Pediatric Interventions Using Noninvasive Vascular Health Indices

Mohamed Ridha, Susan E. Nourse, Elif Seda Selamet Tierney

Online Data Supplement

Heart disease is currently the leading cause of death in the world. It is estimated that greater than a third of the population in the United States has at least 1 type of cardiovascular disease. Although its clinical manifestations typically emerge in middle age, the atherosclerotic process begins in childhood. Proatherosclerotic fatty streaks and raised lesions, which are deposits of cholesterol/esters and fibrous plaques, respectively, are seen in children as young as 3 and increase in number and severity with age. Children with cardiovascular risk factors will develop atherosclerosis in adulthood at an accelerated rate. Therefore, interventions during childhood and adolescence could prevent the development of atherosclerosis in adulthood. Noninvasive modalities are ideal to assess these interventions in children because of their safety and feasibility. Some of these techniques include carotid intima-media thickness (IMT) by ultrasound, endothelial function by reactive hyperemia, and arterial stiffness by tonometry, oscillometry, and ultrasound.

This article reviews studies of diet, exercise, and pharmacologic interventions using noninvasive vascular health indices as outcomes in children and adolescents. An understanding of past investigations will guide future research in this field.

Endothelial Function

One of the earliest detectable cardiovascular changes associated with disease is endothelial dysfunction. In normally functioning vasculature, the endothelium produces nitric oxide in response to shear stress caused by increased blood flow, which results in compensatory vasodilatation. If an appropriate degree of dilation is not reached, this is classified as endothelial dysfunction. Endothelial dysfunction can be caused by the reduction of nitric oxide being released or the inactivation of nitric oxide by an excess of reactive oxidative particles. Endothelial dysfunction is proinflammatory and prothrombotic. However, unlike atherosclerosis, endothelial dysfunction is treatable and reversible.

Reactive hyperemia assessment is an established noninvasive method to assess endothelial function when shear stress in the brachial artery is elicited after temporary occlusion of the vessel. Flow-mediated dilation (FMD), the measurement of the percent change of dimension in the brachial artery during reactive hyperemia using ultrasound, is an independent predictor of future cardiovascular events. Pulse amplitude testing is an alternative method that uses fingertip probes to record arterial pulsatile volume changes. This method is less operator-dependent than FMD and provides a reactive hyperemia index, a validated predictor for major adverse cardiovascular events in adults.

Arterial Stiffness

Arterial stiffness results in increased central pulse pressure, left ventricular hypertrophy, and lowered perfusion pressure in coronary arteries. The pressure generated by the left ventricle during systole emits a wave of increased pressure; as the blood travels through the vasculature, another wave of pressure is reflected back to the heart. In healthy vessels, this reflected wave provides the pressure to drive blood into the coronary arteries during diastole. However, increased vascular stiffness can cause pulse wave velocity (PWV) to increase, thus resulting in the premature return of the wave reflection. This early return results in incomplete perfusion of the myocardium and augmentation of central pressure. The percentage of the central pressure enhancement because of the reflected wave is known as the augmentation index. PWV and augmentation index are independent predictors of cardiovascular mortality in adults. These indices can be measured noninvasively by applanation tonometry, oscillometry, or vascular ultrasound on several arterial sites.

Intima-Media Thickness

IMT is the width of the 2 inner layers of an artery, tunica intima, and tunica media. IMT is most frequently measured in the common carotid artery. Even though not a common place for plaque formation, this vessel has the same atherosclerotic burden as the coronary arteries with a more...
accessible location for observation and monitoring.\textsuperscript{21} Carotid IMT (CIMT) is a significant predictor of stroke and myocardial infarction in adults.\textsuperscript{22} Children with hypertension, obesity, and familial hypercholesterolemia demonstrate higher IMT values than healthy children.\textsuperscript{23–25} Increased IMT values in the femoral artery are also considered a cardiovascular risk factor, although the femoral IMT is studied less frequently than CIMT.\textsuperscript{26}

Methods

An online database search using PubMed (MEDLINE) was performed using the Boolean search terms endothelial function and children, pulse wave and children, IMT and children, vascular and children, endothelial function and adolescent, pulse wave and adolescent, IMT and adolescent, and vascular and adolescent to identify publications on pediatric diet, exercise, or pharmacological interventions that used either endothelial function, IMT, or arterial stiffness as outcome measures. Publication dates were limited to within past 30 years. A total of 7441 were displayed in the results. Inclusion criteria were (1) randomized, controlled trials, (2) pertained to pediatric population, (3) designed interventions aimed at vascular health, (4) outcomes used noninvasive techniques of measuring vascular health, and (5) written in the English language. Forty-eight articles were selected after screening titles and abstracts. A total of 33 articles were selected for inclusion in the final review. Of the 15 articles excluded, 3 could not be located and 12 did not meet criteria after further investigation. The interventions of the selected articles were classified into 4 categories: exercise interventions, diet/supplement interventions, drug interventions, or multiple interventions.

Results

Overview

The majority of the interventions were in obese or overweight children and adolescents, followed by interventions in children with history of chronic kidney disease and familial hypercholesterolemia (Tables S1–S4 in the online-only Data Supplement).

