Influence of Adiposity and Physical Activity on Arterial Stiffness in Healthy Children. The Lifestyle of Our Kids Study

Satoru Sakuragi, Katrina Abhayaratna, Karen J. Gravenmaker, Christine O'Reilly, Wichat Srikusalanukul, Marc M. Budge, Richard D. Telford and Walter P. Abhayaratna

Hypertension published online Mar 9, 2009;
DOI: 10.1161/HYPERTENSIONAHA.108.123364
Hypertension is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0194-911X. Online ISSN: 1524-4563

Influence of Adiposity and Physical Activity on Arterial Stiffness in Healthy Children

The Lifestyle of Our Kids Study

Satoru Sakuragi, Katrina Abhayaratna, Karen J. Gravenmaker, Christine O'Reilly, Wichat Srikusalanukul, Marc M. Budge, Richard D. Telford, Walter P. Abhayaratna

Abstract—Childhood obesity is increasingly prevalent in the community and is related to adverse cardiovascular outcomes during adulthood. In this study of healthy children, we evaluated the influence of adiposity and physical activity on carotid-femoral pulse wave velocity (PWV), an index of arterial stiffness and a marker of cardiovascular risk in adults. In 573 community-based children (mean age: 10.1±0.3 years; 51% boys), we measured body mass index and waist circumference. Percentage body fat was quantitated by dual-energy x-ray absorptiometry. Cardiorespiratory fitness (CRF) and physical activity levels were assessed using a 20-m shuttle run and 7-day pedometer count, respectively. PWV was estimated by applanation tonometry. In univariate analysis, PWV was positively correlated with body mass index (r=0.34), waist circumference (r=0.32), and percentage body fat (r=0.32; P<0.001 for all) and negatively correlated with CRF (r=−0.23; P<0.001) and pedometer count (r=−0.08; P=0.046). In separate multivariable linear regression models, body mass index, waist circumference, and percentage of body fat were independently and positively associated with PWV (P<0.01 for all) after adjusting for age, sex, systolic blood pressure, mean arterial pressure, heart rate, and CRF (P<0.01 for all). The influence of CRF on PWV was attenuated after adjusting for adiposity. In conclusion, increased body mass and adiposity and decreased CRF are associated with arterial stiffening in healthy prepubescent children. **(*Hypertension*. 2009;53:611-616.)**

Key Words: arterial stiffness ■ cardiorespiratory fitness ■ adiposity ■ children

The rising prevalence of obesity in childhood in the community[1] is associated with the premature development of cardiovascular (CV) risk factors such as dyslipidemia,[2] hypertension,[2] and insulin resistance.[3] In addition, there is emerging evidence that such obesity-related metabolic disease predicts the development of CV disease in adulthood.[4] A better understanding of the natural history of obesity-related CV disease may identify markers of subclinical arterial disease and CV risk, which could be used subsequently to target preventative measures at children at high risk before the development of overt CV disease.

The role of arterial stiffness in the development of CV disease is widely accepted.[5] Carotid-femoral pulse wave velocity (PWV), a noninvasive index of arterial stiffness,[6] is an independent predictor of CV mortality in the community.[7] Although the influence of obesity[8] and physical activity[9] on PWV has been documented in adults, there is limited information in healthy children. In particular, previous studies in children have assessed the relationship between adiposity and arterial stiffness using measures of peripheral arterial stiffness and have not accounted for the potential confounding effects of physical activity.[10,11]

In the present study, we evaluated the relationship among adiposity, physical activity, and PWV in community-based children. We hypothesized that the effects of adiposity and physical activity on arterial stiffness are independent of systemic blood pressure (BP) and heart rate.

Methods

The Lifestyle of Our Kids Study was approved by the human research ethics committees of Australian Capital Territory Health and the Australian National University. Recruitment methods for this community-based longitudinal study have been described previously.[12] In brief, the Lifestyle of Our Kids Study is a prospective cohort study designed to investigate the effect of physical activity on health and development. Participating children were recruited from local primary (elementary) schools in which average family income was very close to that of the Australian national average. In 2005, baseline assessments were performed on 830 grade 2 school children (7 to 8 years old) with subsequent biennial visits scheduled until age grade 6 (11 to 12 years old). Parents or guardians of all of the study subjects provided informed consent for the children to undergo the

Received September 21, 2008; first decision October 11, 2008; revision accepted December 16, 2008.

