Impact of Health Status and Lifestyle Modifications on Vascular Structure and Function in Children and Adolescents

Abstract: *Until recently cardiovascular disease is often thought of as a disease that manifests itself during middle age. Researchers and clinicians have begun to realize that the initial signs of cardiovascular disease begin early on in childhood with changes present in both vascular structure and function. This increased recognition has resulted in considerable effort to develop accurate and reliable methods to measure as well as track changes in vascular structure and function applicable to study this process in children and adolescents. Certain genetic abnormalities and chronic diseases, which present or emerge in childhood often result in meaningful changes to vascular structure and function, which aid in our understanding of the vascular disease process. In this review, we will discuss different methods of assessing vascular structure and function, the diseases in childhood associated with decrements and maladaptive changes in the vascular system, and whether modification of lifestyle (ie, weight loss, dietary and/or exercise changes)*

can affect vascular structure and function in children.

Keywords: endothelial dysfunction; ultrasound imaging; cardiovascular disease risk factors; intima-media thickness

identification of the disease has garnered considerable attention. Because of this interest, several noninvasive methods have been developed to assess both vascular structure and function, which are associated with difference stages of the development of CVD.

. . . noninvasive methods are predictive of adulthood CVD [cardiovascular disease] and are associated with more invasive techniques used to measure arterial structure and function.

Almost a quarter of all deaths in the United States are related to heart disease making it the number one cause of death.¹ Heart disease is not just a health concern for the United States but on a global scale, it is also the leading cause of death.² Given the impact that cardiovascular disease (CVD) has on mortality worldwide, early

Cardiovascular disease is typically thought to occur around middle age when the clinical outcomes of heart disease often present themselves. However, the process of atherosclerosis starts early in childhood where postmortem studies have reported fatty streaks and atherosclerotic plaque formation in the intimal of large arteries

DOI: 10.1177/1559827615602226. Manuscript received May 18, 2015; revised August 1, 2015; accepted August 3, 2015. From School of Kinesiology, University of Minnesota, Minneapolis, Minnesota (DRD); Division of Pediatrics, University of Minnesota School of Public Health, Minneapolis, Minnesota (DRD, JRR); and Division of Epidemiology & Community Health, University of Minnesota School of Public Health, Minneapolis, Minnesota (JRR). Address correspondence to Donald R. Dengel, PhD, University of Minnesota, 1900 University Avenue SE, 110 Cooke Hall, Minneapolis, MN 55455; e-mail: dengen001@umn.edu.

For reprints and permissions queries, please visit SAGE's Web site at <http://www.sagepub.com/journalsPermissions.nav>.

Copyright © 2015 The Author(s)

(ie, aorta and carotid).^{3,4} In addition, many health conditions and chronic disease states that emerge in childhood are associated with declines in endothelial function, greater arterial stiffness, and adverse thickening of the arterial lumen.

This review will briefly describe the structure and function of the artery and detail some of the various methods used to measure these features in children and adolescents. We then review different pediatric health status and chronic disease states that are associated with maladaptive consequences for vascular structure and function. In an effort to compare different research studies we will confine our examination to those studies that include a comparison or control group which is then examined against the disease state or health status in question as we feel this enhances the internal validity of these studies, which are mostly cross-sectional in nature. Furthermore, we will attempt to allude to the potential mechanisms that may be underlying the changes in vascular structure and function due to the health conditions and chronic disease states discussed. Finally, we will explore various lifestyle modifications (eg, weight loss, exercise, etc) and their effect on vascular structure and function.

Measuring Vascular Structure and Function

There are a number of invasive and noninvasive methods to measure both arterial structure and function.⁵ In children and adolescents, noninvasive methods to measure arterial structure and function are really only considered.⁶ These noninvasive methods are predictive of adulthood CVD and are associated with more invasive techniques used to measure arterial structure and function.⁷⁻⁹ While the clinical utility of these tools may be limited, they offer an ideal research tool for understanding the pathophysiological development of CVD and a window into characteristics that contribute to accelerated atherosclerosis.

Arterial Structure

Carotid Intima-Media Thickness

To assess arterial structure in both adults and children, high-resolution B-mode ultrasound is commonly used to assess carotid intima-media thickness (cIMT). Typically, measurements are made in the left common carotid artery; however, measurements of intima-media thickness can be made at other sites in both the left and right carotid artery (ie, internal, external, bulb) as well as other arteries in the body. Multiple measurements of the far carotid wall are taken about 1 to 2 cm proximal to the bifurcation. These measurements should be taken at the end of diastole (R wave on electrocardiography). Once measurements are obtained a mean value, typically of 6 to 12 measurements, for the selected areas thickness is calculated using automated wall-tracking software to improve reproducibility and reliability.⁶ For an extensive guide to cIMT testing in pediatric populations we refer readers to an American Heart Association scientific statement by Urbina et al.⁶

Coronary Artery Calcification

Coronary artery calcification (CAC) is a measure of arterial structure and is measured using electron-beam computed tomography (CT). Insoluble calcium deposits within atherosclerotic plaques are a hallmark of atherogenesis. Calcified lesions when detected in vivo, accurately predict the presence of atherosclerotic plaque, and they occur exclusively when coronary atherosclerosis is present.¹⁰ The criteria used for electron-beam CT determination of CAC has been previously established.¹¹ However, despite the accuracy and utility of CAC for measuring arterial structure, the high cost of CT along with the radiation exposure needed, has made this technique limited to youth whom are at very high risk for overt cardiovascular events and whom may be in clinical trials.⁶ However, of the measures CAC may have the most clinical application, as it can be reliably graded in terms of risk stratification.⁶

Arterial Function

Arterial function typically involves determining the ability of the artery to vasodilate in response to some physical or pharmacological challenge. A variety of methods have been developed to evaluate arterial function; however, noninvasive measurements of arterial vasoconstriction and dilation using ultrasound imaging of the brachial artery are the most common technique used.

Flow-Mediated Dilation

Flow-mediated dilation (FMD) is sometimes referred to as endothelial-dependent dilation and is typically examined via ultrasound imaging of the brachial artery. Duplex ultrasound for simultaneous acquisition of B-mode diameter and pulsed-wave Doppler velocity signals is typically used to account for changes in baseline artery diameter along with shear rate.^{12,13} After 20 minutes of supine rest, a baseline image of the brachial artery diameter is measured for 1 minute. After baseline images are acquired, a blood pressure cuff is placed on the forearm about 1 cm below the antecubital fossa (elbow joint). The cuff is inflated for 5 minutes to >200 mm Hg or 50 mm Hg above systolic blood pressure. Image acquisition begins again 1 minute prior to cuff deflation and continues to be acquired for 3 minutes post-cuff deflation. Continuous edge detection and wall tracking should be used to capture changes in peak diameter that occur.

$$\text{FMD (\% dilation)} = \frac{(\text{peak diameter} \times \text{baseline diameter})}{\text{baseline diameter}}$$

Flow-mediated dilation is affected by both baseline vessel diameter and by peak shear rate during the reactive hyperemia induced post-cuff occlusion. It is recommended that adjustment be made for these variables in statistical analysis to account for any potential confounding. While no one method has been established for properly accounting for these variables, several have been proposed which involves either allometric scaling, dividing FMD by shear

rate, or using them as covariates in statistical analysis similar to age and sex effects.^{13,14} Nonetheless, accounting for both baseline artery diameter and shear rate should be considered for interpretation of results. For a more complete understanding of the physiological and methodological considerations for FMD testing we refer readers to 2 excellent articles by Thijssen et al¹² and Harris et al.¹³

Endothelial-Independent Dilation

Endothelial independent dilation (EID) measures the arterial changes induced by administration of a sublingual dose of nitroglycerin, which reflects predominantly the smooth muscle response of the artery. EID is measured through noninvasive ultrasound, similarly to FMD, the only real differences are the stimulus used to induce vasodilation is different and the length of the measurement period. Typically, the EID measurement period is extended to 5 minutes to capture the peak vasodilation and edge-detection software used to track the change in artery diameter over time.^{15,16} A peak dilation and area under-the-curve can be used as an assessment of smooth muscle function. Similar to FMD, baseline artery diameter can affect the results of EID measurement and should be taken into account in analysis. It should be noted that while considered a safe and reliable test for assessment of smooth muscle function, the use of sublingual nitroglycerin in pediatric populations may limit its applicability.