Interventions in Overweight/Obese Children and Adolescents

Several studies used aerobic exercise\textsuperscript{27–31} and 2 used a combination of resistance training and aerobic exercise.\textsuperscript{32,33} The programs ranged from 120 to 270 minutes of exercise per week for 2 to 6 months with the majority resulting in a significant improvement in either FMD (\(P<0.01\)) or CIMT (\(P<0.05\)) (Tables S1–S2).\textsuperscript{27,29,31,33} The 2 interventions that reported no significant improvement in CIMT were (1) randomized, controlled trials, (2) pertained to pediatric population, (3) designed interventions aimed at vascular health, (4) uses noninvasive techniques of measuring vascular health, and (5) written in the English language. Eighty-four articles were selected after screening titles and abstracts. A total of 33 articles were selected for inclusion in the final review. Of the 15 articles excluded, 3 could not be located and 12 did not meet criteria after further investigation. The interventions of the selected articles were classified into 4 categories: exercise interventions, diet/supplement interventions, drug interventions, or multiple interventions.

A few interventions studied the effect of specific diet or supplements on pediatric vascular measures.\textsuperscript{33–35} One study examined the effect of omega-3 fatty acid supplementation for 3 months.\textsuperscript{34} The investigators found an improvement in the reactive hyperemia response curve compared with placebo (\(P<0.01\)). Two studies used dietary interventions. One was a 6-month intervention of a low-calorie diet.\textsuperscript{35} The results displayed a significant improvement in CIMT (0.43±0.07 versus 0.48±0.05 mm; \(P<0.001\)). Furthermore, a significant improvement in body mass index (25.8±3.3 versus 28.3±3.1 kg/m\(^2\); \(P<0.001\)) and C-reactive protein (0.4±1.1 versus 1.5±0.9 μg/L; \(P<0.001\)) was noted. The other incorporated the ShapeDown program, helping subjects to make healthy decisions on when and what to eat. This 5-month intervention did not find any significant change in FMD from baseline. However, there was a significant improvement in body mass index (25.3±4.2 versus 26.8±4.4 kg/m\(^2\); \(P=0.04\)) and C-reactive protein levels (0.17±0.19 versus 0.25±0.24 mg/dL; \(P=0.03\)).\textsuperscript{35}

One study investigated the effects of the medication exenatide on vascular function in obese children for 6 months. The investigators found no significant change in the reactive hyperemia index; although, body mass index was significantly reduced (\(-0.90±1.22\) kg/m\(^2\); \(P=0.010\)).\textsuperscript{36}

Several studies incorporated combinations of multiple therapies.\textsuperscript{37–41} These interventions used aerobic exercise programs ranging from 80 to 270 minutes per week with dietary modifications for durations between 1.5 months and 1 year. All reported significantly improved measures of vascular function from baseline, specifically increased FMD (\(\Delta\) in mean FMD, +1.35 to +3.62%; \(P<0.05\)) or CIMT (\(-0.10\) mm; \(P<0.001\)), decreased CIMT (\(-0.10\) mm; \(P<0.001\)), decreased PWV (\(-0.4\) m/s; \(P<0.05\)).\textsuperscript{38} One study also provided a group with multivitamin supplements along with dietary and aerobic exercise programs.\textsuperscript{38} Their results showed that PWV was only lowered in subjects receiving dietary, exercise, and multivitamin therapy (3.7±0.1 versus 4.1±0.1 m/s; \(P<0.05\)) and not in those receiving diet and exercise alone. Another trial comparing diet alone versus exercise with dietary interventions found a greater improvement in FMD with combination therapy (8.0±1.8 versus 6.8±2.0%; \(P<0.0001\)) than diet alone (7.5±1.9 versus 6.9±2.0%; \(P<0.002\)).\textsuperscript{40}

Interventions in Children With Familial Hypercholesterolemia

Two studies in children with hypercholesterolemia used antioxidant therapy and measured changes in vascular health.\textsuperscript{42,43} Both studies used vitamin-C and E supplements and reported this therapy to improve endothelial function. In one study, FMD increased significantly in response to antioxidant intervention (5.7±2.9–9.5±4.2%; \(P=0.001\)), whereas dietary intervention alone produced no significant change in FMD.\textsuperscript{42} There were no significant effects of diet or antioxidants on other lipid levels or biomarkers of oxidative stress. In the second study, investigators demonstrated that FMD is impaired in children with hyperlipidemia as young as 6 years; however, the degree of low-density lipoprotein (LDL) cholesterol elevation did not correlate with the degree of endothelial dysfunction.\textsuperscript{43} The FMD increased from 2.8±1.6 to 9.1±2.3% (\(P=0.001\)).

Other studies investigated the effects of statin therapy on vascular health in children with familial hypercholesterolemia. A double-blind, placebo-controlled study of 214 children with familial hypercholesterolemia randomly assigned subjects to receive either pravastatin or placebo for 2 years.\textsuperscript{44} Mean CIMT decreased from 0.547±0.060 to 0.494±0.047 mm. The researchers reported that age at statin initiation was an independent predictor for CIMT (\(P=0.016\)). In another study on 50 heterozygous children with familial hyperlipidemia, subjects were randomized to either simvastatin or placebo groups.\textsuperscript{45} At baseline, children with familial hyperlipidemia demonstrated impaired FMD compared with controls (\(P=0.024\)). After the
28-week trial, the change in FMD in the simvastatin group was significantly higher than in the placebo group (3.9±4.3 versus 1.2±3.9%; P=0.05).