From the Academic Unit of Internal Medicine (S.S., K.A., K.J.G., C.O., W.P.A.), Canberra Hospital, Canberra, Australian Capital Territory, Australia; College of Medicine, Biology and Environment (W.S., M.M.B., R.D.T., W.P.A.), Australian National University, Canberra, Australian Capital Territory, Australia; Department of Geriatric Medicine (M.M.B.), Canberra Hospital, Canberra, Australian Capital Territory, Australia; and Commonwealth Institute (R.D.T.), Canberra, Australia.

Correspondence to Walter P. Abhayaratna, Academic Unit of Internal Medicine, Canberra Hospital, Australian Capital Territory 2606, Australia. E-mail walter.abhayaratna@act.gov.au

Hypertension **is available at http://hyper.ahajournals.org** **DOI: 10.1161/HYPERTENSIONAHA.108.123364**

Table 1. Characteristics of Study Population, Stratified by Tertiles of %BF

Characteristic	All %BF, n=573	Tertile 1 (12.7 to 23.0 %BF), n=193	Tertile 2 (23.1 to 29.4 %BF), n=189	Tertile 3 (29.6 to 46.5 %BF), n=191	*P*
Girls, n (%)	278 (49)	54 (28)	96 (51)	128 (67)	<0.0001
Age, y	10.1±0.3	10.1±0.3	10.1±0.3	10.1±0.4	0.39
Height, cm	141.2±6.3	139±6	141±6	143±6	<0.0001
Weight, kg	36.7±7.8	31±4	35±5	44±8	<0.0001
BMI, kg/m^2	18.3±3.0	16.1±1.2	17.6±1.7	21.2±2.9	<0.0001
WC, cm	60.6±6.9	56.4±3.2	59.2±4.8	66.7±7.2	<0.0001
%FB, %	26.6±6.9	19.4±2.4	25.9±1.7	34.7±3.9	<0.0001
Tanner stage (hair)	1.4±0.6	1.4±0.6	1.4±0.5	1.5±0.6	0.50
Tanner stage (genital/breast)	1.7±0.7	1.6±0.6	1.7±0.6	2.0±0.8	0.003
Systolic BP, mm Hg	105.3±8.1	102±7	105±8	109±9	<0.0001
Diastolic BP, mm Hg	62.2±5.9	60±5	62±6	64±6	<0.0001
Pulse pressure, mm Hg	43.1±7.0	42±6	43±7	44±8	0.011
Mean arterial pressure, mm Hg	76.2±6.7	74±5	76±7	79±7	<0.0001
Heart rate, bpm	77.1±10.6	75±10	78±11	78±11	0.004
PWV, m/s	4.4±0.5	4.2±0.4	4.4±0.4	4.6±0.5	<0.0001
Glucose, mmol/L	5.1±0.4	5.1±0.4	5.1±0.4	5.1±0.4	0.37
Glycosylated hemoglobin, %	5.3±0.2	5.3±0.2	5.3±0.2	5.3±0.2	0.001
Total cholesterol, mmol/L	4.5±0.8	4.4±0.8	4.4±0.7	4.7±0.9	0.087
HDL cholesterol, mmol/L	1.4±0.3	1.5±0.3	1.4±0.3	1.3±0.2	<0.0001
Triglyceride, mmol/L	0.8±0.4	0.7±0.3	0.7±0.3	0.9±0.5	<0.0001
Insulin, mU/L	7.7±6.2	5.7±3.3	6.9±3.2	10.4±9.0	<0.0001
HOMA-IR	1.7±1.6	1.3±0.8	1.5±0.8	2.4±2.5	<0.0001
hs-CRP, mg/L	1.8±4.8	0.9±1.8	1.7±6.6	2.5±4.9	<0.0001
CRF, stage	5.0±1.7	6.1±1.8	5.1±1.4	3.8±1.1	<0.0001
Pedometer counts, half steps	98±12	102±11	98±11	94±12	<0.0001

hs-CRP indicates high-sensitivity C-reactive protein. Data are means±SD unless otherwise specified.

second wave of assessments at age 9 to 10 years (grade 4), which were conducted during 2007. A total of 615 healthy children underwent a CV examination. Children with a history of diabetes mellitus, hypertension, or evidence of CV disease were excluded from this study. Of the remaining children, 573 (mean age: 10.1 years; 51% boys) underwent a complete set of examinations and represent the study population.