Arterial Stiffness

Arterial stiffness is a property of the artery that involves not only the structure of the blood vessel, but also the function of the artery. In addition, the arterial pressure is also a major determinant of arterial stiffness for as the arterial pressure increases so does the arterial stiffness.¹⁷ There are a number of ways to measure the different facets of arterial stiffness with the most commonly used methods being (a) measurement of pulse-wave velocity (PWV) and (b)

calculation of the change in diameter (or area) of an artery with respect to the distending pressure (ie, compliance and distensibility).

Pulse-Wave Velocity

Pulse wave velocity is a measure of the velocity of the arterial pressure wave propagation and is used as a surrogate measure of arterial wall stiffness. PWV can be measured in a variety of noninvasive ways, with peripheral artery tonometer emerging as the most often utilized method to make these measures of stiffness. Locations that are often examined are carotid, radial, brachial, femoral, and ankles.¹⁸ Arterial waveforms are recorded at each site and the time delay between the arrival of a predefined point on the waveform from the proximal to peripheral arterial location is obtained by gating to the peak of the R wave on the electrocardiogram. Measurement of distances on the body surface allows an estimate of the distance traveled. PWV is then calculated as distance/time (m/s).¹⁹ For an extensive guide to PWV testing in pediatric populations, we refer readers to an American Heart Association scientific statement by Urbina et al.⁶

Compliance and Distensibility

Compliance and distensibility are measures of arterial elasticity that can be measured in all arteries but commonly taken during carotid measurements. Compliance is the absolute change in arterial volume that reflects the arterial ability to store volume and reduce pressures, whereas distensibility is the relative change in arterial volume against the change in pressure and reflects the mechanical load placed on the arterial wall.²⁰ Compliance and distensibility are typically measured using ultrasound at the left common carotid artery, approximately 1 cm proximal from the carotid bifurcation bulb. The left common carotid artery's lumen diastolic and systolic diameters are recoded with images collected for 10 seconds to ensure the capture of full arterial diameter change during a cardiac cycle. The mean diameter through the

10-second cycle is then used to calculate compliance and distensibility. The minimum (diastolic) arterial lumen diameter, the maximum (systolic) arterial lumen diameter, and pulse pressure are used in different equations for determining each variable for compliance and distensibility. A comprehensive list of each formula can be found in our groups' prior work.²¹ For a guide to the mathematical models used to compute carotid compliance and distensibility, we refer readers to a recent publication from our group.²¹

Influence of Chronic Disease on Vascular Structure and Function

A number of childhood health conditions and diseases can affect vascular structure and function (Table 1). Researchers have employed 2 basic types of research designs: cross-sectional or longitudinal. Cross-sectional and longitudinal designs can be used to address the same question; however, the longitudinal research design is more powerful but takes more time to complete the data collection and resources than the cross-sectional research design. The next sections explore the effect of these childhood health conditions and diseases on both vascular structure and function.

Congenital Heart Diseases

Individuals born with congenital heart diseases, due to advances in clinical care are surviving considerably longer with mortality shifting into adulthood.⁴⁵ As a consequence, several congenital heart diseases have been associated with vascular dysfunction, which leads to greater CVD risk in adulthood. One of the most common congenital heart diseases is tetralogy of Fallot, a combination of 4 heart defects that commonly occur together (Table 1). A study by de Groot and colleagues,²⁶ examined whether children with repaired tetralogy of Fallot had vascular dysfunction compared with age-matched controls. They observed that children with tetralogy of Fallot had impaired

Table 1.

Effect of Pediatric Diseases and Disorders on Vascular Structure and Function.

Diseases and Disorders	No. of Participants	Vascular Function	Vascular Structure	Arterial Stiffness	Reference
ADHD (treatment)	n = 85 (ADHA medications); n = 53 (control)	FMD ↔		PWV ↔	22
Chronic renal disease (treatment)	n = 10 (dialysis); n = 10 (control)	FMD ↓			23
Cancer survivor (treatment)	n = 319 (cancer); n = 208 (control)	FMD ↓ EID ↓	cIMT ↔ LD ↔	cIEM ↔ cDD ↓ cCSD ↓	24
Cystic fibrosis	n = 15 (cystic fibrosis); n = 15 (control)	FMD ↓			25
Congenital heart disease					
Tetralogy of Fallot (treatment)	n = 11 (ToF); n = 17 (control)	FMD ↓	cIMT ↔ LD ↔		26
Kawasaki disease	n = 24 (KD); n = 41 (control)	FMD ↓			27
Diabetes mellitus					
T1DM	n = 32 (T1DM); n = 42 (control)	FMD ↓ EID ↓	cIMT ↑ LD ↔		28
	n = 57 (T1DM); n = 10 (control)	FMD ↓ EID ↓			29
	n = 45 (T1DM); n = 30 (control)	FMD ↓	cIMT ↑		30
	n = 49 (T1DM); n = 41 (control)	FMD ↓			27
T2DM	n = 15 (T2DM); n = 13 (control)	FMD ↓	cIMT ↑		31
	n = 128 (T2DM); n = 182 (lean control)		cIMT ↑	cIEM ↑	32
Familial hypercholesterolemia	n = 38 (FH); n = 41 (control)	FMD ↓ EID ↓			33
	n = 30 (FH); n = 30 (control)	FMD ↓	cIMT ↔	PWV ↔	34
Hypertension	n = 34 (hypertensive); n = 35 (control)	FMD ↓	cIMT ↑		35

(continued)

Table 1. (continued)

Diseases and Disorders	No. of Participants	Vascular Function	Vascular Structure	Arterial Stiffness	Reference
Inflammatory bowel disease(s)	n = 27(Crohn's disease); n = 25 (ulcerative colitis); n = 31 (control)	FMD ↓	cIMT ↑		36
Metabolic syndrome	n = 27 (METs); n = 134 (without METs)	FMD ↔ EID ↔	cIMT ↔ LD ↔	cIEM ↔ cDD ↔ cCSD ↔	37
Mucopolysaccharidosis	n = 25 (MPS); n = 406 (control)		cIMT ↑	cIEM ↑ cDD ↓ cCSD ↓	38
Nonalcoholic fatty liver disease	n = 100 (NAFLD); n = 150 (control) n = 14 (NAFLD); n = 14 (obese control)	FMD ↓ FMD ↔	cIMT ↑		39 40
Obesity					
Dysfunction	n = 48 (obese); n = 27 (control)	FMD ↓ EID ↓	cIMT ↔	cIEM ↑ cDD ↓ cCSD ↓	41
	n = 145 (obese); n = 54 (control)	FMD ↓	cIMT ↑		42
Protection	n = 264 (obese); n = 5273 (control)	FMD ↔		PWV ↑	43
Obstructive sleep apnea	n = 27 (OSA); n = 24 (without OSA)	FMD ↔ EID ↓	cIMT ↔	cIEM ↓	44

Abbreviations: ADHD, attention deficit/hyperactivity disorder; FMD, flow-mediated dilation; PWV, pulse wave velocity; EID, endothelium-independent dilation; cIMT, carotid intima-media thickness; LD, lumen diameter; cIEM, carotid interelastic modulus; cDD, carotid diameter distensibility; cCSD, carotid cross-sectional distensibility; ToF, tetralogy of Fallot; KD, Kawasaki disease; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; FH, familial hypercholesterolemia; JIA, juvenile idiopathic arthritis; METs, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; MPS, mucopolysaccharidosis type 1 and 2; OSA, obstructive sleep apnea.