**Interventions in Children With Chronic Kidney Disease**

Two studies examined the effects of supplements on vascular measures in children with chronic kidney disease.46,47 A randomized, crossover, placebo-controlled, double-blinded study measured the effects of folic acid for two 8-week periods with an 8-week washout between.47 Twenty-five study subjects were included. Their results showed a significant improvement in FMD in the intervention group (7.21±2.81–8.47±3.01%; P=0.036). In the second study, 61 patients were given 1α-hydroxycholecalciferol, a form of vitamin-D that does not require activation by the kidneys, for a year.46 The findings demonstrated that both low and high levels of 1,25(OH)2D are associated with an increase in CIMT (P<0.0001). There have also been some reports suggesting that an increase in CIMT may be associated with length of time on dialysis and can be improved by earlier renal transplantation.58

**Exercise Interventions**

All exercise interventions used programs where subjects engaged in activity 2 to 4× per week for 1 hour, ranging from 2 to 6 months. Aerobic exercise interventions were the most common, although circuit training and strengthening regimens were also investigated.77,30,49 Exercise interventions focused primarily on obese and overweight subjects,27–32,49 and FMD was the most widely measured noninvasive vascular health outcome.27–31,49

At baseline, prepubertal subjects typically displayed healthier values in FMD and CIMT than adolescents; however, the interventions showed greater influence on the values of older than younger subjects with a significant improvement in both groups (∆ in mean FMD from baseline +3.5% versus +1.35%, respectively).30,31 Aerobic exercise programs alone portrayed overall better effectiveness in improving vascular indices in obese children (60-minute aerobic exercise, 3× per week for 8 weeks improved FMD after the intervention: 7.35±0.99 versus 6.00±0.69%; P<0.05) than programs with aerobic exercise and resistance training (50-minute aerobic exercise and resistance training, 3× per week for 3 months showed no significant change in FMD).27,31 Furthermore, resistance and strengthening interventions had the best results in adolescent subjects (∆ in mean FMD from baseline, +2.1 to +3.5%; P<0.05) versus prepubertal children (50-minute aerobic exercise resistance training, 3× per week showed no significant change in FMD).27,30,31,49

**Diet/Supplement Intervention**

Dietary and supplement interventions were categorized together because investigations observing the effect of a supplement require dietary monitoring to control for extraneous sources. The supplement interventions involved omega-3 polyunsaturated fatty acid, vitamins, or a cereal-based nutritional supplement. Aerobic exercise interventions were consistent in successful reduction of FMD and CIMT function (increase in reactive hyperemia response curve, P=0.01), whereas a 5-year intervention starting at infancy with the same supplement demonstrated no change in CIMT, augmentation index, or PWV in healthy children.54 Two studies investigating vitamin-D supplement interventions found that changing levels of vitamin-D in the blood stream can significantly improve vascular health.46,50 In one study, healthy black adolescents with vitamin-D deficiency displayed significant decreases in PWV after vitamin-D supplementation (5.33±0.79 versus 5.41±0.73 m/s; P<0.05).50 Another study reported that both excessively elevated and excessively depressed levels of biologically active 1,25(OH)2D resulted in a significant increase in CIMT in pediatric dialysis patients (P<0.0001).46 Interventions involving vitamins B9, C, and E all indicated significantly improved FMD (Δ in mean FMD, +1.26 to +6.3%; P<0.05).43,47,52

The interventions with diet alone all lasted a minimum of 6 months.20,35,51,53 Subjects with obesity or malnourishment showed greater improvement in vascular health indices, including decreasing CIMT (0.43±0.07 versus 0.48±0.05 mm, P<0.001) and lowered augmentation index (2.5±11.4 versus 5.6±9.1%; P=0.011) after dietary enhancements in contrast to healthy subjects undergoing dietary interventions (low-salt diet showed no significant differences in PWV41 and low-saturated fat diet showed no significant improvement in FMD after adjustment for total serum cholesterol at ages 7 months 2 years).50,53

**Drug Interventions**

All drug interventions persisted for at least 6 months. Statin treatments were tested on adolescents and children with familial hypercholesterolemia, Kawasaki disease, and obesity.55 Two of these interventions reported significant improvement in FMD (∆ in mean FMD, +1.58 to +3.8%; P<0.05) and PWV (1027.2±166.4 versus 1175.4±277.3 mm/s; P=0.001).44,45 Furthermore, in these studies, statin treatment resulted in significant total cholesterol reduction (∆ in mean total cholesterol, −0.6993 to −2.16 mmol/L; P<0.0001).45,53 Earlier initiation of statin treatment for subjects with familial hypercholesterolemia was associated with significantly thinner CIMT values compared with later initiation (P=0.016).44

Two nonstatin drug interventions targeted obese subjects with nondiabetic/nonobesity and polycystic ovary syndrome. Nondiabetic/nonobesity obese subjects were treated using Exenatide, used in adults to improve glycemic control, and the reactive hyperemia index was measured.36 In the second study, patients with polycystic ovary syndrome took rosiglitazone, a hepatic and skeletal muscle insulin sensitizer. Vascular health was measured by CIMT and PWV.56 Neither treatment resulted in significant improvement in vascular health indices.