Body weight and height were measured without shoes and in light clothing, and body mass index (BMI) was calculated. Waist circumference (WC), an index of total abdominal fat, was measured at the midpoint between the lower border of the rib cage and the iliac crest, at the narrowest section of the waist. Body fat was quantitated using dual-energy x-ray absorptiometry (DXA, Hologic Discovery QDR Series, Hologic Inc). Total body scans were analyzed using Hologic QDR System Software 12.4 to estimate percentage of body fat (%BF).

Cardiorespiratory fitness (CRF) and physical activity levels were assessed using a 20-m shuttle run and a 7-day AT pedometer count (New-Lifestyles, Lee's Summit), respectively, as described previously.[12] Supine brachial BP and heart rate were determined using an automated oscillometric Omron 7051T. The average of 2 measurements made at 1-minute intervals was recorded. PWV was assessed noninvasively using the Sphygmocor system (AtCor Medical). ECG-gated carotid and femoral waveforms were recorded using applanation tonometry. Carotid-femoral path length was measured as the difference between the surface distances joining 1) the suprasternal notch, the umbilicus, and the femoral pulse and 2) the suprasternal notch and the carotid pulse. Carotid-femoral transit time was estimated in 8 to 10 sequential femoral and carotid waveforms as the average time difference between the onset of the femoral and carotid waveforms. PWV was calculated as the carotid-femoral path length divided by the carotid-femoral transit time.

Blood samples were collected after an overnight fast to measure glucose, glycosylated hemoglobin, total cholesterol, high-density lipoprotein cholesterol (HDL), triglycerides, insulin level, and high-sensitivity C-reactive protein. The insulin resistance index by homeostasis model assessment (HOMA-IR) was calculated from fasting plasma glucose and insulin levels with the following formula: HOMA-IR=[fasting insulin (μIU/mL)×fasting glucose (mmol/L)/22.5][13] Pubertal development was determined by Tanner stage, based on self-assessment of pubic hair development, breast stage in girls, and genitalia development in boys.[14,15]

Statistical Analysis

Characteristics of the study population were compared according to tertiles of %BF using ANOVA. Univariable relationships between PWV and clinical/metabolic characteristics were assessed using Pearson's correlation and univariate linear regression. Independent associations between each adiposity parameter and PWV were assessed using a stepwise multivariable linear regression analysis. In the initial model (model 1), the relationship between adiposity parameters and PWV was assessed with adjustment for age, sex, systolic BP, mean arterial pressure, and heart rate. Extended models were used to assess whether the influence of adiposity on PWV was attenuated by the potential confounding effects of metabolic factors (model 2) or physical activity (model 3). Independent relationships between CRF and PWV and HOMA-IR and PWV were also assessed using a multivariable linear regression analysis, with initial adjust-

Table 2. Univariate Associations Between PWV and Physical/ Metabolic Characteristics