FMD and an increased wall/lumen ratio in the femoral artery compared to the age-matched controls. Despite these differences, no differences between groups were found for the femoral, brachial, and carotid artery diameter. A trend toward elevated cIMT was also observed in the children with tetralogy of Fallot.²⁶ These data highlight that under repaired conditions, endothelial dysfunction and potentially maladaptive consequences for vascular structure are occurring in youth with tetralogy of Fallot.

Children who have undergone the Fontan procedure, which involves diverting venous blood from the right atrium to the pulmonary arteries without passing through the morphologic right ventricle, also exhibit vascular dysfunction.⁴⁶ Jin et al⁴⁶ observed that Fontan patients compared with controls had significantly reduced FMD ($6.5\% \pm 2.4\%$ vs $11.1\% \pm 1.4\%$, respectively; $P < .001$), reduced EID ($13.3\% \pm 5.2\%$ vs $19.4\% \pm 6.2\%$, respectively; $P = .035$), and higher cIMT (0.44 ± 0.07 vs 0.38 ± 0.06 mm, respectively; $P = .008$) (Table 1).

These declines in endothelial function are also present in children with irreversible pulmonary hypertension due to cyanotic and acyanotic congenital heart disease.⁴⁷ Compared with the control group, FMD was significantly reduced in the cyanotic group ($5.3\% \pm 2.4\%$ and $9.5\% \pm 2.6\%$, respectively; $P < .001$) (Table 1). No significant difference was observed between the groups in cIMT. These data are suggestive that most forms of congenital heart disease have adverse consequences for arterial structure and function. These likely

contribute to higher CVD disease progression and event rates in adulthood.

Type 1 and 2 Diabetes Mellitus

Adults with type 1 and 2 diabetes mellitus, even under well-controlled conditions, are at significantly elevated risk for developing CVD, as well as CVD morbidity and mortality.^{48,49} Children with type 1 diabetes, with a duration of less than 5 years, have already started to exhibit some of the early subclinical manifestations of the atherosclerotic process.²⁷⁻³⁰ Järvisalo and colleagues³⁰ compared youth with type 1 diabetes with healthy, age-matched controls and observed that youth with type 1 diabetes had significantly lower FMD ($4.4\% \pm 3.4\%$ vs $8.7\% \pm 3.6\%$, respectively; $P < .001$) and higher cIMT (0.47 ± 0.03 vs 0.43 ± 0.03 mm, respectively; $P < .001$) (Table 1). These data are supported by Ce et al,²⁹ whom additionally observed youth with type 1 diabetes to have significantly impaired EID compared with healthy controls ($22.3\% \pm 9.8\%$ vs $29.3\% \pm 4.2\%$, respectively; $P = .02$). Importantly, both studies demonstrate vascular dysfunction without the presence of adverse levels of traditional CVD risk factors (ie, low-density lipoproteins, high-density lipoproteins, triglycerides, and systolic blood pressure) suggesting a potential alternative mechanism of action. Fortunately, physical activity may be able to mitigate some of the deleterious effects of type 1 diabetes on vascular structure and function. Trigona et al,²⁸ while observing that youth with type 1 diabetes had reduced FMD, higher cIMT, and reduced EID, similar to findings of others, additionally observed that youth with type 1 diabetes who meet current evidenced-based physical activity recommendation (>60 min/d),⁵⁰ were protected against endothelial dysfunction exhibiting similar levels as that of healthy controls (Table 1).

Type 2 diabetes also has important vascular consequences. Naylor and colleagues,³¹ observed that youth with type 2 diabetes when compared with a lean control group, exhibited significantly reduced FMD ($7.9\% \pm 0.5\%$

vs $10.4\% \pm 1.0\%$, respectively; $P < .05$) and has significantly higher cIMT than lean and obese controls (0.54 ± 0.01 vs 0.46 ± 0.02 vs 0.46 ± 0.02 mm, respectively, all P s $< .01$) (Table 1). In a more comprehensive study of carotid structure and function, Urbina et al,³² observed youth with type 2 diabetes to have significantly greater cIMT than lean and obese participants for the common carotid artery and carotid bulb but did not differ for the internal carotid artery (all P s $< .05$) (Table 1). The group with type 2 diabetes also had greater carotid interelastic modulus (cIEM) and other measures of arterial stiffness than lean participants, but did not differ from obese participants. Potentially, the most important findings from Urbina et al,³² were the age-related increases in cIMT observed in youth with type 2 diabetes. While the trajectory (slope) of increase in cIMT across age was flat (no increase) in lean youth, youth with type 2 diabetes had a significant increase across age, which is indicative of faster progression of subclinical atherosclerosis. Taken together and with support of adult data, pediatric type 1 and type 2 diabetes, places an increased burden of CVD through a pathway of endothelial dysfunction, arterial stiffness, and vascular structure abnormalities.

Obesity, Metabolic Syndrome, and Comorbid Conditions

There is conflicting evidence on whether obesity is associated with endothelial dysfunction, increased cIMT, and arterial stiffness. As for endothelial function, the largest body of literature lies on the side suggesting that obesity in childhood is associated with endothelial dysfunction.^{41,42,51-55} However, there are several studies that show no relationship between obesity and endothelial function in youth,^{31,56} and more recent evidence showing obesity is associated with greater FMD (Table 1).⁴³ Several of the studies that support obesity being positively associated with endothelial dysfunction are limited by small samples sizes ($n = 10-40$) and lack of control for important variables such as pubertal maturation, gender, and brachial artery

diameter. Nevertheless, they consistently reported endothelial dysfunction in youth with obesity compared to lean and overweight youth.⁵¹⁻⁵⁵ Recently, these findings have been called into question. In the largest study to date ($n > 6000$), Charakida et al,⁴³ in a group of mostly prepubertal children, reported that obese children had larger brachial artery diameters, increased blood flow, and marginally increased endothelial function measured by FMD compared with normal-weight and overweight children (Table 1). In addition, they show that an increase in dual energy x-ray absorptiometry (DXA)-derived body fat to be associated with increased FMD after controlling for age, sex, and baseline artery diameter. These data suggest that in childhood, excess body fat may offer vascular protection, which might offer a “window of opportunity” to prevent declines in vascular function observed in obesity in adulthood. What mechanism(s) may be regulating vascular protection in obese youth requires further investigation. Moreover, understanding the longitudinal time-course by which obesity become consistently maladaptive may provide important implication in terms of intervention timing and robustness of interventions strategies need to prevent further declines in obesity-related vascular dysfunction.

It could be hypothesized that it may not be obesity per se that results in vascular dysfunction but instead a constellation of risk factors, including abdominal obesity, known as the metabolic syndrome which exacerbates vascular abnormalities in youth. Mimoun and colleagues³⁷ examined whether differences in vascular structure and function existed in obese youth with and without the metabolic syndrome using multiple definitions of the metabolic syndrome. Despite youth with the metabolic syndrome exhibiting multiple risk factors, they observed no differences in FMD, cIMT, EID, or arterial stiffness between obese youth with and without the metabolic syndrome (Table 1).³⁷ Moreover, no significant relationships between body mass index (BMI) z-score

and FMD, cIMT, EID, or arterial stiffness were observed, giving further support that obesity in childhood may not be associated with vascular dysfunction and structural abnormalities. However, it should be noted it may be necessary for obese youth to exhibit a proinflammatory state, which often accompanies obesity, in order for endothelial dysfunction to be present.⁴² Thus, more clarity is needed to fully elucidate why some obese youth exhibit a compromised vascular system and while others have yet to exhibit issues.

However, obesity is associated with a number of comorbid conditions, which in youth are associated with vascular dysfunction. In a study of youth with severe obesity, Dubern et al,⁴⁴ observed that youth with chronic obstructive sleep apnea to have reduced EID in comparison with severely obese youth without ($14.1\% \pm 1.0\%$ vs $18.0\% \pm 1.1\%$; $P = .02$) and increased arterial stiffness measured by cIEM (Table 1). However, despite the decline in smooth muscle function and increased arterial stiffness, no differences were observed for FMD or cIMT.