**Multiple Interventions**

Interventions using multiple approaches typically combined exercise with dieting and sometimes behavioral therapy, drug treatment, or dietary supplements.37,38,40–42,57,58 CIMT was used universally in multi-interventional studies. Obese subjects were consistent in successful reduction of FMD and CIMT.
values in comparison with other populations (Δ in mean FMD, +0.1 to +1.2%; P<0.05 and Δ in mean CIMT, −0.07 to −0.12 mm; P<0.001, respectively). Subjects participating in interventions with vitamin supplements, exercise, and diet displayed greater improvements in PWV (3.7±0.1 versus 4.1±0.1 m/s; P<0.05) than those only involved in exercise and dieting (no significant reduction in PWV). National Cholesterol Education Program-II diet with vitamin-C and E supplements showed improved FMD from baseline (9.5±4.2 versus 5.7±2.9%; P<0.001); however, there was no significant alteration in FMD from diet alone. Another trial demonstrated that exercising and dieting subjects developed better FMD alterations from baseline (8.0±1.8 versus 6.8±2.0%; P<0.0001) than those only dieting (7.5±1.9 versus 6.9±2.0%; P<0.002). Most of the studies that measured LDL cholesterol found that LDL cholesterol levels were lowered significantly (Δ in mean LDL, −0.3 to −0.518 mmol/L) when vascular health indices improved. However, in one study in patients with hyperlipidemia, endothelial function by FMD did not improve when LDL cholesterol was reduced (4.54±1.2432 versus 4.84±1.269 mmol/L; P<0.01) using a diet program. Interestingly, a significant improvement in FMD from baseline was observed (9.5±4.2 versus 5.7±2.9%; P<0.001) with addition of antioxidant treatment of vitamin-C and E to the diet intervention without any significant decrease in LDL cholesterol.

Oxidative Stress

Several studies measured biomarkers of oxidative stress or inflammation. Including C-reactive protein and oxidized LDL. The majority of these studies demonstrated a significant improvement in at least 1 noninvasive measure of vascular health, with 6 showing a significant improvement in at least 1 marker of inflammation or oxidative stress. In the interventions that did not demonstrate a significant improvement in any vascular health index, all but 1 did not result in a significant change in inflammatory or oxidative stress biomarkers.

Discussion

This study provides a descriptive review of vascular interventions assessed by noninvasive techniques on children. Although the interventions varied in design and results, some consistency can be seen in the outcomes. Numerous diet and exercise interventions that showed improvements in vascular health indices also reported a decrease in LDL cholesterol. Furthermore, 2 of the statin interventions that lowered LDL cholesterol also significantly improved vascular health. However, interventions that showed improvements in pediatric vascular health indices without decreasing LDL cholesterol have been reported. A relationship between LDL cholesterol and vascular health has been questioned previously in adults. The findings portray mixed results; some studies in adults showed LDL cholesterol to be a significant independent predictor of endothelial function, whereas another study demonstrated that improvements in endothelial function because of exercise were not associated with a reduction in LDL cholesterol. A possible alternative for improvement in FMD is a reduction specifically in oxidized LDL rather than general LDL. Oxidized LDL reacts with the endothelium of arteries causing tissue damage and inflammation. Circulating oxidized LDL in adults is a significant marker of coronary artery disease. In addition, thiobarbituric acid reactive substances have been studied as a measure of oxidative stress in children with primary hypertension and demonstrated significant correlation with CIMT. In a diet and exercise intervention on obese adolescents, changes in oxidized LDL levels were inversely correlated with endothelial function by FMD. Furthermore, interventions using supplemental antioxidants, including folic acid, zinc, vitamin-C, and vitamin-E, demonstrated improvement in vascular health in a wide variety of subject populations: children with hyperlipidemia, increased body mass index, chronic renal failure, and type-1 diabetes mellitus. Similarly, studies have shown antioxidants to improve endothelial function in adults with coronary artery disease.

The improvement of vascular health in children also increased when multiple interventions were used together. Although diet and exercise interventions can individually improve pediatric vascular health, more impressive results are generated when both are used. Moreover, endothelial function and arterial stiffness improve after addition of antioxidants to diet interventions in children. Adult studies exhibit a similar trend; in one study, mildly hypertensive subjects were treated with either a hypocaloric diet and an antihyperensive/insulin-sensitizer drug, miconoxine, or solely a hypocaloric diet. Endothelial function by FMD rose significantly (P=0.01) in both these treatment groups, but the subjects given a diet and drug intervention had more increase in their FMD values than those with diet alone.

Common limitations can be observed in these studies. The sample sizes were often small, which warrants careful extrapolation of results to more generalized populations. Also, in studies involving multiple interventions, it was difficult to differentiate the effects of diet from those of exercise on vascular health. These studies are also susceptible to limitations in the noninvasive measurement of vascular health in pediatrics because PWV, reactive hyperemia index, and CIMT change significantly throughout childhood and adolescence. Thus, standardized values of vascular measures should be analyzed, rather than absolute values. Pediatric normative data on PWV and CIMT have been published and can be used to standardize values in future studies.

Perspectives

This review of pediatric vascular health interventions using noninvasive measures as outcomes has compiled a summary of recent investigations. The investigations suggest oxidative stress to be a potential pathogenesis of endothelial dysfunction leading to subsequent atherosclerosis later in life. Although a combination of multiple interventions has had the most consistent improvement in vascular health indices, therapies directed at reducing reactive oxygen species are promising for future research in this field.
Conclusions
These investigations demonstrate that cardiovascular health can be modulated in young individuals, and vascular health indices can be used as surrogates of cardiovascular outcomes. Overall, the paucity of data in pediatric intervention studies using vascular health outcomes, particularly in comparison with adult studies, suggests that additional attention must be given to this field of research essential for timely preventive care of future generations.

Disclosures
None.