Characteristic	r	β	β 95% CI	P
Sex (girls)	. . .	0.130	0.054 to 0.207	0.001
Age, y	−0.082	−0.113	−0.227 to −0.004	0.049
Height, cm	0.104	0.008	0.002 to 0.014	0.013
Weight, kg	0.309	0.019	0.014 to 0.024	<0.0001
BMI, kg/m^2	0.339	0.054	0.042 to 0.067	<0.0001
WC, cm	0.320	0.023	0.016 to 0.029	<0.0001
%BF, %	0.318	0.022	0.016 to 0.027	<0.0001
Tanner stage (hair)	−0.020	−0.016	−0.102 to 0.070	0.713
Tanner stage (genital/breast)	0.091	0.060	−0.014 to 0.129	0.094
Systolic BP, mm Hg	0.316	0.018	0.014 to 0.023	<0.0001
Diastolic BP, mm Hg	0.326	0.026	0.020 to 0.032	<0.0001
Pulse pressure, mm Hg	0.074	0.005	−0.001 to 0.010	0.079
Mean arterial pressure, mm Hg	0.277	0.019	0.014 to 0.025	<0.0001
Heart rate, bpm	0.248	0.011	0.007 to 0.014	<0.0001
Glucose, mmol/L	0.031	0.037	−0.066 to 0.139	0.483
Glycosylated hemoglobin, %	0.045	0.096	−0.089 to 0.281	0.310
Total cholesterol, mmol/L	0.053	0.031	−0.019 to 0.081	0.225
HDL cholesterol, mmol/L	−0.130	−0.234	−0.388 to −0.080	0.003
Triglyceride, mmol/L	0.201	0.234	0.135 to 0.332	<0.0001
Insulin, mU/L	0.167	0.013	0.006 to 0.019	0.0001
HOMA-IR	0.158	0.045	0.021 to 0.070	0.0003
hs-CRP, mg/L	0.153	0.014	0.006 to 0.023	0.0013
CRF, stage	−0.233	−0.064	−0.088 to −0.041	<0.0001
Pedometer counts, half steps	−0.083	−0.003	−0.007 to −0.00006	0.046

hs-CRP indicates high-sensitivity C-reactive protein.

ment for age, sex, systolic BP, mean arterial pressure, and heart rate (model 1) and subsequent adjustment for BMI, WC, and %BF in extended models. All of the analyses were performed with SPSS software (Version 11.0 for Windows, SPSS Inc).

Results

Characteristics of the study population are described in Table 1, stratified for tertiles of %BF. Higher %BF was associated with female sex, increased height, Tanner stage (genital/breast), heart rate, BP, PWV, and metabolic-inflammatory markers, such as triglyceride, insulin, HOMA-IR, and high-sensitivity C-reactive protein levels, as well as decreased HDL levels, pedometer counts, and CRF.

The results of univariate analysis of the relationship between clinical/metabolic variables and PWV are shown in Table 2. BMI (r=0.34), WC (r=0.32), and %BF (r=0.32) (Figure 1A) were positively correlated with PWV (all P<0.001). CRF was negatively associated with PWV (r=−0.23; P<0.001; Figure 1B) and pedometer counts (r=−0.08; P=0.046). Metabolic parameters, such as lower HDL and higher triglyceride, fasting insulin, and HOMA-IR, were related to increased PWV (all P<0.01).

Percentage body fat was negatively correlated with CRF (r=−0.58) and pedometer counts (r=−0.26; P<0.0001 for both). In bivariate analysis, PWV increased according to increasing tertiles of %BF (P<0.0001) and decreasing tertiles of CRF (P=0.054; Figure 2).

In multivariable analysis, BMI, WC, and %BF were associated with increased PWV after adjusting for age, sex, systolic BP, mean arterial pressure, and heart rate (model 1; Table 3; P<0.01 for all). The independent association between adiposity parameters and PWV was evident even after adjusting for metabolic factors (HDL, triglyceride, and HOMA-IR) or CRF (model 2 and model 3, respectively). The positive relationship between insulin resistance and PWV was attenuated by adjusting for body mass (β=0.016; P=0.22), WC (β=0.020; P=0.13), or %BF (β=0.022; P=0.09).

In multivariable analysis of the association between CRF and arterial stiffness; CRF was associated with increased PWV after adjusting for age, sex, systolic BP, mean arterial pressure, and heart rate (Table 3). However, the association between CRF and PWV was attenuated when adjusted for adiposity.

Because increased abdominal girth has the potential to systematically bias the association between adiposity and PWV (ie, path length can be systematically overestimated in children with increased central adiposity), we evaluated the effect of BMI and %BF on PWV in bivariate models that included WC as an independent variable. BMI (β=0.057; P<0.001) and %BF (β=0.013; P=0.002) were independently associated with PWV, after adjustment for WC.