Another common condition observed in youth with obesity is nonalcoholic fatty liver disease (NAFLD). Diagnosis of NAFLD is challenging, with primary criterion being based on a liver biopsy, which is not routine in clinical practice or research studies. Noninvasive tools (ie, ultrasound and magnetic resonance imaging) for measuring liver fat are often used as surrogate indicators for hepatic fat content. Weghuber and colleagues⁴⁰ using magnetic resonance imaging–defined criterion for diagnosis of NAFLD (hepatic fat fraction $>5.5\%$) observed obese youth with NAFLD to have no difference in FMD compared with obese youth without NAFLD (Table 1). However, these data are in conflict with findings from Pacifico et al,³⁹ who observed that youth with ultrasound and biomarker (ie, liver enzymes) defined NAFLD to have reduced FMD and higher cIMT compared with obese and normal-weight controls without NAFLD. While the study by Weghuber et al⁴⁰ presents with a more robust diagnostic

criterion for NAFLD, the study from Pacifico and colleagues³⁹ is supported by a sample size that is more than 10 times larger ($n = 28$ vs 400 , respectively). Therefore, more definitive studies need to be undertaken in order to address the effects of NAFLD on arterial structure and function in youth.

Other Common Pediatric Diseases

Kadono and colleagues²⁷ first observed that youth who survived Kawasaki disease had significantly impaired FMD compared with normal-weight controls and youth with type 1 diabetes (Table 1). Despite this decline in endothelial function, youth with Kawasaki disease did not exhibit higher cIMT or differences in vessel diameter (arterial remodeling). In subgroup analysis, these observed youth who exhibited an aneurysm had significantly impaired endothelial function in comparison with youth with Kawasaki disease without an aneurysm. These data suggest that the inflammatory effects of Kawasaki disease have adverse consequences for endothelial function, which likely contributes to long-term vascular consequence placing youth at higher risk for premature CVD in adulthood.

Inflammatory bowel diseases, which include Crohn's disease and ulcerative colitis, are chronic inflammatory conditions which involve intestinal immune systems. Since, inflammation plays a key role in the pathogenesis of CVD, it is likely that peripheral inflammatory conditions such as inflammatory bowel diseases have effects on vascular structure and function. Aloï et al³⁶ observed patients with Crohn's disease and ulcerative colitis to have significantly reduced FMD and higher cIMT than healthy control without inflammatory bowel diseases (Table 1). Furthermore, they demonstrated the association between cIMT and inflammatory bowel disease to be independent of BMI but associated with systemic inflammation measured by high-sensitivity C-reactive protein, suggesting inflammation as a potential mediator.

Cystic fibrosis is a genetic disorder that not only affects pulmonary function but also, due to the impairment in oxygen saturation ability, causes systemic organ dysfunction. Poore et al²⁵ demonstrated that youth with cystic fibrosis have significantly reduced FMD in terms of both percent dilation and area under the curve (AUC) compared with healthy controls (Table 1). The impairment in endothelial function was associated with lung function and exercise capacity, suggesting reduced oxygen saturation and impaired fitness likely play an important role in the dysfunction observed.

Familial hypercholesterolemia (FH), an inherited disorder that affects lipoprotein metabolism resulting in increased low-density lipoprotein cholesterol and total cholesterol that are much higher than normal even under well-controlled dietary conditions. Several studies have shown that youth with FH have reduced endothelial function as measured by FMD (Table 1).^{33,34} Furthermore, Charakida et al³³ showed youth with FH to have impaired smooth muscle function as measured by EID compared with controls. Interestingly, Vlahos and colleagues³⁴ demonstrated that despite endothelial dysfunction, youth with FH (age = 12 ± 2 years) had no difference in cIMT or PWV compared with healthy controls. However, in a sibling case-control study, which likely offers better control for genetic variability, youth with FH exhibited significantly elevated cIMT in comparison with their siblings.³⁸ Together, these data suggest that youth with FH exhibit a vascular profile that places these youth at very high risk for future CVD complications.

Mucopolysaccharidoses (MPS) is a group of inherited systemic diseases in which glycosaminoglycans are deposited throughout the body resulting in multiorgan dysfunction, in particular glycosaminoglycans are deposited in the myocardium, the cardiac valves, the great vessels and the coronary arteries. Wang and colleagues²⁴ compared children whom were receiving treatment for MPS with healthy controls. Despite treatment, youth with MPS exhibited higher cIMT,

increased cIEM, and decreased cCSD compared with healthy controls (Table 1).²⁴ These data suggest that arterial structure thickening and stiffness likely contribute to the higher CVD mortality often observed in youth with MSP.

Treatments for Cancer, Chronic Kidney Disease, and Attention Deficit/Hyperactivity Disorder

Cancer is the leading cause of death among young children (age 1-14 years).²³ Because of advances in medicine, survival rates have increased among this population. Childhood cancer survivors, thus represent a unique study population for examine the effects of the often life-saving treatments on arterial structure and function. Our group has demonstrated that children who survive leukemia have reduced FMD, EID, cCSD, and higher cIEM with no differences in cIMT or lumen diameter (LD) compared with noncancer sibling controls. Furthermore, survivors of central nervous system tumors had reduced EID and cCSD with no differences in FMD, cIEM, or cIMT observed. Interestingly, youth who survived solid tumors exhibit no declines in any of the measures of arterial structure or function (Table 1).⁵⁷ These data suggest that compared with sibling controls, childhood cancer survivors have differences in both vascular structure and function that were present relatively soon after treatment. This likely contributes to the high CVD mortality rate among youth receiving treatment for cancer.

Cardiovascular complications are the leading cause of death among children with end-stage renal disease.⁵⁸ Lilien and colleagues⁵⁹ demonstrated that youth with end-stage renal disease on dialysis had impaired FMD compared with healthy controls ($6.0\% \pm 4.1\%$ vs $14.2\% \pm 5.8\%$, respectively; $P = .002$) (Table 1). They further demonstrated that hemodialysis induced a further decline in FMD at 30 minutes posttreatment. These differences in FMD were observed without difference in vessel diameter or distensibility. This study demonstrates that the acute treatment and chronic

effects of kidney disease result in endothelial dysfunction.

Attention deficit/hyperactivity disorder (ADHD) is a commonly diagnosed and treated childhood psychological condition.⁶⁰ The treatment of ADHD often involves the use of stimulants, which affect the central nervous system. Kelly and colleagues⁶¹ investigated the effects of children currently taking medication for treatment of ADHD compared with healthy, nonmedicated controls (Table 1). They observed that youth being treated for ADHD with stimulant medication had significantly higher carotid augmentation index (AI) and PWV than healthy control, indicating increased arterial stiffness with differences in FMD were observed. Other potential long-term cardiovascular consequences of the ADHD medication were observed, as youth on ADHD stimulant medication had elevated blood pressure and higher sympathetic nervous system activity. This study gives caution to the overprescription and potential long-term consequences of ADHD treatment via stimulant medication.

Therapies to Improve Vascular Structure and Function

Lifestyle interventions such as aerobic exercise training, resistance training, weight loss, and dietary supplementation have been successfully used in adults to improve both vascular structure and function.⁵ However, given the fact that many cardiovascular and metabolic diseases have beginnings in early life, research to examine the effect of lifestyle interventions in both healthy children and those with cardiovascular and metabolic risk on vascular structure and function are warranted to reduce the long-term disease burden. In general, many lifestyle interventions such as aerobic exercise training, weight loss, and dietary or antioxidant supplementation have been demonstrated to improve vascular health in adolescents with and without cardiovascular and metabolic risk factors.

Exercise

Studies that examine the role of exercise on vascular structure and function can be divided into cross-sectional or longitudinal. Those studies that are cross-sectional in design typically examine physical activity and encompass both planned and unplanned exercise as well as participation in sport. Longitudinal studies, on the other hand, examine planned exercise that involves monitoring both frequency, intensity, and duration.