References
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Pediatric Interventions Using Noninvasive Vascular Health Indices:
A Review

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Short Title: Pediatric Interventions Assessing Vascular Health
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<td>Healthy and young subjects; Thus results cannot be generalized to older adults or those with cardiovascular disease. Small sample size (n=26).</td>
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<tr>
<td>Watts et al.</td>
<td>60 minute aerobic exercise, 3x/week</td>
<td>Obese children</td>
<td>Improved FMD after the intervention (7.35±0.99 vs. 6.00±0.69 %, p&lt;0.05).</td>
<td>2 months</td>
<td>8.9±1.6 years</td>
<td>No significant changes in cholesterol.</td>
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</table>

FMD, Flow mediated dilation by brachial ultrasound; CIMT, Carotid Intima-media thickness; PWV, Pulse-wave velocity; BMI, Body mass index (kg/m^2); RHI, Reactive Hyperemia Index by EndoPAT. *B; °By oscillometric device; †By radial artery ultrasound, ‡The exact age of the study cohort was not reported.
<table>
<thead>
<tr>
<th>Reference</th>
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<th>Other Results</th>
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<tbody>
<tr>
<td>Avolio et al.⁹</td>
<td>Low salt diet (cross-sectional study, analysis by age groups)</td>
<td>Normotensive patients</td>
<td>PWV²</td>
<td>No differences aortic or arm PWV of the pediatric group on low salt diet versus a regular diet however there was a significant decrease in the leg PWV (-11.2%, p&lt;0.05)</td>
<td>Subjects not matched for sex. Small sample size (n=16).</td>
<td>2.18±5.4 years</td>
<td>10.4±2.5 years (group 1)</td>
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<tr>
<td>Ayer et al.⁹⁰</td>
<td>Omega-3 poly unsaturated fatty acid supplement (randomized to intervention or control, n=616)</td>
<td>Healthy children</td>
<td>CIMT, AI, PWV⁶</td>
<td>No significant vascular benefits of diet at age 8.</td>
<td>Single measurements of plasma fatty acids may not reflect the long-term dietary habits. The discontinuation rate was high.</td>
<td>5 years</td>
<td>6 months to 5 years for intervention, data collected at age 8±0.1 years</td>
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<tr>
<td>Dangardt et al.¹¹</td>
<td>1.2 grams/day Omega-3 poly unsaturated fatty acid supplement (randomized to supplement or placebo)</td>
<td>Obese adolescents (BMI 34±4.0)</td>
<td>RIMT, PWV⁶, RHI</td>
<td>Reactive hyperemia response curves increased in the intervention group (p=0.01). RHI, AI, PWV, and radial IMT did not change.</td>
<td>Detecting structural vascular changes associated with omega-3 poly unsaturated fatty acid supplements may require a longer intervention length. The sample size was small (n=25).</td>
<td>3 months</td>
<td>15.7±1.0 years</td>
<td>In the intervention group, the number of lymphocytes decreased (2.5±0.6 vs. 2.7±0.7 10⁹/L, p&lt;0.05), number of monocytes decreased (0.54±0.13 1 vs. 0.61±0.14 10⁹/L, p&lt;0.05), and serum concentrations of n-3 PUFA increased by 65% (p&lt;0.0001). No significant change in LDL.</td>
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<td>Study</td>
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<td>Follow-up</td>
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<tr>
<td>Dong et al.(^{12})</td>
<td>2000-IU/day Vitamin D supplements (randomized to 2000 IU or 400 IU group, n=49)</td>
<td>Normotensive, African-American adolescents</td>
<td>Improved PWV in the intervention group (5.33±0.79 vs. 5.41±0.73 m/sec, (p&lt;0.05)), while the control group PWV increased (5.71±0.75 vs. 5.38±0.53 m/sec, (p&lt;0.05)).</td>
<td>4 months</td>
<td>During 2000 IU/d vitamin D intervention, adiposity was inversely correlated with 25(OH) vitamin D concentrations, a marker of vitamin D sufficiency in blood stream ((p&lt;0.05)).</td>
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<td>Iannuzzi et al.(^{13})</td>
<td>Hypocaloric diet (randomized to high glycemic or low glycemic hypocaloric diet)</td>
<td>Healthy, obese children (BMI &gt; 95th percentile)</td>
<td>In both groups combined, significant decreases in CIMT (0.43 ± 0.07 vs. 0.48 ± 0.05 mm, (p&lt;0.001)) and stiffness index (2.98 ± 0.94 vs. 3.57 ± 1.04, (p=0.002))</td>
<td>Small sample size (n=26).</td>
