

Effects of Diet and Exercise on Obesity-Related Vascular Dysfunction in Children

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Background—The prevalence of obesity in both adults and children is increasing rapidly. Obesity in children is independently associated with arterial endothelial dysfunction and wall thickening, key early events in atherogenesis that precede plaque formation.

Methods and Results—To evaluate the reversibility of obesity-related arterial dysfunction and carotid intima-media thickening by dietary and/or exercise intervention programs, 82 overweight children (body mass index, 25 ± 3), 9 to 12 years of age, were randomly assigned to dietary modification only or diet plus a supervised structured exercise program for 6 weeks and subsequently for 1 year. The prospectively defined primary end points were ultrasound-derived arterial endothelial function (endothelium-dependent dilation) of the brachial artery and intima-media thickness of common carotid artery. At 6 weeks, both interventions were associated with decreased waist-hip ratio ($P < 0.02$) and cholesterol level ($P < 0.05$) as well as improved arterial endothelial function. Diet and exercise together were associated with a significantly greater improvement in endothelial function than diet alone ($P = 0.01$). At 1 year, there was significantly less thickening of the carotid wall ($P < 0.001$) as well as persistent improvements in body fat content and lipid profiles in the group continuing an exercise program. Vascular function was significantly better in those children continuing exercise ($n = 22$) compared with children who withdrew from the exercise program ($n = 19$) ($P < 0.05$).

Conclusions—Obesity-related vascular dysfunction in otherwise healthy young children is partially reversible with diet alone or particularly diet combined with exercise training at 6 weeks, with sustained improvements at 1 year in those persisting with diet plus regular exercise. (*Circulation*. 2004;109:1981-1986.)

Key Words: endothelium ■ exercise ■ atherosclerosis ■ lifestyle ■ obesity

The prevalence of obesity in adults is increasing rapidly in the developing world, having already become extremely common in industrialized nations.¹ Of even greater concern, the prevalence of obesity is also increasing rapidly in children,² now being $>10\%$ in developed countries.

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Atherosclerosis is a complex multifactorial disease, the earliest stages of which are known to commence in childhood.³ We and others have demonstrated that obesity in children is independently associated with arterial endothelial dysfunction and wall thickening,^{4,5} key early events in atherogenesis and markers of arterial damage that precede plaque formation. To assess the reversibility of such early arterial damage in children, we studied obese children before and after random assignment to an intervention program of diet alone or diet with exercise training to define potentially effective strategies to improve obesity-related vascular abnormalities.

Methods

Subjects

We evaluated 82 overweight or obese children (body mass index [BMI] ≥ 21)⁶ before and after an intervention program involving diet only or diet with regular exercise. To be eligible, children had to have no known medical illness and no alternative cause for their obesity, no family history of premature cardiovascular disease, be taking no regular medications or vitamin supplementation, and have resting brachial artery diameter >2.5 mm (previously shown by us to be the optimal size for vascular reactivity testing).

For the recruitment of obese children, invitations to participate were sent to apparently obese children 9 to 12 years of age by school teachers in 13 local primary schools; 170 children and their parents showed interest and were invited to the hospital for basic anthropometric measurements. All children who were obese (BMI >23)⁶ or overweight (BMI, 21 to 23) were further assessed for any coexisting medical illnesses. Children with a history of diabetes, renal disease, or cardiovascular disease or those whose sexual maturity status was more advanced than Tanner stage 2 were excluded; 151 children were eligible by these criteria. Of these, 82 children agreed to participate and were enrolled into the intervention study.

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Anthropometric Measurement and Clinical Examination

Each child visited the hospital initially for physical examination and venesection after a 12-hour overnight fast. Body weight was measured with an electronic body weight scale (Seca Delta Model 707) with subjects dressed in a light T-shirt and shorts. Height was measured with a Harpenden stadiometer. Body fat content was determined by dual-energy radiographic absorptiometry, with the fan beam model (Hologic QDR-4500). Fasting serum cholesterol and triglycerides were assayed enzymatically by using the Boehringer Mannheim Hitachi 911 analyzer. HDL cholesterol was measured after precipitation with phosphotungstate-magnesium. LDL cholesterol was calculated by the Friedewald formula.

