Childhood Risk Factors and Surrogate Markers of Cardiovascular Disease in Adulthood

While data linking childhood risk factors to adult CV events remain limited, the use of surrogate markers of CVD provides for a more convenient, albeit less direct, evaluation of the degree to which risk in childhood may predict CVD risk in adulthood [19]. Numerous studies support the use of carotid intima-media thickness (cIMT) as an independent predictor of future CV events, even in asymptomatic adults [20–23]. The Cardiovascular Health Study showed a linear relationship between cIMT and the relative risk of CV events (defined as stroke or myocardial infarction) in adults without clinical CVD [20], and was suggested as a tool to independently predict CV events in asymptomatic adults [21]. A meta-analysis comparing data from eight adult studies calculated a relative risk of myocardial infarction of 1.26 (95% CI, 1.21 to 1.3) for every one standard deviation of cIMT difference, and a relative risk of 1.15 (95% CI, 1.12 to 1.17) for every 0.1 mm difference in cIMT [23].

The Bogalusa Heart Study, Muscatine Study, and The Cardiovascular Risk in Young Finns Study provide much of our knowledge of associations between pediatric risk factors and surrogate markers of CV disease in adulthood. In the Muscatine Study, a longitudinal population-based study of a cohort of children in Muscatine, Iowa who have been followed since 1971, a total of 725 participants had risk factors determined in childhood (age 8 to 18 years), and again in young adulthood (age 33–42 years) [24]. Childhood total cholesterol was a significant predictor of adult cIMT in both men and women whereas BMI was predictive of adult cIMT in women only.

In the Bogalusa Heart Study, a cohort of 486 participants had measurement of traditional risk factors in childhood (age 4 to 17 years) and again as adults (25 to 37 years) [25]. Childhood LDL and BMI were significant predictors of adult cIMT. When risk factors were measured as a cumulative burden from childhood to adulthood (all participants had at least 3 separate measurements), LDL, HDL (inverse association), triglyceride, systolic BP, and BMI were all correlated with cIMT, with LDL showing the strongest association.

In the Young Finns Study, a cohort of 2264 Finnish participants had risk factors measured in childhood (3 to 18 years) and again 21 years later (24 to 39 years) [26]. Childhood LDL cholesterol, BP, BMI, and smoking predicted increased cIMT in adulthood. The effects of childhood risk factors on later cIMT was independent of adulthood risk factors. In a separate analysis of the Young Finns Study [27], participants who were overweight/obese as children had higher adult cIMT than normal weight participants independent of metabolic abnormalities. Metabolic abnormalities were defined as a systolic BP and/or diastolic BP > 90th percentile, LDL cholesterol > 90th percentile, triglyceride level > 90th percentile, HDL cholesterol < 10th percentile, or glucose > 90th percentile.

The Bogalusa Heart Study and Young Finns Study were combined to evaluate pediatric metabolic syndrome as a risk factor for adult CVD as measured by cIMT [28]. 1781 participants ages 9 to 18 years at baseline were re-examined 14 to 27 years later at ages 24 to 41 years. Using various definitions, youth with metabolic syndrome had approximately 2 times the risk of having high cIMT as adults compared with those without metabolic

syndrome as youth. Interestingly, in this study childhood BMI alone was found to be equal if not superior to childhood metabolic syndrome in predicting adult cIMT.

The Atherosclerosis Risk in Young Adults study, a longitudinal study of 750 individuals in Netherlands, showed that for every standard deviation increase in adolescent BMI, cIMT in young adulthood increased by 0.0023mm (95% CI, 1.3 to 3.3) [29]. Further, obese adolescents who lost weight and were no longer obese as adults had cIMT values that were comparable to those without a history of obesity/overweight.

Measurement of cIMT is a useful research tool to identify subclinical atherosclerosis in children as well. Data regarding the use of cIMT measurements in pediatrics are less robust than in adults, however increased cIMT has been identified in children with several CV risk factors including familial hypercholesterolemia, type 1 diabetes, hypertension, obesity, and metabolic syndrome, which indicates that subclinical atherosclerotic changes do occur in children and are able to be identified with similar techniques as in adults [19]. Children with heterozygous familial hypercholesterolemia demonstrate a more rapid increase in cIMT with age compared to their healthy siblings, with a statistically significant deviation in cIMT by the age of 12 years [30]. Statin use has been shown to significantly reduce cIMT compared to placebo over a 2 year duration in a randomized controlled trial of children with familial hypercholesterolemia (Figure 2) [31]. In a 10 year follow-up to this study, the participants who were originally randomized to statin therapy continued to have a significantly lower cIMT compared to those originally randomized to placebo, despite all study participants being prescribed a statin after the completion of the initial 2 year trial [32].