Physical Activity

Cross-sectional studies examining the role of physical activity on vascular health have produced mixed results. Abbott and Davies⁶² reported that daily physical activity levels in children between the ages of 5 and 11 years was significantly related to FMD with most active children having the highest FMD. In support of this, Schack-Nielsen et al⁶³ reported that in 10-year-olds the time spent in play or sport participation was inversely related to the arterial stiffness. Conversely, Reed et al²² found no significant relationship between the total amount of physical activity (estimated with a 7-day questionnaire) with arterial compliance in 9- to 11-year-old children. Similarly, in a group of healthy children and child cancer survivors we found no effect of physical activity levels on measures of carotid compliance and distensibility.⁶⁴ There are a number of reasons that may explain the difference in results in these studies. The methods used to determine physical activity (ie, questionnaire, accelerometers, etc) to the age of the children examined need to be considered when comparing the results of these various studies. Another possible explanation may be the intensity of the physical activity that the children and adolescents engaged in. Hopkins et al⁶⁵ examined measures of body fatness, peak oxygen uptake (VO_{2peak}), levels of physical activity measured using accelerometers, and their relationship to FMD in healthy 10- to 11-year-olds. The authors reported that moderate-to-vigorous physical activity (>8 km/h) was the most important variable in terms of influence on those with impaired

Table 2.

The Effect of Exercise Training Interventions on Vascular Structure and Function.

Interventions	Participants	Vascular Function	Vascular Structure	Arterial Stiffness	Reference
Aerobic 3×/week; 60 min/session	Obese children (BMI >97th percentile)	FMD ↔ EID ↔	cIMT ↔	cIEM ↔	63
Aerobic 4×/week; 30-50 min/session	Overweight children (BMI >85th percentile)	FMD ↑ EID ↔			22
Aerobic 3×/week; combined circuit training and aerobic exercise	Obese adolescents (BMI >95th percentile)			PWV ↔	68
Aerobic 3×/week; 60-90 min	Obese adolescents (BMI >97th percentile)	FMD ↑	cIMT ↓		64
Resistance 2×/week	Healthy adolescents	FMD ↑		PWV ↓	72
Combined resistance and aerobic exercise 3×/week; 80 min/session	Overweight adolescents		cIMT ↓		67
Circuit training 3×/week; 60 min/session	Obese adolescents	FMD ↑			65
Aerobic 3×/week; 60 min/session	Obese children	FMD ↑			66
Combined exercise and weight loss program over 1 year	Obese adolescents		cIMT ↓		73
Combined aerobic and games 60 min/session; 3×/week	Obese adolescents	FMD ↑	cIMT ↔		71
Combined aerobic and weight loss for 6 weeks	Obese children	FMD ↑			70
Aerobic exercise 4 × 4 min high-intensity interval training 2×/week for 3 months	Overweight adolescents	FMD ↑			69

Abbreviations: BMI, body mass index; FMD, flow-mediated dilation; EID, endothelium-independent dilation; cIMT, carotid intima-media thickness; cIEM, carotid incremental elastic modulus; PWV, pulse wave velocity.

vascular function. The link with physical activity was independent in the lowest FMD tertile and stronger than any other variable measured. The results of this study suggest that the intensity of the physical activity is important in improving vascular health, especially in children with impaired vascular health.

Aerobic Exercise Training

To date, longitudinal studies that have examined the effects of aerobic exercise training on vascular health have been

done in overweight and/or obese children and adolescents.⁶⁶⁻⁷¹ We have demonstrated that an 8-week progressive aerobic (50% to 80% of each individual's peak cardiorespiratory fitness [$\text{VO}_{2\text{peak}}$]) exercise program delivered 4 times a week for 30 to 50 minutes per session resulted in improvement in FMD in overweight (BMI >85th percentile) youth (Table 2).⁶⁷ Similarly, Watts et al⁷⁰ demonstrated similar findings in a group of obese (BMI >95th percentile) children after an 8-week of 3 times per week for 60 minutes per session

(Table 2). Meyer et al⁶⁸ assessed a 6-month aerobic exercise program of 3 times per week for 60 min in obese children (Table 2). In addition to an improvement in FMD, Meyer et al⁶⁸ reported an improvement in cIMT after the 6-month exercise program. It should be noted that as quickly as an improvement in FMD as a result of aerobic exercise training appears it can be lost just as quickly with physical inactivity. Watts et al⁷⁰ reported that after only 6 weeks of inactivity FMD returned to its previous levels (Table 2).

Not all aerobic exercise training studies have reported an improvement in vascular function in children following aerobic exercise training. Two interventions^{52,73} reported no improvement in vascular function after aerobic exercise training. One possible reason for the lack of improvement may be the intensity of the aerobic exercise training program. Farpour-Lambert et al⁶⁶ had obese children exercise for 30 minutes at a low (55% to 65% of $\text{VO}_{2\text{peak}}$) level aerobic exercise followed by 20 minutes of strength training 3 times per week for 12 weeks (Table 2). The aerobic exercise consisted of walking, ball games, and swimming, which may not have been intensive enough to stimulate a change in vascular structure or function. Lee et al⁷³ used a similar training program of strength training and low-intensity aerobic exercise training consisting of badminton, soccer, basketball, baseball, and so on, 3 times per week for 10 weeks and reported no improvement in PWV (Table 2). In support of the theory that intensity of the exercise training program is critical to an improvement in vascular function Tjønnå et al⁷⁴ compared an aerobic interval training (AIT) program that consisted of 4 × 4 minute intervals at 90% of maximal heart rate with each interval separated by 3 minutes at 70% maximal heart rate twice a week for 3 months to a multidisciplinary (MTG) approach that included a very low-intensity physical activity session in obese adolescents (Table 2). After 3 months, the AIT and MTG groups increased their FMD by 5.1% and 3.9%, respectively. The 2 groups were encouraged to continue their programs for another 9 months. At 12 months, the AIT group had a 6.1% increase in FMD while the MTG group's FMD had returned to baseline.⁷⁴ Therefore, similar to the relationship of FMD and physical activity,⁶⁵ the intensity of the exercise training appears to be critical to foster improvements in vascular function in children and adolescents.

Weight Loss

In studies examining vascular health in overweight and obese youth aerobic exercise training and weight loss interventions are frequently combined.

This makes examining the independent effects of aerobic exercise and weight loss difficult. Woo et al⁷⁵ examined the effects of weight loss alone and combined with aerobic exercise training in overweight and obese adolescents (Table 3). After 6 weeks there was a significant improvement in FMD in both groups; however the improvement in FMD was greater in the combined weight loss and aerobic exercise group. There was no improvement in EID or cMT in either of the 2 intervention groups. It should be pointed out that although both groups had an improvement in waist-to-hip ratio, neither group had a change in body mass, percent fat, or fat-free mass. A subset of the children in this study continued to exercise for a full year. In this subset there was a further increase in FMD and a significant reduction in cMT. Kelishadi et al⁷⁶ performed a 6-week combined aerobic exercise and weight loss program (Table 3). The aerobic exercise program consisted of 60 min/session of 30 minutes of fitness activities and 30 minutes of playing games and running, 3 times per week.⁷⁶ The authors reported a significant decrease in body weight (57.1 ± 10.2 to 54.7 ± 9.8 kg; $P = .02$) and a significant increase in FMD ($3.3\% \pm 0.3\%$ to $3.4\% \pm 0.4\%$; $P = .005$). However, there was no improvement in cMT (0.34 ± 0.05 to 0.32 ± 0.06 mm; $P = \text{nonsignificant}$).