<td>BMI and systolic blood pressure were lower in both groups combined (25.8±3.3 vs. 28.3±3.1 kg/m(^2), (p=0.001), and 110±11 vs. 119±12 mmHg, (p&lt;0.001), respectively). In the low glycemic-index diet group, insulin resistance and carotid beta stiffness index decreased (2.4±1.1 vs. 3.1±1.5 HOMA, (p=0.04) and 3.07±1.09 vs. 3.71±1.18, (p=0.004), respectively).</td>
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<tr>
<td>Kaufman et al.(^{14})</td>
<td>ShapeDown® diet program</td>
<td>Overweight children (BMI&gt;85th percentile)</td>
<td>No change in FMD</td>
<td>The study could not directly control the adherence of the subjects to the diet. Small sample size (n=15 with 3 drop outs), no control group.</td>
<td>5 months</td>
<td>Subjects displayed enhanced cardiac parasympathetic activity and significant decreases in BMI (25.3±4.2 vs. 26.8±4.4 m/kg2, (p=0.04)).</td>
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<tr>
<td>Study Reference</td>
<td>Intervention</td>
<td>Study Population</td>
<td>Outcome Measures</td>
<td>Follow-Up</td>
<td>Comments</td>
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<tr>
<td>Kinra et al. (^{15})</td>
<td>Protein and calorie supplementation (n=1165)</td>
<td>Undernourished pregnant women and children from India</td>
<td>AI</td>
<td>Up to 6 years</td>
<td>Children from the intervention villages had lower AI (2.5±11.4 vs. 5.6±9.1%, p=0.011) compared to the control population. Non-randomization in baseline studies may have led to biased results; no data on current diet and patterns of physical activity.</td>
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<tr>
<td>Raitakari et al. (^{16})</td>
<td>Low-saturated fat diet (randomized to low saturated fat or unrestricted diet, n=1062)</td>
<td>Healthy 7-month old infants</td>
<td>FMD</td>
<td>7 years</td>
<td>Only males showed improvement in FMD (9.62±3.53% vs. 8.36±3.85%, p=0.012); however, after adjusting for total serum cholesterol between ages 7 months-2 years, the difference became non-significant.</td>
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<tr>
<td>Shroff et al. (^{17})</td>
<td>Daily oral 1-alpha hydroxy-vitamin D supplements (61 patients on dialysis and 40 age- and gender-matched control subjects)</td>
<td>Children on dialysis for more than 3 months</td>
<td>CIMT, PWV</td>
<td>4.9 [0.2-6.8] years</td>
<td>High levels and low levels of active 1, 25-dihydroxy-vitamin D resulted in increased CIMT (p&lt;0.0001). No difference in PWV. No correlation between C-reactive protein levels and CIMT found, possibly due to small sample size.</td>
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<tr>
<td>Bennett-Richards et al. (^{18})</td>
<td>Oral Folic Acid (Vitamin B9) (randomized crossover trial)</td>
<td>Children with chronic renal failure</td>
<td>FMD</td>
<td>8 weeks</td>
<td>After folic acid intervention FMD improved (7.21±2.8 vs. 8.47±3.01%, p=0.04). No change after the placebo phase. After a crossover period with placebo, final FMD showed no significant difference from baseline. Small sample size, n=25.</td>
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<td>Children in intervention area were an average of 14 mm taller compared to control counterparts without intervention (p&lt;0.05) and displayed lower insulin resistance (HOMA score 3.16 (1.00 to 10.00) vs. 3.79 (1.22 to 11.73), p&lt;0.05)</td>
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<tr>
<td>Study</td>
<td>Intervention</td>
<td>Participants</td>
<td>FMD</td>
<td>Effect</td>
<td>Sample Size</td>
<td>Duration</td>
<td>Age</td>
<td>Additional Information</td>
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<tr>
<td>Mietus-Snyder et al.</td>
<td>Antioxidant Vitamin E 400 IU x2/day and Vitamin C, 500 mg x2/day</td>
<td>Children with either familial hypercholesterolemia or familial combined hyperlipoproteinemia</td>
<td>FMD</td>
<td>Improved FMD (2.8±1.6 vs. 9.1±2.3 %, p = 0.001)</td>
<td>Small sample size (n=11)</td>
<td>6 weeks</td>
<td>13.3±4.0 years</td>
<td>No change in LDL-cholesterol</td>
</tr>
<tr>
<td>Pena et al.</td>
<td>5mg/day oral Folic Acid (randomized crossover trial)</td>
<td>Children and adolescents with type 1 diabetes</td>
<td>FMD</td>
<td>The same intervention was performed on two groups, with no significant differences in baseline between them. Both displayed an increase in FMD (Group A: 2.7±3.6 vs. 5.7±3.0, p&lt;0.001; Group B: 3.4±3.3 vs. 5.5±3.8, p&lt;0.001)</td>
<td>Small sample size (n=36). A longer period of intervention required to assess if the improvements in endothelial function would be maintained.</td>
<td>8 weeks</td>
<td>13.6±2.6 years</td>
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</table>