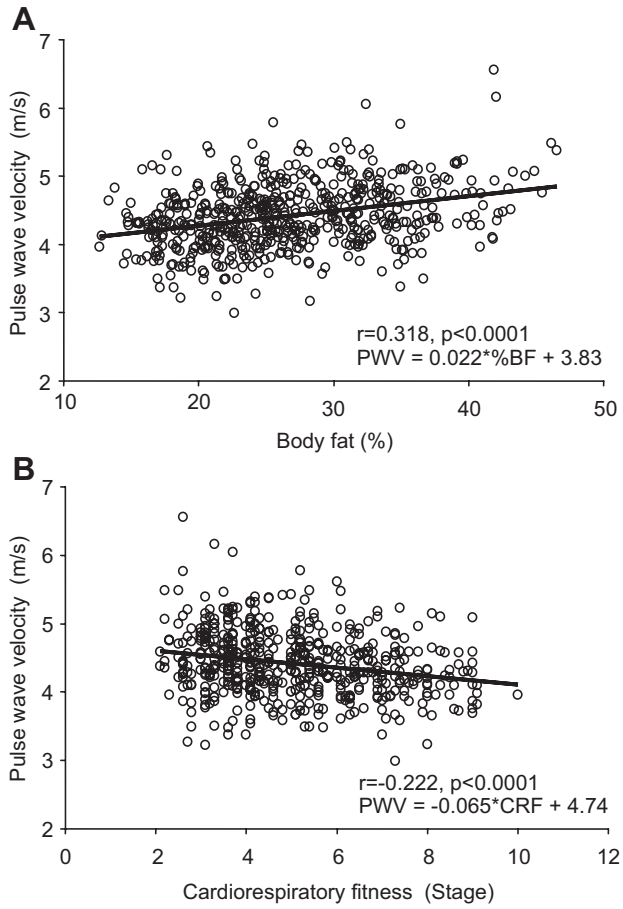

Figure 1. Scatterplot showing the positive association between (A) %BF and PWV and (B) CRF and PWV in boys (○) and girls (●).

Discussion

The main findings from the present study of healthy children are that adiposity and decreased CRF were related to PWV, an index of arterial stiffness and marker of CV risk. These relationships were independent of clinical and metabolic factors, including systemic BP and heart rate. In addition, the influence of adiposity on PWV was independent of the potential intermediary effects of physical activity and CRF. There was evidence to suggest that CRF may be an effect modifier in the relationship between adiposity and arterial stiffness.

Although the influence of obesity[8] and physical activity[9] on PWV has been reported in adults, the effect of body mass, adiposity, and physical activity on arterial stiffness has not been determined in healthy children. Our findings provide first evidence that an effect of adiposity and CRF on arterial stiffness exists (and is measurable by noninvasive methods) in prepubescent children who are otherwise healthy and have no known medical conditions that would promote premature CV disease, such as diabetes mellitus or hypertension. In a smaller study of one-hundred 10-year olds, radial-femoral PWV measured by optical method was related to fat energy percentage, period of breastfeeding, and physical activity but not associated with body fat.[10] In another study of 970 healthy children, PWV measured between the brachium and ankle using a plethysmographic method was associated with increased age, BP, and heart rate but not BMI.[11] The discrepancy in results between studies may be attributable to differences in the methodology for the assessment of PWV. Although carotid-femoral PWV is a measure of central aortic stiffness, radial- and brachial-femoral PWV also incorporate the measurement of peripheral arterial stiffness, which is strongly influenced by factors that affect smooth muscle tone.

Although the mechanisms whereby increased adiposity may promote arterial stiffening are unable to be determined using our cross-sectional data, several possibilities exist. Increased BMI and adiposity are accompanied by increases in heart rate,[16] BP,[17] and intermediary CV metabolic risk factors such as insulin resistance,[18] dyslipidemia,[19] and inflammation.[20] Such factors may mediate alterations in arterial function. Furthermore, proximate risk factors such as physical inactivity may be associated with both an increase in adiposity and increased arterial stiffness. In the present study, we have confirmed a positive association between these factors and PWV; however, only the relationship between increased adiposity and PWV remained after adjustment for these potential confounders.

Endothelial dysfunction, which may occur early in the course of atherosclerosis and during childhood,[21] is a potential mechanism underlying the interrelationships among adiposity, physical activity, and increased arterial stiffness.