Wunsch et al⁸² also performed a combined weight loss and exercise program in obese children (Table 3). After 1 year, the authors reported a significant reduction in cMT.⁸² The authors reported that only those children who had a significant decrease in body weight over the 1-year program demonstrated a significant decrease in cMT. To examine the effects of weight loss only on vascular function in children, we performed a 5-month weight loss only study in overweight adolescents, which resulted in significant decreases in body weight (62.5 ± 10.8 vs 60.9 ± 11.2 kg; $P = .03$) and percent fat ($42.9\% \pm 6.1\%$ vs $39.9\% \pm 7.2\%$; $P = .03$) (Table 3).⁸⁰ After 5 months of weight loss, there was an improvement in EID ($21.5\% \pm 4.5\%$ vs $25.7\% \pm 5.4\%$; $P = .05$) and a trend for an improvement in FMD ($5.8\% \pm 2.1\%$ vs $6.7\% \pm 2.2\%$; $P = .08$). Iannuzzi et al⁷⁹ examined the effects

of a 6-month hypocaloric, low-glycemic index diet and a hypocaloric, high-glycemic index diet on vascular health in obese children (Table 3). Both hypocaloric diets observed a significant reduction in cMT and arterial stiffness following the 6-month diet period. There was no difference in the reductions based on the glycemic index of the diet.

Dietary Supplementation

A few weight loss studies have also involved dietary or supplement interventions such as omega-3 polyunsaturated fatty acid and vitamin supplementation (Table 3).^{35,72,77,78,81,83-85} Dangardt et al³⁵ randomly assigned obese adolescents to either 3 months of placebo or 1.2 g/d of omega-3 polyunsaturated fatty acid (Table 3). After the 3-month intervention, the authors reported that there was no difference in cMT, PWV, or reactive hyperemia index (RHI) between placebo and the omega-3 polyunsaturated fatty acid intervention.³⁵ The AI was significantly lower in the omega-3 polyunsaturated fatty acid intervention group. Engler et al⁸⁶ examined the effect of the National Cholesterol Education Program Step II (NCEP-II) diet or supplementation with docosahexaenoic acid (DHA) with the diet on vascular function in children with familial hypercholesterolemia (FH) or the phenotype of familial combined hyperlipidemia (FCH) (Table 3). Children were randomly assigned to supplementation with docosahexaenoic acid (DHA 1.2 g/d) or placebo for 6 weeks, followed by a washout phase of 6 weeks and crossover phase of 6 weeks while continuing the NCEP-II diet. FMD increased significantly after DHA supplementation compared to baseline ($P < .001$), diet alone ($P < .002$), placebo ($P < .012$), and washout ($P < .001$) phases of the study.

In a 6-week study, Mietus-Snyder and Malloy,⁸³ examined vitamin C (500 mg 2x/d) and vitamin E (400 IU 2x/d) supplementation in children of FH or FCH on FMD (Table 3). There was a significant increase in FMD ($2.8\% \pm 1.6\%$ to $9.1\% \pm 2.3\%$, $P = .001$) after 6 weeks of supplementation. In a similar

Table 3.

The Effect of Dietary Modification on Vascular Structure and Function.

Interventions	Participants	Vascular Function	Vascular Structure	Arterial Stiffness	Reference
Low salt diet	Normotensive children			PWV ↓	77
Omega-3-poly unsaturated fatty acid supplement (1.2 g/d) for 3 months	Obese adolescents	FMD ↑		PWV ↔	78
Vitamin D supplement (2000 IU/d) for 4 months	Normotensive adolescents			PWV ↓	79
High or low glycemic hypocaloric diet for 6 months	Obese children (BMI >95th percentile)		cIMT ↓	cIEM ↓	75
Hypocaloric diet for 5 months	Overweight children (BMI >85th percentile)	FMD ↔			74
Vitamin E (400 IU ×2/d) and vitamin C (500 mg ×2/d) for 6 weeks	Children with familial hypercholesterolemia or familial hyperlipoproteinemia	FMD ↑			76
Folic acid (5 mg/d) for 8 weeks	Adolescents with type 1 diabetes	FMD ↑			80
Vitamin E (400 IU) and vitamin C (500 mg) for 6 weeks	Familial hypercholesterolemia	FMD ↑			81

Abbreviations: FMD, flow-mediated dilation; PWV, pulse wave velocity; BMI, body mass index; cIMT, carotid intima-media thickness; cIEM, carotid incremental elastic modulus.

randomized, double-blind, placebo-controlled trial, Engler et al⁷⁷ examined the effects of antioxidant vitamins C (500 mg/d) and E (400 IU/d) for 6 weeks and the NCEP-II diet for 6 months on FMD in children with FH or FCH. There was no significant change in FMD as a result of NCEP-II diet alone. However, FMD increased significantly from baseline in response to combination of vitamins C and E supplementation and diet ($5.7\% \pm 2.9\%$ vs $9.5\% \pm 4.2\%$; $P < .001$). It should be noted that vitamin C has been shown to be a potent vasodilator acutely, thus, whether the improvements shown were due to long-term or acute effects of supplementation are unknown.

To date, one study⁸¹ has examined the effects of vitamin D supplementation on

vascular function in children (Table 3). Dong et al⁸¹ reported that in healthy black adolescents with vitamin D deficiency, who were supplemented with vitamin D (2000 IU/d) there was a reduction in carotid-femoral PWV after 16 weeks of supplementation.

Peña et al⁷² examined the effect of 8 weeks of oral folic acid (5 mg/d) supplementation on FMD in Type 1 diabetic children (Table 3). Using a randomized crossover design, the authors reported that folic acid supplementation increased FMD by 2.58% whereas there was no change in the placebo group. In addition, there was no change in EID after folic acid supplementation. Using a similar crossover design in children with chronic renal failure Bennett-Richards

et al⁸⁵ reported that folic acid supplementation (5 mg/m²/d) for 8 weeks resulted in a significant improvement in FMD, but no change in nitrate-mediated dilation (Table 3).

Conclusion and Future Directions

It has been well described that human aging results in IMT thickening within the arterial wall. Either separately or in conjunction with this increase in IMT the artery starts to stiffen and lose elasticity with advancing age. Ultimately these changes in vascular structure and function lead to an overall decline in vascular health with age. What is not known is whether these changes in vascular

structure and function are a natural part of the aging process or simply a result of lifestyle choices. Children and adolescents serve as a natural control to investigate the role of aging and lifestyle choices on vascular health. Clearly, diseases such as type 1 and type 2 diabetes, obesity, hypertension, and inflammatory conditions negatively affect vascular structure and function early on in a child's life. Interventions that affect one's lifestyle such as increased exercise, weight loss, or manipulations in nutrient composition can alter the impact of these conditions on vascular structure and function.

Although research in the past decade has increased our overall knowledge about the structure and function of the vasculature little is known regarding the mechanisms that result in improvements in vascular structure and function after exercise training or weight loss or other lifestyle modifications. This is especially true in children where the use of lifestyle modifications to treat various disease and chronic health conditions is just gaining interest. In addition, information regarding the optimal exercise prescription (ie, duration, frequency, intensity) or dietary composition that result in sustained improvements in vascular structure and function is lacking. Future studies need to focus on understanding the mechanisms as well as the exact lifestyle prescription that are necessary to bring about vascular health.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. [AJLM](#)