Arterial Reactivity and Intima-Media Thickness Studies

The ultrasound method for measuring endothelium-dependent and endothelium-independent dilation was performed as described previously^{7,8} on days separate from exercise program. In brief, the diameter of the brachial artery was measured from high-resolution B-mode ultrasound images (ATL 5000 system, L10–5 transducer) at rest, in response to reactive hyperemia (with increased flow producing endothelium-dependent dilation EDD), again at rest, and after sublingual nitroglycerin (400 μ g) (producing endothelium-independent vasodilation, NTG). The experiments were conducted in quiet environment, and no significant changes in their heart rate and blood pressure were observed.

For the evaluation of arterial intima-media thickness (IMT), carotid scans were performed by operators according to a standardized scanning protocol for the right and left carotid arteries, as described previously,⁹ using images of the far wall of the distal 10 mm of the common carotid arteries.

Scans were recorded on super-VHS videotape for subsequent off-line analysis at months after study acquisition. The scan analyzer was blinded to the identity of studied subjects and stage of the experiment. The accuracy, reproducibility, low interobservation error, and in control subjects over time for measurements of arterial physiology have been documented previously by us.^{7,10} Endothelium-dependent dilation of the brachial artery is mainly due to nitric oxide release by the endothelium, correlates well with coronary endothelial function in the same subjects, and appears to be predictive of cardiovascular events.⁸

Carotid scans were analyzed with a computerized edge-detection system that we have previously described and validated.^{9,11} Two end-diastolic frames were selected, digitized, and analyzed for mean IMT, and the average reading from these 2 frames was calculated for both right and left carotid arteries. Carotid IMT is significantly correlated with the severity and extent of coronary artery disease and is predictive of stroke and coronary events in asymptomatic adults.¹²

Interventional Programs

Of the 82 subjects, half were randomly assigned to dietary modification only and the other half to diet plus a regular supervised exercise program. After 6 weeks, 22 of the 41 children randomly assigned to diet plus exercise agreed to continue the weekly exercise program, and the other 19 children stopped regular supervised exercise but continued 2-monthly diet monitoring program, as did all the original 41 diet only children, for 1 year (Figure 1). All children were instructed to maintain their other usual lifestyle activities during the monitoring period. Physical assessment, blood tests, and arterial reactivity studies were repeated in all subjects after completion of the 6-week and 1-year programs. During the same time, no significant changes in BMI of their parents were observed. Consent was obtained from the children and their accompanying parents. The study was approved by our institutional committee on ethical practice.

Dietary Intervention

Compliance with the intervention in both groups was promoted with an incentive award of a sporty-look souvenir watch on completion.

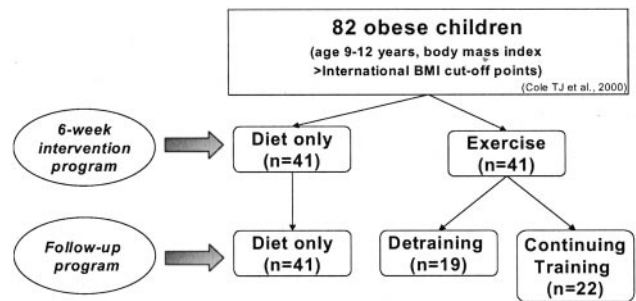


Figure 1. Study design.

Both groups (children and parents) participated in the same diet education program and were interviewed by the same dietitian, who was blinded to the exercise program allocation, 2 weekly for the first 6 weeks and 2 monthly subsequently. The diet prescribed was a balanced hypocaloric diet that provided 900 to 1200 kcal daily. The menu varied according to the child's age and eating habits. It was low in fat (20% to 25%), high in complex carbohydrate (50% to 60%), and sufficient in protein (25% to 30%) to support growth. A 3-day dietary recording was done by the children with the help of their parents at baseline and before each scheduled follow-up. Compliance for follow-up attendance was 85% and for dietary advice 80%. Noncompliance with dietary advice was usually related to social gatherings, excessive consumption of soft drinks in summer, and higher-than-recommended intake of fast food after exercise in cold seasons.