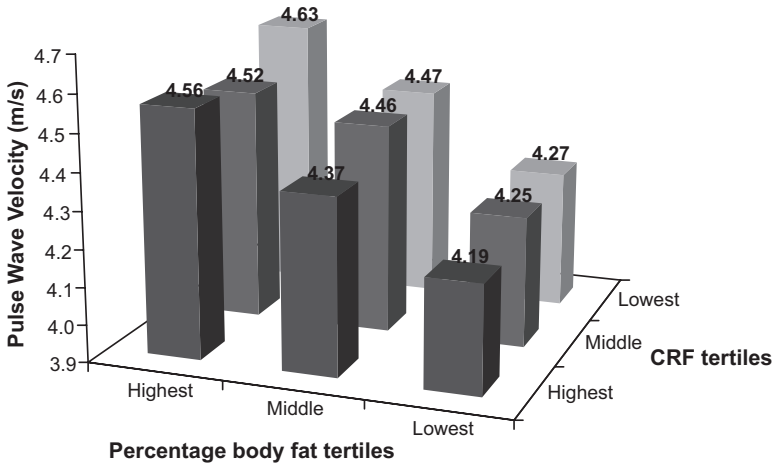

Figure 2. PWV by tertiles of %BF and CRF. An interaction between cardiorepiratory fitness and %BF was evident such that carotid-femoral PWV increased with decreasing CRF for each tertile of %BF.

Table 3. Association Between PWV and Adiposity/CRF in Multivariable Models

Model	Covariates	$\beta_{(Adiposity)}$	95% CI	*P*	Adjusted R^2
BMI					
Model 1	Age, sex, systolic BP, mean arterial pressure, heart rate	0.041	0.028 to 0.055	<0.0001	0.201
Model 2	Model 1+HDL cholesterol, triglyceride, HOMA-IR	0.033	0.017 to 0.049	<0.0001	0.176
Model 3	Model 1+CRF	0.036	0.020 to 0.052	<0.0001	0.206
WC					
Model 1	Age, sex, systolic BP, mean arterial pressure, heart rate	0.017	0.011 to 0.024	<0.0001	0.182
Model 2	Model 1+HDL cholesterol, triglyceride, HOMA-IR	0.014	0.006 to 0.022	0.0003	0.166
Model 3	Model 1+CRF	0.016	0.008 to 0.023	<0.0001	0.190
%BF					
Model 1	Age, sex, systolic BP, mean arterial pressure, heart rate	0.015	0.009 to 0.021	<0.0001	0.189
Model 2	Model 1+HDL cholesterol, triglyceride, HOMA-IR	0.012	0.005 to 0.018	0.0004	0.169
Model 3	Model 1+CRF	0.012	0.0004 to 0.019	0.002	0.190
CRF					
Model 1	Age, sex, systolic BP, mean arterial pressure, heart rate	−0.047	−0.07 to −0.024	<0.0001	0.176
Model 2a	Model 1+BMI	−0.024	−0.049 to −0.0004	0.054	0.206
Model 2b	Model 1+WC	−0.022	−0.050 to 0.006	0.127	0.190
Model 2c	Model 1+%BF	−0.023	−0.051 to 0.004	0.094	0.190

Several studies have documented a relationship between obesity or physical activity and endothelial dysfunction in adults[22,23] and children.[24] Obesity-related decrease in adiponectin[25] and increases in inflammatory cytokines derived from adipose tissue, such as interleukin 6 and tumor necrosis factor α, may be involved in the development of endothelial dysfunction.[26] In children, insulin resistance has been shown to be related to endothelial dysfunction,[24] although the relationship between insulin resistance and PWV in childhood is yet to be determined. In the present study, the positive relationship between insulin resistance and PWV was attenuated by body mass and adiposity. These findings may simply reflect the intermediary role of insulin resistance in the relationship between adiposity and arterial stiffness. It is also possible that the period of exposure to insulin resistance may not be sufficient in prepubescent children to affect an increase in central arterial stiffness, because it has been shown that the incidence of insulin resistance increases greatly after puberty.[27]

Although our findings show an attenuation of the effects of physical activity and CRF on PWV when statistically adjusting for body mass or adiposity, these results should be considered within the context of our methodology. In particular, we do not wish to imply that body mass and adiposity are more important than physical activity or CRF as determinants of arterial stiffness. CRF, as determined by a shuttle run, and physical activity, as assessed by pedometer counts, are not simple constructs, are prone to considerable variability over short periods, and are more likely to be influenced by external factors, such as compliance and motivation of the children to complete the assessment. Accordingly, it is possible that the attenuation of the effects of physical activity and CRF on PWV in the present study is attributable to lower face validity and higher measurement error of these parameters when compared with the indexes of adiposity that were used in the study.