References

- Heron M. Deaths: leading causes for 2010. *Natl Vital Stat Rep*. 2013;62(6):1-96.
- Pagidipati NJ, Gaziano TA. Estimating deaths from cardiovascular disease: a review of global methodologies of mortality measurement. *Circulation*. 2013;127:749-756.
- Newman WP, Wattigney W, Berenson GS. Autopsy studies in United States children and adolescents. *Ann N Y Acad Sci*. 1991;623:16-25.
- Strong J, McGill H. The natural history of coronary atherosclerosis. *Am J Pathol*. 1962;40:37-49.
- Dengel D, Bronas U. The role of endothelial dysfunction on development and progression of atherosclerosis and methods to assess vascular function and structure. *Am J Lifestyle Med*. 2010;4:445-456.
- Urbina EM, Williams RV, Alpert BS, 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;54:919-950.
- Raitakari OT, Juonala M, Kähönen M. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA*. 2003;290:2277-2283.
- Raitakari OT, Juonala M, Taittonen L, et al. Pulse pressure in youth and carotid intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *Stroke*. 2009;40:1519-1521.
- Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. *Circulation*. 2007;115:1285-1295.
- Margolis JR, Chen JT, Kong Y, Peter RH, Behar VS, Kisslo JA. The diagnostic and prognostic significance of coronary artery calcification. a report of 800 cases. *Radiology*. 1980;137:609-616.
- Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990;15:827-832.
- Thijssen DHJ, Black MA, Pyke KE, et al. Assessment of flow mediated dilation (FMD) in humans: a methodological and technical guideline. *Am J Physiol Heart Circ Physiol*. 2011;300:H2-H12.
- Harris RA, Nishiyama SK, Wray DW, Richardson RS. Ultrasound assessment of flow-mediated dilation. *Hypertension*. 2010;55:1075-1085.
- Atkinson G, Batterham AM. Allometric scaling of diameter change in the original flow-mediated dilation protocol. *Atherosclerosis*. 2013;226:425-427.
- Marlatt KL, McCue MC, Kelly AS, Metzger AM, Steinberger J, Dengel DR. Endothelium-independent dilation in children and adolescents. *Clin Physiol Funct Imaging*. 2011;31:390-393.
- Thelen AM, Kelly AS, Williamson EB, Dengel DR. Examining the time course of endothelium-independent dilation by nitroglycerin. *Ultrasound Med Biol*. 2008;34:1217-1220.
- Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006;27:2588-2605.
- Yamashina A, Tomiyama H, Takeda K, et al. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res*. 2002;25:359-364.
- Wilkinson IB, Fuchs SA, Jansen IM, et al. Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. *J Hypertens*. 1998;16(12 pt 2):2079-2084.
- Reneman RS, Meinders JM, Hoeks AP. Non-invasive ultrasound in arterial wall dynamics in humans: what have we learned and what remains to be solved. *Eur Heart J*. 2005;26:960-966.
- Marlatt KL, Kelly AS, Steinberger J, Dengel DR. The influence of gender on carotid artery compliance and distensibility in children and adults. *J Clin Ultrasound*. 2013;41:340-346.
- Reed KE, Warburton DE, Lewanczuk RZ, et al. Arterial compliance in young children: the role of aerobic fitness. *Eur J Cardiovasc Prev Rehabil*. 2005;12:492-497.
- Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin*. 2008;58:71-96.
- Wang RY, Braunlin EA, Rudser KD, et al. Carotid intima-media thickness is increased in patients with treated mucopolysaccharidosis types I And II, and correlates with arterial stiffness. *Mol Gene Metab*. 2014;111:128-132.
- Poore S, Berry B, Eidson D, McKie KT, Harris RA. Evidence of vascular endothelial dysfunction in young patients with cystic fibrosis. *Chest*. 2013;143:939-945.
- de Groot PC, Thijssen D, Binkhorst M, Green DJ, Schokking M, Hopman MT. Vascular function in children with repaired tetralogy of Fallot. *Am J Cardiol*. 2010;106:851-855.
- Kadono T, Sugiyama H, Hoshiai M, et al. Endothelial function evaluated by flow-mediated dilatation in pediatric vascular disease. *Pediatr Cardiol*. 2005;26:385-390.
- Trigona B, Aggoun Y, Maggio A, et al. Preclinical noninvasive markers of atherosclerosis in children and adolescents with type 1 diabetes are influenced by physical activity. *J Pediatr*. 2010;157:533-539.

29. Ce GV, Rohde LE, da Silva AM, Punaes MK, de Castro AC, Bertoluci MC. Endothelial dysfunction is related to poor glycemic control in adolescents with type 1 diabetes under 5 years of disease: evidence of metabolic memory. *J Clin Endocrinol Metab*. 2011;96:1493-1499.
30. Järvisalo MJ, Raitakari M, Toikka JO, et al. Endothelial dysfunction and increased arterial intima-media thickness in children with type 1 diabetes. *Circulation*. 2004;109:1750-1755.
31. Naylor LH, Green DJ, Jones TW, et al. Endothelial function and carotid intima-medial thickness in adolescents with type 2 diabetes mellitus. *J Pediatr*. 2011;159:971-974.
32. Urbina EM, Kimball TR, McCoy CE, Khoury PR, Daniels SR, Dolan LM. Youth with obesity and obesity-related type 2 diabetes mellitus demonstrate abnormalities in carotid structure and function. *Circulation*. 2009;119:2913-2919.
33. Charakida M, Tousoulis D, Skoumas I, et al. Inflammatory and thrombotic processes are associated with vascular dysfunction in children with familial hypercholesterolemia. *Atherosclerosis*. 2009;204:532-537.
34. Vlahos AP, Naka KK, Bechlioulis A, et al. Endothelial dysfunction, but not structural atherosclerosis, is evident early in children with heterozygous familial hypercholesterolemia. *Pediatr Cardiol*. 2014;35:63-70.
35. Dangardt F, Osika W, Chen Y, et al. Omega-3 fatty acid supplementation improves vascular function and reduces inflammation in obese adolescents. *Atherosclerosis*. 2010;212:580-585.
36. Aloï M, Tromba L, Di Nardo G, et al. Premature subclinical atherosclerosis in pediatric inflammatory bowel disease. *J Pediatr*. 2012;161:589-594.
37. Mimoun E, Aggoun Y, Pousset M, et al. Association of arterial stiffness and endothelial dysfunction with metabolic syndrome in obese children. *J Pediatr*. 2008;153:65-70.
38. Kusters DM, Wiegman A, Kastelein JJ, Hutten BA. Carotid intima-media thickness in children with familial hypercholesterolemia. *Circ Res*. 2014;114:307-310.
39. Pacifico L, Anania C, Martino F, et al. Functional and morphological vascular changes in pediatric nonalcoholic fatty liver disease. *Hepatology*. 2010;52:1643-1651.
40. Weghuber D, Roden M, Franz C, et al. Vascular function in obese children with non-alcoholic fatty liver disease. *Int J Pediatr Obes*. 2011;6:120-127.
41. Tounian P, Aggoun Y, Dubern B, et al. Presence of increased stiffness of the common carotid artery and endothelial dysfunction in severely obese children: a prospective study. *Lancet*. 2001;358:1400-1404.
42. Kapiotis S, Holzer G, Schaller G, et al. A proinflammatory state is detectable in obese children and is accompanied by functional and morphological vascular changes. *Arterioscler Thromb Vasc Biol*. 2006;26:2541-2546.
43. Charakida M, Jones A, Falaschetti E, et al. Childhood obesity and vascular phenotypes: a population study. *J Am Coll Cardiol*. 2012;60:2643-2650.
44. Dubern B, Aggoun Y, Boule M, Fauroux B, Bonnet D, Tounian P. Arterial alterations in severely obese children with obstructive sleep apnoea. *Int J Pediatr Obes*. 2010;5:230-236.
45. Khairy P, Ionescu-Ittu R, Mackie AS, Abrahamowicz M, Pilote L, Marelli AJ. Changing mortality in congenital heart disease. *J Am Coll Cardiol*. 2010;56:1149-1157.
46. Jin SM, Noh CI, Bae EJ, Choi JY, Yun YS. Impaired vascular function in patients with Fontan circulation. *Int J Cardiol*. 2007;120:221-226.
47. Çiftel M, Şimşek A, Turan Ö, Kardelen F, Akçurur G, Ertuş H. Endothelial dysfunction and atherosclerosis in children with irreversible pulmonary hypertension due to congenital heart disease. *Ann Pediatr Cardiol*. 2012;5:160-164.
48. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;339:229-234.
49. de Ferranti SD, de Boer IH, Fonseca V, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. *Diabetes Care*. 2014;37:2843-2863.
50. Strong WB, Malina RM, Blimkie CJ, et al. Evidence based physical activity for school-age youth. *J Pediatr*. 2005;146:732-737.
51. Aggoun Y, Farpour-Lambert NJ, Marchand LM, Golay E, Maggio AB, Beghetti M. Impaired endothelial and smooth muscle functions and arterial stiffness appear before puberty in obese children and are associated with elevated ambulatory blood pressure. *Eur Heart J*. 2008;29:792-799.
52. Farpour-Lambert NJ, Aggoun Y, Marchand LM, Martin XE, Herrmann FR, Beghetti M. Physical activity reduces systemic blood pressure and improves early markers of atherosclerosis in pre-pubertal obese children. *J Am Coll Cardiol*. 2009;54:2396-2406.
53. Peña AS, Wiltshire E, MacKenzie K, et al. Vascular endothelial and smooth muscle function relates to body mass index and glucose in obese and nonobese children. *J Clin Endocrinol Metab*. 2006;91:4467-4471.
54. Miniello VL, Faienza MF, Scicchitano P, et al. Insulin resistance and endothelial function in children and adolescents. *Int J Cardiol*. 2014;174:343-347.
55. Woo KS, Chook P, Yu CW, et al. Overweight in children is associated with arterial endothelial dysfunction and intima-media thickening. *Int J Obes Relat Metab Disord*. 2004;28:852-857.
56. Tryggestad JB, Thompson DM, Copeland KC, Short KR. Obese children have higher arterial elasticity without a difference in endothelial function: the role of body composition. *Obesity*. 2012;20:165-171.
57. Dengel DR, Kelly AS, Zhang L, Hodges JS, Baker KS, Steinberger J. Signs of early sub-clinical atherosclerosis in childhood cancer survivors. *Pediatr Blood Cancer*. 2014;61:532-537.
58. Groothoff JW, Gruppen MP, Offringa M, et al. Mortality and causes of death of end-stage renal disease in children: a Dutch cohort study. *Kidney Int*. 2002;61:621-629.
59. Lilien MR, Koomans HA, Schroder CH. Hemodialysis acutely impairs endothelial function in children. *Pediatr Nephrol*. 2005;20:200-204.
60. Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2011;128:1007-1022.
61. Kelly AS, Rudser KD, Dengel DR, et al. Cardiac autonomic dysfunction and arterial stiffness among children and adolescents with attention deficit hyperactivity disorder treated with stimulants. *J Pediatr*. 2014;165:755-759.
62. Abbott HM, Davies PS. Correlation of habitual physical activity levels with flow-mediated dilation of the brachial artery in 5-10-year-old children. *Atherosclerosis*. 2002;160:233-239.
63. Schack-Nielsen L, Molgaard C, Larsen D, Martyn C, Michaelsen KF. Arterial stiffness in 10-year-old children: current and early determinants. *Br J Nutr*. 2005;94:1004-1011.
64. Slater ME, Ross JA, Kelly AS, et al. Physical activity and cardiovascular risk factors in