Exercise Training

A fitness assessment test was carried out before the commencement of the program. Each child's exercise ability was measured, and customized training was prescribed by trained physiotherapists. The exercise sessions were all carried out in the hospital and supervised by the same physiotherapist team and were of circuit style, with a preset sequence of 18 workout stations; each child had to go through 9 stations in each session, twice per week for 6 weeks and then once weekly for 1 year. Aerobic exercise including dance was incorporated into the training. Each training session lasted 75 minutes, including 10 minutes of warm up, 30 minutes of resistance training, 10 minutes of aerobic exercise, 10 minutes of agility training, 5 minutes of cool-down, and short rest periods between stations. All children maintained an exercise intensity at 60% to 70% of predicted maximum heart rate during the aerobic exercise (using pulse oximetry). Participation in the exercise training program averaged 83% of scheduled visits during the first 6 weeks and 79% for subsequent visits.

Statistical Analysis

Descriptive data are expressed as mean $\pm$ SD. Baseline characteristics and changes after intervention between groups were compared by use of independent-samples *t* tests. Within-group changes were assessed by paired Student's *t* tests and repeated-measures ANOVA. The prospectively defined primary end points of the study were arterial endothelium-dependent dilation and intima-media thickness; all other comparisons were adjusted for multiple tests by use of Hochberg's modification of the Bonferroni procedure.¹³ The determinants of endothelium-dependent dilation and carotid intima-media thickness (and their changes after intervention) were assessed by univariate and multivariate linear regression analyses with SPSS (version 10.0). Statistical significance was inferred at a 2-tailed probability value of <0.05 .

Results

Short-Term (6-Week) Interventional Program in Overweight and Obese Children

The BMI of our subjects was 25.0 ± 3.0 . Fifty-four children were obese (BMI >23) and the 28 others were overweight, with BMI 21 to 23. Mean age was 9.9 ± 1.0 years, and 54 were boys.

TABLE 1. Short-Term Results of the Interventional Programs in Overweight/Obese Children (Diet Only Versus Diet and Exercise)

	Diet Only		Diet+Exercise	
	Baseline	6 Weeks	Baseline	6 Weeks
No. of subjects	41	41	41	41
Male	27	27	27	27
Mean age, y	9.9±0.9	10.0±0.9	10.0±1.0	10.1±1.0
Weight, kg	50.3±8.5	50.9±8.2	54.6±9.5	55.2±9.5
Height, cm	143.3±6.7	145.1±6.9*	146.1±7.4	147.6±6.9
BMI, kg/m ²	24.5±2.9	24.1±2.7	25.4±3.1	25.3±3.2
Body fat, %	37.3±3.8	37.0±3.5	37.9±3.6	37.3±4.0
Waist hip ratio	0.89±0.07	0.86±0.05†	0.88±0.05	0.85±0.09*
Fat free mass, kg	32.0±5.7	32.3±6.4	32.6±8.3	32.8±6.8
Total cholesterol, mmol/L	4.8±0.9	4.5±0.8‡	4.8±0.9	4.5±0.8*
HDL cholesterol, mmol/L	1.3±0.3	1.2±0.2‡	1.3±0.3	1.2±0.3
LDL cholesterol, mmol/L	2.9±0.9	2.7±0.7	2.9±0.9	2.6±0.8*
LDL/HDL cholesterol ratio	2.3±0.8	2.4±0.8	2.4±0.9	2.2±0.8‡
Triglycerides, mmol/L	1.2±0.5	1.2±0.6	1.2±0.5	1.5±0.7
Glucose, mmol/L	4.5±0.5	4.3±0.6	4.8±0.3	4.4±0.6*
Brachial artery diameter, mm	2.8±0.2	2.8±0.2	2.8±0.2	2.8±0.2‡
Endothelium-dependent dilation, %	6.9±2.0	7.5±1.9*	6.8±2.0	8.0±1.8§
NTG-induced dilation, %	20.3±2.3	20.5±1.7	19.7±2.0	20.1±2.2
Hyperemia, %	626±116	632±107	614±123	627±110
Carotid IMT, mm	0.47±0.05	0.47±0.04	0.47±0.04	0.46±0.04

Comparing baseline and 6 weeks: * $P<0.002$; † $P<0.02$; ‡ $P<0.05$; § $P<0.0001$.

Improvement in EDD was significantly greater in the diet with exercise group compared with diet only ($P=0.01$).