Diabetes is a known risk factor for adult CVD [33], however the influence of hyperglycemia in childhood on adult cIMT has not been well characterized, owing to the small numbers of children with diabetes in the large cohort studies described above. A recent cross-sectional study illustrates the effect of hyperglycemia on cIMT in childhood. Obese youth with prediabetes (n=102) were compared to obese youth with normal glucose tolerance (n=139) and found to have increased arterial thickness (increased cIMT) and stiffness (lower brachial dispensability) [34]. These data suggest that prediabetes is associated with subclinical CVD risk early in life.

Conclusion

Traditional risk factors that are predictive of adult CVD are present in childhood, and their presence in childhood alone is predictive of future CVD. The ability of childhood BMI to predict future CVD is remarkably consistent, sometimes outperforming other established adult CVD risk factors. As prevalence rates of childhood obesity increase, the burden of future CVD should be expected to increase as well. Research efforts should focus on the mechanisms by which childhood obesity increases future risk of CVD, as well as developing effective prevention approaches that decrease the burden of disease.

Acknowledgments

Funding: Drs. Olson and Shaibi were supported by grant number R01DK107579 from the National Institutes of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health.

References

1. Writing Group, M. et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation*. 2016; 133(4):e38–360. [PubMed: 26673558]
2. McGill HC Jr, et al. Origin of atherosclerosis in childhood and adolescence. *Am J Clin Nutr*. 2000; 72(5 Suppl):1307S–1315S. [PubMed: 11063473]
3. McGill HC Jr, McMahan CA. Determinants of atherosclerosis in the young. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *Am J Cardiol*. 1998; 82(10B): 30T–36T.
4. Enos WF, Holmes RH, Beyer J. Coronary disease among United States soldiers killed in action in Korea; preliminary report. *J Am Med Assoc*. 1953; 152(12):1090–3. [PubMed: 13052433]
5. Berenson GS, et al. Atherosclerosis of the aorta and coronary arteries and cardiovascular risk factors in persons aged 6 to 30 years and studied at necropsy (The Bogalusa Heart Study). *Am J Cardiol*. 1992; 70(9):851–8. [PubMed: 1529936]
6. Berenson GS, et al. Rationale to study the early natural history of heart disease: the Bogalusa Heart Study. *Am J Med Sci*. 1995; 310(Suppl 1):S22–8. [PubMed: 7503119]
7. Wissler RW. USA Multicenter Study of the pathobiology of atherosclerosis in youth. *Ann N Y Acad Sci*. 1991; 623:26–39. [PubMed: 2042833]
8. McGill HC Jr, et al. Effects of serum lipoproteins and smoking on atherosclerosis in young men and women. The PDAY Research Group. Pathobiological Determinants of Atherosclerosis in Youth. *Arterioscler Thromb Vasc Biol*. 1997; 17(1):95–106. [PubMed: 9012643]
9. McGill HC Jr, et al. Relation of glycohemoglobin and adiposity to atherosclerosis in youth. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *Arterioscler Thromb Vasc Biol*. 1995; 15(4):431–40. [PubMed: 7749853]
10. Relationship of atherosclerosis in young men to serum lipoprotein cholesterol concentrations and smoking. A preliminary report from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *JAMA*. 1990; 264(23):3018–24. [PubMed: 2243430]
11. Twig G, et al. Body-Mass Index in 2.3 Million Adolescents and Cardiovascular Death in Adulthood. *N Engl J Med*. 2016; 374(25):2430–40. [PubMed: 27074389]
12. Baker JL, Olsen LW, Sorensen TI. Childhood body-mass index and the risk of coronary heart disease in adulthood. *N Engl J Med*. 2007; 357(23):2329–37. [PubMed: 18057335]
13. Must A, et al. Long-term morbidity and mortality of overweight adolescents. A follow-up of the Harvard Growth Study of 1922 to 1935. *N Engl J Med*. 1992; 327(19):1350–5. [PubMed: 1406836]
14. Engeland A, et al. Body mass index in adolescence in relation to total mortality: 32-year follow-up of 227,000 Norwegian boys and girls. *Am J Epidemiol*. 2003; 157(6):517–23. [PubMed: 12631541]
15. Lawlor DA, et al. Association of body mass index measured in childhood, adolescence, and young adulthood with risk of ischemic heart disease and stroke: findings from 3 historical cohort studies. *Am J Clin Nutr*. 2006; 83(4):767–73. [PubMed: 16600926]
16. Morrison JA, et al. Pediatric triglycerides predict cardiovascular disease events in the fourth to fifth decade of life. *Metabolism*. 2009; 58(9):1277–84. [PubMed: 19501856]
17. McBride PE. Triglycerides and risk for coronary heart disease. *JAMA*. 2007; 298(3):336–8. [PubMed: 17635897]
18. Morrison JA, Glueck CJ, Wang P. Childhood risk factors predict cardiovascular disease, impaired fasting glucose plus type 2 diabetes mellitus, and high blood pressure 26 years later at a mean age of 38 years: the Princeton-lipid research clinics follow-up study. *Metabolism*. 2012; 61(4):531–41. [PubMed: 22001337]
19. Urbina EM, et al. Noninvasive assessment of subclinical atherosclerosis in children and adolescents: recommendations for standard assessment for clinical research: a scientific statement from the American Heart Association. *Hypertension*. 2009; 54(5):919–50. [PubMed: 19729599]
20. O'Leary DH, et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N Engl J Med*. 1999; 340(1):14–22. [PubMed: 9878640]