In this cross-sectional study, we were unable to determine the causal mechanisms underlying the relationship among physical activity, adiposity, and increased PWV. We have observed that adiposity, physical activity, and clinical/metabolic factors only account for a small proportion of the variability in PWV in healthy children. We hypothesize that, at such an early stage of life, the effects of genetic factors are likely to predominate, although this requires confirmation in other studies. Because the majority of our study population was white, and all of the subjects were of the same birth cohort, our results may not be generalizable to children of other ethnic/racial groups or ages. In addition, although the limited range in age of the children facilitated effective analyses within this age group, we were unable to assess the influence of age on the relationship between adiposity and PWV. We acknowledge the potential for increased abdominal girth to overestimate true carotid-femoral path length and, consequently, to systematically overestimate PWV and, therefore, bias the relationship between adiposity and PWV. However, we have confirmed that the BMI-PWV and %BF-PWV relationships are independent of WC.

Perspectives

Our observation that increased body mass and adiposity and decreased CRF are associated with arterial stiffening at an early age has important public health and clinical implications. First, it supports the adoption of population-level strategies directed at the prevention of childhood overweight and obesity through the promotion of lifestyle measures, including increased physical activity, CRF, and dietary modification. Second, PWV may represent a marker of subclinical arterial disease and CV risk, which is easily measured and could be subsequently used to target preventative measures at children at high risk. Although weight loss has been shown to improve obesity-related vascular dysfunction, such as arterial compliance,[28] carotid arterial distensibility,[29] and endothelial function,[30] further studies are required to evaluate whether public health efforts to promote physical activity and weight loss in children will reduce arterial stiffness, attenuate the progression of subclinical CV disease, and prevent the development of subsequent CV events in the community.

Acknowledgments

We thank the children, parents, teachers, and other staff associated with the Australian Capital Territory Department of Education and Training for their willing cooperation.

Sources of Funding

This work was supported by Commonwealth Education Trust (United Kingdom) and Commonwealth Institute (Australia).

Disclosures

None.