At baseline, the overweight children exhibited an impaired endothelium-dependent vasodilation ($6.9\pm2.0\%$) as compared with a previously described nonobese control group ($9.7\pm3.5\%$).⁵ The two intervention groups (diet only and diet plus exercise) were well matched for age, gender, BMI, body fat content, waist-to-hip ratio, lipid profiles, and glucose levels (Table 1). After intervention, waist-to-hip ratio decreased in both groups, but there was no significant change in

body fat content, fat-free mass, and BMI. A significant decrease in total cholesterol was seen in both groups and in LDL cholesterol in the exercise group. Fasting glucose ($P<0.002$) reduced slightly in the exercise group only. An improvement in EDD but not NTG of brachial artery after 6 weeks' intervention was evident in both groups, but the changes were significantly greater after diet plus exercise than with diet alone ($P=0.01$) (Table 1 and Figure 2). On

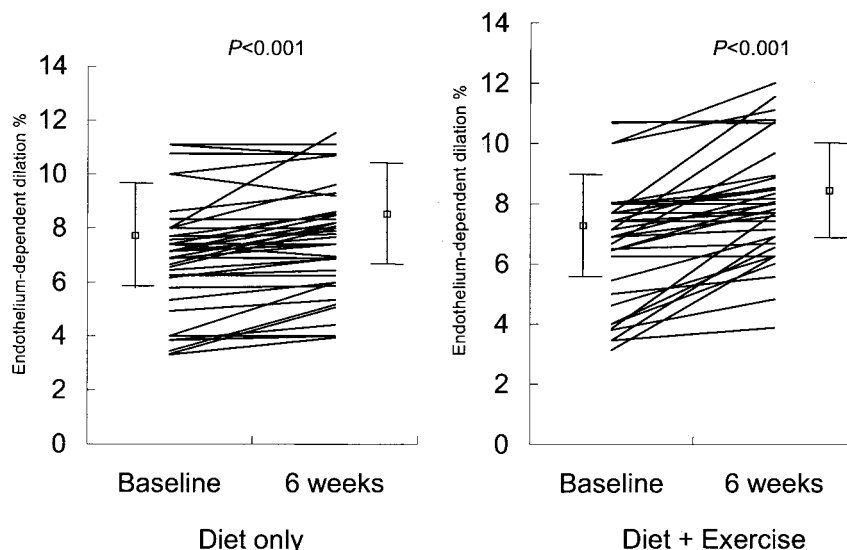


Figure 2. Endothelium-dependent dilation at baseline and after 6 weeks of intervention with either dietary modification only (left panel) or dietary modification plus supervised exercise program (right panel) (mean±SD) presented. Improvement in EDD was significantly greater after diet with exercise, compared with diet only ($P=0.01$).

TABLE 2. Vascular Reactivity Changes in Overweight and Obese Children With Either Intervention (Diet Only or Diet With Exercise)

	BMI 21–23 (n=28)		BMI >23 (n=54)	
	Baseline	6 Weeks	Baseline	6 Weeks
Brachial artery diameter, mm	2.7±0.1	2.7±0.2	2.8±0.2	2.8±0.2
EDD, %	7.4±2.1	8.4±2.0*	6.5±1.8	7.3±2.0*
NTG-induced dilation, %	19.6±2.7	21.0±1.7	20.2±1.7	20.0±2.0
Hyperemia, %	612±121	622±103	627±119	635±111

* $P<0.001$ compared with baseline.

multivariate analysis, both exercise training ($\beta=0.54$; $P=0.02$) and changes in LDL cholesterol ($\beta=0.54$; $P=0.03$) but not changes in waist-to-hip ratio or BMI were independently associated with the observed improvement in EDD (model $R=0.40$; $F=3.18$; $P=0.019$). Considering both interventions together, improvement in arterial endothelial function was seen both in children who were moderately overweight as well as those who were obese (Table 2).