- childhood cancer survivors. *Pediatr Blood Cancer*. 2014;62:305-310.
65. Hopkins ND, Stratton G, Tinken TM, et al. Relationships between measures of fitness, physical activity, body composition and vascular function in children. *Atherosclerosis*. 2009;204:244-249.
 66. Farpour-Lambert N, Marchand LM, Martin X, Herrmann F, Beghetti M. Physical activity reduces systemic blood pressure and improves early markers of atherosclerosis in pre-pubertal obese children. *J Am Coll Cardiol*. 2009;54:2396-2406.
 67. Kelly, Wetzsteon RJ, Kaiser DR, Steinberger J, Bank AJ, Dengel DR. Inflammation, insulin, and endothelial function in overweight children and adolescents: the role of exercise. *J Pediatr*. 2004;145:731-736.
 68. Meyer AA, Kundt G, Lenschow U, Schuff-Werner P, Kienast W. Improvement of early vascular changes and cardiovascular risk factors in obese children after a six-month exercise program. *J Am Coll Cardiol*. 2006;48:1865-1870.
 69. Watts K, Beye P, Siafarikas A, et al. Exercise training normalizes vascular dysfunction and improves central adiposity in obese adolescents. *J Am Coll Cardiol*. 2004;43:1823-1827.
 70. Watts K, Beye P, Siafarikas A, et al. Effects of exercise training on vascular function in obese children. *J Pediatr*. 2004;144:620-625.
 71. Park JH, Miyashita M, Kwon YC, et al. A 12-week after-school physical activity programme improves endothelial cell function in overweight and obese children: a randomised controlled study. *BMC Pediatr*. 2012;12:111-120.
 72. Shroff R, Egerton M, Bridel M, et al. A bimodal association of vitamin D levels and vascular disease in children on dialysis. *J Am Soc Nephrol*. 2008;19:1239-1246.
 73. Lee YH, Song YW, Kim HS, et al. The effects of an exercise program on anthropometric, metabolic, and cardiovascular parameters in obese children. *Korean Circ J*. 2010;40:179-184.
 74. Tjønnå AE, Stølen TO, Bye A, et al. Aerobic interval training reduces cardiovascular risk factors more than a multitreatment approach in overweight adolescents. *Clin Sci (Lond)*. 2009;116:317-326.
 75. Woo KS, Chook P, Yu CW, et al. Effects of diet and exercise on obesity related vascular dysfunction in children. *Circulation*. 2004;109:1981-1986.
 76. Kelishadi R, Hashemi M, Mohammadifard N, Asgary S, Khavarian N. Association of changes in oxidative and proinflammatory states with changes in vascular function after a lifestyle modification trial among obese children. *Clin Chem*. 2008;54:147-153.
 77. Engler MM, Engler MB, Malloy MJ, et al. Antioxidant vitamins C and E improve endothelial function in children with hyperlipidemia: Endothelial Assessment of Risk from Lipids in Youth (EARLY) trial. *Circulation*. 2003;108:1059-1063.
 78. Raitakari OT, Rönnemaa T, Järvisalo MJ, et al. Endothelial function in healthy 11-year-old children after dietary intervention with onset in infancy: the Special Turku Coronary Risk Factor Intervention Project For Children (STRIP). *Circulation*. 2005;112:3786-3794.
 79. Iannuzzi A, Licenziati MR, Vacca M, et al. Comparison of two diets of varying glycemic index on carotid subclinical atherosclerosis in obese children. *Heart Vessels*. 2009;24:419-424.
 80. Kaufman CL, Kaiser DR, Kelly AS, Dengel JL, Steinberger J, Dengel DR. Diet revision in overweight children: effect on autonomic and vascular function. *Clin Auton Res*. 2008;18:105-108.
 81. Dong Y, Stallmann-Jorgensen IS, Pollock NK, et al. A 16-week randomized clinical trial of 2000 international units daily vitamin D₃ supplementation in black youth: 25-hydroxyvitamin D, adiposity, and arterial stiffness. *J Clin Endocrinol Metab*. 2010;95:4584-4591.
 82. Wunsch R, de Sousa G, Toschke AM, Reinehr T. Intima-media thickness in obese children before and after weight loss. *Pediatrics*. 2006;118:2334-2340.
 83. Mietus-Snyder M, Malloy MJ. Endothelial dysfunction occurs in children with two genetic hyperlipidemias: improvement with antioxidant vitamin therapy. *J Pediatr*. 1998;133:35-40.
 84. Peña AS, Wiltshire E, Gent R, Hirte C, Couper J. Folic acid improves endothelial function in children and adolescents with type 1 diabetes. *J Pediatr*. 2004;144:500-504.
 85. Bennett-Richards K, Kattenhorn M, Donald A, et al. Does oral folic acid lower total homocysteine levels and improve endothelial function in children with chronic renal failure? *Circulation*. 2002;105:1810-1815.
 86. Engler MM, Engler MB, Malloy M, et al. Docosahexaenoic acid restores endothelial function in children with hyperlipidemia: results from the EARLY study. *Int J Clin Pharmacol Ther*. 2004;42:672-679.