AI, Augmentation index by applanation tonometry; BMI, Body mass index (kg/m²); FMD, Flow mediated dilation; CIMT, Carotid intima-media thickness; PWV, Pulse-wave velocity; RIMT: Radial intima-media thickness; RHI, Reactive Hyperemia.

*By vascular ultrasound and pulsed Doppler, †By applanation tonometry, ‡The exact age of the study cohort was not reported.
**Table S3. Drug Interventions**

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<th>Reference</th>
<th>Intervention Type</th>
<th>Subjects</th>
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<tr>
<td>de Jongh <em>et al.</em></td>
<td>Simvastatin (randomized to Simvastatin or placebo, n=50)</td>
<td>Adolescents and children with familial hypercholesterolemia</td>
<td>FMD</td>
<td>Children with familial hypercholesterolemia on Simvastatin showed improved FMD compared to baseline (15.5±5.4 vs. 11.7±5.0, p&lt;0.05)</td>
<td>Since nitroglycerin was not administered, changes in vascular smooth muscle cell reactivity could be a potential cause of the altered FMD response.</td>
<td>7 months</td>
<td>14.2±3, 1 years</td>
<td>Lower LDL-cholesterol in the intervention group (3.17±0.96 vs. 5.31±1.14 mmol/l, p=0.0001)</td>
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<tr>
<td>Hamaoka <em>et al.</em></td>
<td>3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, fluvastatin</td>
<td>Kawasaki disease patients</td>
<td>FMD, PWV</td>
<td>Compared to baseline, patients had improved vascular health indices with significantly increased FMD and significantly decreased PWV (10.87±3.11 vs. 9.29±3.41, p&lt;0.001 and 1027.2±166.4 vs. 1175.4±277.3 cm/s, p=0.001, respectively)</td>
<td>Small sample size (n=11).</td>
<td>1 year</td>
<td>14.5±6, 1 years</td>
<td>Decreased total cholesterol levels (144.1±7.8 vs. 171.1±13.1 mg/dL, p=0.00001)</td>
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<tr>
<td>Kelly <em>et al.</em></td>
<td>Exenatide drug (randomized cross over trial; life style modification or life style modification plus Exenatide)</td>
<td>Extremely obese children and adolescents (BMI≥35)</td>
<td>RHI</td>
<td>No improvement in endothelial function</td>
<td>Not blinded, small sample size (n=12).</td>
<td>3 months</td>
<td>12.7±2.1 years</td>
<td>Significant decrease in BMI, body weight loss and fasting insulin levels in Exenatide group (−1.7 kg/m2, p=0.01; −3.9 kg, p=0.02; −7.5 mU/l, p=0.02, respectively)</td>
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<tr>
<td>Rodenburg et al.24</td>
<td>Pravastatin (patients previously on a placebo controlled trial, n=214)</td>
<td>Adolescents and children with familial hypercholesterolemia</td>
<td>CIMT</td>
<td>The earlier statin treatment is initiated, the thinner the CIMT (multivariate regression coefficient for age at statin initiation: 0.003±0.001, p=0.016)</td>
<td>The treatment during the follow-up period was not placebo controlled.</td>
<td>4.5 years [2.1–7.4]</td>
<td>13.7±3.1</td>
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<td>Tfayli et al.25</td>
<td>Drospirenone/Ethyl Estradiol Versus Rosiglitazone Treatment (n=46)</td>
<td>Obese subjects with polycystic ovary syndrome (BMI ≥ 85th percentile).</td>
<td>CIMT, PWV</td>
<td>Neither treatment altered CIMT or PWV</td>
<td>Bleeding caused by Drospirenone/EE led to unblinding as well as high discontinuation rates. Short treatment length</td>
<td>6 months</td>
<td>Drosperine/E Estradiol Age: 16.2±0.3 years; Rosiglitazone Age: 15.7±0.3 years</td>
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<td>Rosiglitazone was more effective in improving fasting insulin levels (24.9±3.2 vs. 32.8±3.2U/ml, p&lt;0.05), lowering triglycerides (79.2±6.3 vs. 106.7±8.1U/ml, p&lt;0.05), while Drospirenone/EE was superior in decreasing androgemia (1.9±0.3 vs. 7.5±0.9pg/ml, p&lt;0.001) but increased total cholesterol (185.2±9.1 vs. 156.5±6.9mg/dl, p&lt;0.001) and raised night diastolic BP (62.6±1.1 vs. 58.6±1.6mmHg, p&lt;0.05).</td>
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FMD, Flow mediated dilation by brachial ultrasound; IMT, Intima-media thickness; PWV, Pulse-wave velocity; BMI, Body mass index (kg/m^2); RHI, Reactive Hyperemia Index by EndoPAT. a By oscillometric device bPWV using vascular ultrasound and pulsed Doppler
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<td>Engler et al.</td>
<td>Vitamin C and vitamin E supplementation and National Cholesterol Education Program Step II (NCEP-II) diet (randomized placebo controlled crossover trial, placebo group also followed NCEP-II diet)</td>
<td>Children and adolescents with familial hyperlipidemia</td>
<td>Using NCEP-II diet with vitamin C and E supplements showed improved FMD (9.5±4.2 vs. 5.7 ± 2.9 %, p&lt;0.001) compared to baseline. No change in FMD from diet alone.</td>
<td>Small sample size (n=15). 6 months (6 weeks per intervention period)</td>
<td>6 months (6 weeks per intervention period)</td>
<td>9-20 years</td>
<td>NCEP-II diet alone reduced LDL (172±48 vs. 187±49 mg/dl, p&lt;0.01).</td>
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<tr>
<td>Kelishadi et al.</td>
<td>Well-balanced diet and 60-minute, 3 days per week, aerobic exercise intervention (n=35)</td>
<td>Obese adolescents (BMI≥95th percentile)</td>
<td>Improved FMD (3.4±0.3 vs. 3.3±0.3 %, p=0.005). No change in CIMT</td>
<td>FMD and CIMT measurements were performed by only 1 investigator. However, for clinical applicability, these measurements must be reproducible by multiple investigators. Sample size was small (n=35)</td>
<td>1.5 months</td>
<td>14.1±2 years</td>
<td>Decreased LDL-cholesterol (2.7±0.4 vs. 3.1±0.5 mmol/L, p=0.03).</td>
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<tr>
<td>Study</td>
<td>Intervention</td>
<td>Outcome</td>
<td>Duration</td>
<td>Discontinuation Rate</td>
<td>Additional Findings</td>
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<tr>
<td>Khaldikar et al. 28</td>
<td>Well-balanced diet, 45-minute daily aerobic exercise and multivitamin containing zinc and vitamin C (n=74, randomly assigned to diet-exercise counseling with multivitamin and zinc supplementation or diet-exercise counseling or placebo without diet and exercise counseling)</td>
<td>CIMT, PWV, carotid stiffness compared to baseline, subjects had significantly lower PWV (3.7±0.1 vs. 4.1±0.1 m/s, p&lt;0.05). Intervention of diet and exercise alone did not significantly lower PWV. CIMT or stiffness did not change in any groups after intervention.</td>
<td>4 months</td>
<td>11.3±2.9 years</td>
<td>Compared to baseline, subjects in the diet+exercise+supplementation group had significantly lower BMI (24.8±0.6 vs. 25.6±0.6 kg/m², p&lt;0.05) and LDL-cholesterol (86.8±5.6 vs. 106.5±8.0 mg/dl, p&lt;0.05). Intervention of diet and exercise alone did not significantly lower BMI or LDL-cholesterol.</td>
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<td>Lass et al. 29</td>
<td>Exercise program once per week, behavior therapy twice a month, and nutrition course twice a month (n=59)</td>
<td>Obese girls with polycystic ovarian syndrome (BMI 33.2±5.6 kg/m²) CIMT In the subjects with successful weight loss (decrease in BMI &gt;0.2 kg/m²) CIMT values improved significantly (0.054±0.002 vs. 0.066±0.005 cm, p&lt;0.001). The effect of diet, exercise, and weight loss on polycystic ovarian syndrome cannot be differentiated.</td>
<td>1 year</td>
<td>14.9±0.8 years</td>
<td>HDL cholesterol was higher in the subjects with successful weight loss vs. subjects without successful weight loss (53±13 vs. 45±9 mg/dl, p&lt;0.001)</td>
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### Tjonna et al.30