Long-Term (1-Year) Interventional Program in Overweight and Obese Children

In those children continuing exercise, EDD improved further from 6 weeks to 1 year ($6.9\pm1.5\%$ at baseline; $8.0\pm1.5\%$ at 6 weeks; $8.6\pm1.8\%$ at 1 year). With exercise withdrawal, by contrast, EDD returned toward baseline ($6.7\pm2.3\%$ at baseline; $7.9\pm2.2\%$ at 6 weeks; $7.4\pm2.5\%$ at 1 year, $P=0.1$ compared with EDD at 6 weeks) ($P=0.035$ compared with EDD at 1 year in children continuing exercise) (Figure 3). Similar results were observed in the diet alone group ($6.9\pm2.0\%$ at baseline; $7.5\pm2.0\%$ at 6 weeks; $7.1\pm1.5\%$ at 1 year, $P=0.2$ compared with baseline EDD). At 1 year, there was significant regression of carotid IMT in the children continuing exercise training (mean decrease in IMT of 0.018 mm; 95% confidence interval, 0.008 to 0.028 mm; $P<0.001$), and in children on diet only (mean decrease, 0.015 mm; 95% confidence interval, 0.006 to 0.025 mm; $P=0.02$). There were significant improvements in body fat content in children continuing exercise training ($P<0.01$) associated with significant changes in LDL cholesterol and HDL cholesterol but not BMI (Table 3). On multivariate analysis, continued exercise training ($\beta=0.27$; $P=0.016$) was

independently correlated with long-term improvement in EDD (model $R=0.47$; $F=4.8$; $df=5$; $P=0.002$) after adjustment for age, blood pressure, and lipid levels.

Discussion

This study demonstrates that the vascular dysfunction associated with obesity in children is partially reversible by even a short program of dietary modification. The addition of an individualized exercise training program for children enhanced the beneficial arterial effects, which could be sustained when training continued for 1 year. These data underscore the potential importance of diet and exercise in improving outcomes from obesity-related arterial disease, even commencing from an early age.

Body mass index tends to increase in childhood and throughout life.⁶ In adults, obesity is regarded as BMI >30 . In children, by contrast, the 95th percentile for BMI is 21, and we therefore used this as our prospectively defined criterion for overweight (BMI, 21 to 23) and obesity (BMI >23) in the current study.⁶ Because our study subjects were growing children, we also measured their height, weight, body fat content, fat-free mass, and waist-to-hip ratio as well as their BMI to provide more comprehensive measures of "fatness" before and after intervention. Only small changes in these parameters were observed during the short (6-week) intervention period; however, changes in body fat content were more obvious after 1 year.

After 6-week intervention, significant improvements in endothelium-dependent dilation were evident. The improvement in arterial endothelial function was greater in the diet and exercise group compared with the diet alone group, and

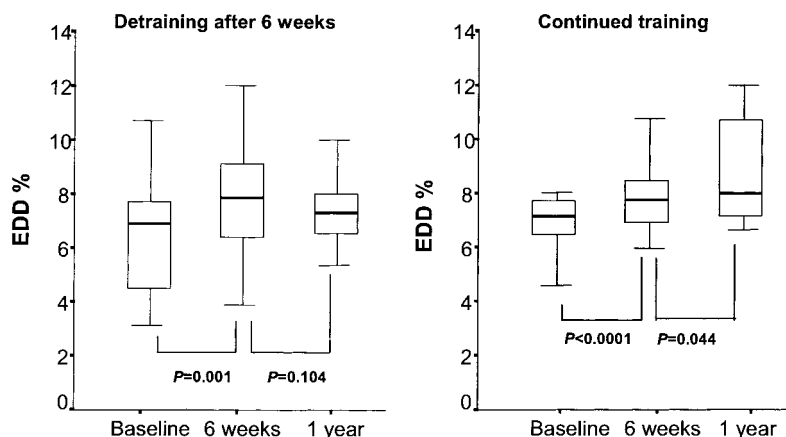


Figure 3. Endothelium-dependent dilation at baseline and after 6 weeks and 1 year of intervention with diet and exercise for 6 weeks but subsequent withdrawal from exercise (detraining group) and with continuing diet and exercise (training group). Exercise training was independently correlated with improvement in EDD on multivariate analysis (partial $R=0.47$; $F=4.8$; $P=0.002$). EDD was significantly better at 1 year in the continued training compared with the detraining group ($P=0.035$). In each intervention group, box represents interquartile range (between 25th and 75th percentiles), with the median value shown as a horizontal bar within each box; bars outside each box show the range of 95% of values.