References

1. Ogden CL, Flegal KM, Carroll MD, Johnson CL. Prevalence and trends in overweight among US children and adolescents, 1999–2000. *JAMA*. 2002;288:1728–1732.
2. Thompson DR, Obarzanek E, Franko DL, Barton BA, Morrison J, Biro FM, Daniels SR, Striegel-Moore RH. Childhood overweight and cardiovascular disease risk factors: the National Heart, Lung, and Blood Institute Growth and Health Study. *J Pediatr*. 2007;150:18–25.
3. Freedman DS, Dietz WH, Srinivasan SR, Berenson GS. The relation of overweight to cardiovascular risk factors among children and adolescents: the Bogalusa Heart Study. *Pediatrics*. 1999;103:1175–1182.
4. Morrison JA, Friedman LA, Gray-McGuire C. Metabolic syndrome in childhood predicts adult cardiovascular disease 25 years later: the Princeton Lipid Research Clinics Follow-Up Study. *Pediatrics*. 2007;120:340–345.
5. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension*. 2001;37:1236–1241.
6. Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac AM, Target R, Levy BI. Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. *Hypertension*. 1995;26:485–490.
7. Willum-Hansen T, Staessen JA, Torp-Pedersen C, Rasmussen S, Thijs L, Ibsen H, Jeppesen J. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation*. 2006;113:664–670.
8. Wildman RP, Mackey RH, Bostom A, Thompson T, Sutton-Tyrrell K. Measures of obesity are associated with vascular stiffness in young and older adults. *Hypertension*. 2003;42:468–473.
9. Vaitkevicius PV, Fleg JL, Engel JH, O'Connor FC, Wright JG, Lakatta LE, Yin FC, Lakatta EG. Effects of age and aerobic capacity on arterial stiffness in healthy adults. *Circulation*. 1993;88:1456–1462.
10. 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.
11. Niboshi A, Hamaoka K, Sakata K, Inoue F. Characteristics of brachial-ankle pulse wave velocity in Japanese children. *Eur J Pediatr*. 2006;165:625–629.
12. Telford RD, Bass SL, Budge MM, Byrne DG, Carlson JS, Coles D, Cunningham RB, Daly RM, Dunstan DW, English R, Fitzgerald R, Eser P, Gravenmaker KJ, Haynes W, Hickman PE, Javaid A, Jiang X, Lafferty T, McGrath M, Martin MK, Naughton GA, Potter JM, Potter SJ, Prosser L, Pyne DB, Reynolds GJ, Saunders PU, Seibel MJ, Shaw JE, Southcott E, Srikusalanukul W, Stuckey D, Telford RM, Thomas K, Tallis K, Waring P. The Lifestyle of our Kids (LOOK) Project: outline of methods. *J Sci Med Sport*. 2009;12:156–163.
13. Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, Quon MJ. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J Clin Endocrinol Metab*. 2000;85:2402–2410.
14. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child*. 1969;44:291–303.
15. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child*. 1970;45:13–23.
16. Abate NI, Mansour YH, Tuncel M, Arbique D, Chavoshan B, Kizilbash A, Howell-Stampley T, Vongpatanasin W, Victor RG. Overweight and sympathetic overactivity in black Americans. *Hypertension*. 2001;38:379–383.
17. Torrance B, McGuire KA, Lewanczuk R, McGavock J. Overweight, physical activity and high blood pressure in children: a review of the literature. *Vasc Health Risk Manag*. 2007;3:139–149.
18. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature*. 2006;444:875–880.
19. Glowinska B, Urban M, Koput A, Galar M. New atherosclerosis risk factors in obese, hypertensive and diabetic children and adolescents. *Atherosclerosis*. 2003;167:275–286.
20. Bastard JP, Jardel C, Delattre J, Hainque B, Bruckert E, Oberlin F. Evidence for a link between adipose tissue interleukin-6 content and serum C-reactive protein concentrations in obese subjects. *Circulation*. 1999;99:2221–2222.
21. Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, Lloyd JK, Deanfield JE. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet*. 1992;340:1111–1115.
22. Perticone F, Ceravolo R, Candigliota M, Ventura G, Iacopino S, Sinopoli F, Mattioli PL. Obesity and body fat distribution induce endothelial dysfunction by oxidative stress: protective effect of vitamin C. *Diabetes*. 2001;50:159–165.
23. Black MA, Green DJ, Cable NT. Exercise prevents age-related decline in nitric-oxide-mediated vasodilator function in cutaneous microvessels. *J Physiol*. 2008;586:3511–3524.
24. Tounian P, Aggoun Y, Dubern B, Varille V, Guy-Grand B, Sidi D, Girardet JP, Bonnet D. Presence of increased stiffness of the common carotid artery and endothelial dysfunction in severely obese children: a prospective study. *Lancet*. 2001;358:1400–1404.
25. Beauloye V, Zech F, Tran HT, Clapuyt P, Maes M, Brichard SM. Determinants of early atherosclerosis in obese children and adolescents. *J Clin Endocrinol Metab*. 2007;92:3025–3032.
26. Chudek J, Wiecek A. Adipose tissue, inflammation and endothelial dysfunction. *Pharmacol Rep*. 2006;58(suppl):81–88.
27. Goran MI, Gower BA. Longitudinal study on pubertal insulin resistance. *Diabetes*. 2001;50:2444–2450.
28. Yamashita T, Sasahara T, Pomeroy SE, Collier G, Nestel PJ. Arterial compliance, blood pressure, plasma leptin, and plasma lipids in women are improved with weight reduction equally with a meat-based diet and a plant-based diet. *Metabolism*. 1998;47:1308–1314.
29. Balkestein EJ, van Aggel-Leijssen DP, van Baak MA, Struijker-Boudier HA, Van Bortel LM. The effect of weight loss with or without exercise training on large artery compliance in healthy obese men. *J Hypertens*. 1999;17:1831–1835.
30. Ziccardi P, Nappo F, Giugliano G, Esposito K, Marfella R, Cioffi M, D'Andrea F, Molinari AM, Giugliano D. Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year. *Circulation*. 2002;105:804–809.