**Aerobic interval training**
- 2x/week vs. healthy lifestyle education intervention every 2 weeks (randomized, n=54)
- **Overweight/obese adolescents (BMI 33.3±4.5 kg/m²)**
- **FMD**

- Aerobic intervention improved FMD more than the lifestyle intervention at 3 months (5.1% vs. 3.9% change, p<0.01). After 12 months the healthy lifestyle education intervention group had no significant improvement in FMD.

- The adolescents went through natural hormonal changes due to pubertal development that could confound the results.

- Aerobic interval training: 3 months
- Healthy lifestyle education intervention: 1 year

**Aerobic intervention group:** 13.9±0.3 years
**Lifestyle education group:** 14.2±0.3 years

### Woo et al.31

**Hypocaloric diet and circuit training exercise with aerobic and resistance training, 1-2x/week**
- Randomized to diet or diet and exercise, n=82
- **Overweight children (BMI≥21)**
- **CIMT, FMD**

- Improved FMD in both groups but more so in the diet with exercise intervention (p=0.01; diet and exercise group: 8.0±1.8 vs. 6.8±2.0%, p<0.0001; diet only group: 7.5±1.9 vs. 6.9±2.0%, p<0.002).
- Less thickening of CIMT in exercise group (p=0.001).

- The intensity of the exercise intervention could be difficult to apply and sustain in obese children.

**Exercise program 1x/week, behavior therapy, and nutrition course**
- Pre-pubertal obese children (BMI>97th percentile)
- **CIMT**

- The subjects who reduced their BMI by greater than half a standard deviation score after the intervention had improved CIMT values (0.55±0.51-0.59 vs. 0.62±0.58-0.68 mm, p<0.001). Changes in CIMT were significantly correlated with weight loss (p<0.001).

- CIMT measurements were performed by only one investigator.

**Exercise program group:** 13.9±1.0 years
**Behavior therapy and nutrition course group:** 1 year

**LDL-cholesterol was decreased in both groups after one year (diet only: 2.5±0.7 vs. 2.9±0.9 mmol/L, p<0.01; diet+exercise: 2.7±1.0 vs. 3.0±0.9 mmol/L, p<0.05)***
| Litwin *et al.*<sup>33</sup> | Pharmacological (ACE inhibitor) and non-pharmacological (diet and exercise) primary hypertension therapy (n=86) | Children with newly diagnosed primary hypertension | CIMT, FIMT | Compared to baseline, pharmacological and non-pharmacological therapy displayed a decrease in CIMT values 0.42±0.04 vs. 0.44±0.05 mm, p=0.0001. | Due to the observational design of the study, the effects of non-pharmacological and pharmacological therapy could not be differentiated. | 1 year | 14.1±2.4 years | Decrease in 24-hour systolic blood pressure (126±8 vs. 130±8 mmHg, p=0.0001) and 24-hour diastolic blood pressure (70±7 vs. 73±7 mmHg, p=0.004). Blood pressure reduction was greater in the pharmacological and non-pharmacological treatment group compared with patients treated only with non-pharmacological (systolic BP: −6±10 vs. −1±8 mmHg, p=0.01; diastolic BP: −5±10 vs. 0.5±5 mmHg, p=0.01). |

FMD, Flow mediated dilation; BIMT: Brachial intima-media thickness; CIMT, Carotid intima-media thickness; FIMT: Femoral intima-media thickness; PWV, Pulse-wave velocity; BMI, Body mass index (kg/m<sup>2</sup>); HDL, High density lipoprotein.<sup>a</sup> The exact age of the study cohort was not reported. <sup>b</sup>By vascular ultrasound and pulsed Doppler.