TABLE 3. Changes in Obesity Markers, Lipid and Insulin Profiles, and Vascular Parameters at 1 Year

	Diet Only		Detraining		Continuing Training	
	Baseline	1 Year	Baseline	1 Year	Baseline	1 Year
BMI, kg/m ²	24.7±3.1	24.5±3.3	26.1±4.0	26.1±4.2	25.3±2.4	25.4±2.4
Waist-hip ratio	0.89±0.07	0.88±0.07	0.89±0.05	0.86±0.06	0.87±0.05	0.87±0.06
Body fat, %	37.3±3.8	36.0±4.1	37.1±3.1	39.2±6.1	38.8±3.8	33.9±5.0*
Total cholesterol, mmol/L	4.7±0.9	4.5±0.8†	4.7±0.7	4.6±1.1	4.8±1.1	4.8±1.1
LDL cholesterol, mmol/L	2.9±0.9	2.5±0.7*	2.7±0.8	2.5±0.9	3.0±0.9	2.7±1.0†
HDL cholesterol, mmol/L	1.3±0.3	1.5±0.3	1.4±0.4	1.4±0.3	1.2±0.3	1.4±0.3*
Triglycerides, mmol/L	1.2±0.5	1.4±0.7	1.3±0.6	1.4±0.7	1.3±0.6	1.4±0.7
LDL/HDL cholesterol ratio	2.3±0.9	1.7±0.6‡	2.1±1.8	1.8±0.7*	2.6±1.0	1.9±0.8‡
EDD, %	6.9±2.0	7.1±1.5	6.7±2.3	7.4±2.5†	6.9±1.5	8.6±1.8‡
IMT, mm	0.47±0.05	0.45±0.04*	0.47±0.05	0.46±0.03	0.48±0.04	0.46±0.03‡

Comparing baseline and 1 year: * $P<0.01$; † $P<0.05$; ‡ $P<0.001$.

multivariate regression analysis confirmed the independent effect of exercise training on improved arterial function. Furthermore, the improvement in vascular reactivity was seen over a wide range of BMIs, from 21 to >25, highlighting the potential benefit of such intervention in overweight as well as obese children. Longer intervention and sustained for 1 year produced greater anthropometric and lipoprotein improvements and near normalization of vascular parameters, including endothelium-dependent dilation and carotid IMT. With detraining, some of the early improvements in arterial reactivity were lost, but their EDD at 1 year was still better than the diet only control group, whose vascular improvement was only transient. Although continued training in the exercise group (versus detraining) was voluntary rather than by randomization, our study results suggest the importance of perseverance with exercise and dietary programs in reversing obesity-related vascular dysfunction in children. As endothelial abnormalities are known to be associated with risk of future cardiovascular events,⁸ such changes may prove to be associated with clinical benefits in the longer term.

Several other groups have previously demonstrated that exercise improves arterial endothelial function in adults without vascular risk factors¹⁴ or with established coronary disease.¹⁵ Our current study extends these findings, documenting a benefit of exercise on obesity-related arterial disease, in an age group in which exercise capacity and enjoyment are usually at a high level. The mechanism of this benefit is thought to be related (at least in part) to shear stress-related upregulation of endothelial nitric oxide synthase and consequent improvements in vascular production of this vasodilator substance.¹⁴ Other contributing mechanisms might include improvements in insulin sensitivity, proinflammatory cytokines, and/or lipoprotein profiles.¹⁶

Sedentary habits and a lifestyle lacking in exercise are becoming increasingly prevalent worldwide. Almost half of young people 12 to 21 years of age fail to engage in vigorous activity on a regular basis in the United States, and 1 in 4 children gets no physical education in school at all. Currently 1 in 10 American and British children are obese, and the prevalence of overweight is also rapidly increasing in Asia and the developing world.¹⁷ These factors are important

contributors to the major public health problems of diabetes mellitus and coronary artery disease, affecting even developing countries such as China.