21. Greenland P, et al. Prevention Conference V: Beyond secondary prevention: identifying the high-risk patient for primary prevention: noninvasive tests of atherosclerotic burden: Writing Group III. *Circulation*. 2000; 101(1):E16–22. [PubMed: 10618318]
22. Chambless LE, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987–1993. *Am J Epidemiol*. 1997; 146(6):483–94. [PubMed: 9290509]
23. Lorenz MW, et al. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation*. 2007; 115(4):459–67. [PubMed: 17242284]
24. Davis PH, et al. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: The Muscatine Study. *Circulation*. 2001; 104(23):2815–9. [PubMed: 11733400]
25. Li S, et al. Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study. *JAMA*. 2003; 290(17):2271–6. [PubMed: 14600185]
26. Raitakari OT, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA*. 2003; 290(17):2277–83. [PubMed: 14600186]
27. Koskinen J, et al. Youth overweight and metabolic disturbances in predicting carotid intima-media thickness, type 2 diabetes, and metabolic syndrome in adulthood: the Cardiovascular Risk in Young Finns study. *Diabetes Care*. 2014; 37(7):1870–7. [PubMed: 24742659]
28. Magnussen CG, et al. Pediatric metabolic syndrome predicts adulthood metabolic syndrome, subclinical atherosclerosis, and type 2 diabetes mellitus but is no better than body mass index alone: the Bogalusa Heart Study and the Cardiovascular Risk in Young Finns Study. *Circulation*. 2010; 122(16):1604–11. [PubMed: 20921439]
29. Oren A, et al. Change in body mass index from adolescence to young adulthood and increased carotid intima-media thickness at 28 years of age: the Atherosclerosis Risk in Young Adults study. *Int J Obes Relat Metab Disord*. 2003; 27(11):1383–90. [PubMed: 14574350]
30. Wiegman A, et al. Arterial intima-media thickness in children heterozygous for familial hypercholesterolaemia. *Lancet*. 2004; 363(9406):369–70. [PubMed: 15070569]
31. Wiegman A, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA*. 2004; 292(3):331–7. [PubMed: 15265847]
32. Kusters DM, et al. Ten-year follow-up after initiation of statin therapy in children with familial hypercholesterolemia. *JAMA*. 2014; 312(10):1055–7. [PubMed: 25203086]
33. Laing SP, et al. The British Diabetic Association Cohort Study, II: cause-specific mortality in patients with insulin-treated diabetes mellitus. *Diabet Med*. 1999; 16(6):466–71. [PubMed: 10391393]
34. Shah AS, et al. Prediabetes: the effects on arterial thickness and stiffness in obese youth. *J Clin Endocrinol Metab*. 2014; 99(3):1037–43. [PubMed: 24423349]

Figure 1.
BMI during Adolescence and Subsequent Cardiovascular Mortality

Figure 2.
Mean IMT Changes From Baseline for the Different Carotid Arterial Wall Segments in the Pravastatin and Placebo Groups