Limitations of the present study include the relative intensity of the exercise program, which might be difficult to apply and/or sustain in all obese children, and the possibility of a selection bias in the recruitment process. However, neither BMI nor school performance differed significantly in children who declined participation compared with those who were enrolled. Inclusion of an exercise only group, a nonintervention (ie, no change in lifestyle) group of obese children, and a nonobese sedentary and exercise control group may also have provided further information; however, we thought it difficult to recruit such subjects, particularly without dietary advice also. All ultrasound-derived vascular functions were measured by a blinded investigator, and the high reproducibility between serial observations and in control subjects over time have been documented by us previously.^{7,10} It is possible, however, that hormonal changes over time may have influenced vascular function in these children, but any such differences would be expected to be similar across all the groups of children studied. Furthermore, the improvement observed in carotid IMT after 1-year intervention, although statistically significant, was small and therefore of uncertain clinical significance; this small change may reflect the interaction between improved arterial structure with intervention, counterbalanced in part by the natural growth in vessel walls of children growing rapidly. In adults, 1 SD increase in carotid IMT has been associated with an ≈2-fold increased risk of ischemic stroke or myocardial infarction¹²; thus even small changes of carotid IMT may correspond to important health gains at a population level.

The treatment of obesity remains difficult. Certain effective drug therapies have been withdrawn from the market because of dangerous cardiovascular effects,¹⁸ and therefore medical treatment of obesity is currently not available for overweight or obese children. Nonpharmacological measures such as diet and exercise therefore represent the mainstays of obesity prevention and treatment in developed and developing countries.

In summary, we have found that diet, especially combined with sustained exercise, improves early signs of arterial dysfunction and thickening in overweight and obese children. In this context, improving obesity-related arterial dysfunction in children by diet and exercise should be regarded as an important strategy for modifying vascular risk in this population.

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References

1. Kopelman PG. Obesity as a medical problem. *Nature*. 2000;404:635–643.
2. Reilly JJ, Dorosty AR, Emmett PM. Prevalence of overweight and obesity in British children: cohort study. *Br Med J*. 1999;319:1039.
3. Berenson GS, Srinivasan SR, Bao W, et al, for the Bogalusa Heart Study. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. *N Engl J Med*. 1998;338:1650–1656.
4. 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.
5. Woo KS, Chook P, Yu CW, et al. Overweight in children is associated with arterial endothelial dysfunction and intima-media thickening. *Int J Obesity*. In press.
6. Ogden CL, Kuczmarski RJ, Flegal KM, et al. Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. *Pediatrics*. 2002;109:45–60.
7. Woo KS, Chook P, Lolin YI, et al. Folic acid improves arterial endothelial function in adults with hyperhomocysteinemia. *J Am Coll Cardiol*. 1999;34:2002–2006.
8. Raitakari OT, Celermajer DS. Testing for endothelial dysfunction. *Ann Med*. 2000;32:293–304.
9. Woo KS, Chook P, Raitakari OT, et al. Westernization of Chinese adults and increased subclinical atherosclerosis. *Arterioscler Thromb Vasc Biol*. 1999;19:2487–2493.
10. Sorensen KE, Celermajer DS, Spiegelhalter DJ, et al. Non-invasive measurement of human endothelium dependent arterial responses: accuracy and reproducibility. *Br Heart J*. 1995;74:247–53.
11. Adams MR, Nakagomi A, Keech A, et al. Carotid intima-media thickness is only weakly correlated with the extent and severity of coronary artery disease. *Circulation*. 1995;92:2127–2134.
12. O'Leary DH, Polak JF, Kronmai RA, et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med*. 1999;340:14–22.
13. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika*. 1988;75:800–802.
14. Kingwell BA, Sherrard B, Jennings GL, et al. Four weeks of cycle training increases basal production of nitric oxide from the forearm. *Am J Physiol*. 1997;272:H1070–H1077.
15. Hambrecht R, Wolf A, Gielen S, et al. Effect of exercise on coronary endothelial function in patients with coronary artery disease. *N Engl J Med*. 2000;342:454–460.
16. Yudkin JS, Stehouwer CDA, Emeis JJ, et al. C-reactive protein in healthy subjects: Associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol*. 1999;19:972–978.
17. Martorell R, Kettel Khan L, Hughes ML, et al. Overweight and obesity in preschool children from developing countries. *Int J Obes Relat Metab Disord*. 2000;24:959–967.
18. Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med*. 1997;337:581–588.

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