Lifetime Risk Factors and Arterial Pulse Wave Velocity in Adulthood

The Cardiovascular Risk in Young Finns Study

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Abstract—Limited and partly controversial data are available regarding the relationship of arterial pulse wave velocity and childhood cardiovascular risk factors. We studied how risk factors identified in childhood and adulthood predict pulse wave velocity assessed in adulthood. The study cohort consisted of 1691 white adults aged 30 to 45 years who had risk factor data available since childhood. Pulse wave velocity was assessed noninvasively by whole-body impedance cardiography. The number of conventional childhood and adulthood risk factors (extreme quintiles for low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, body mass index, and smoking) was directly associated with pulse wave velocity in adulthood ($P=0.005$ and $P<0.0001$, respectively). In multivariable regression analysis, independent predictors of pulse wave velocity were sex ($P<0.0001$), age ($P<0.0001$), childhood systolic blood pressure ($P=0.002$) and glucose ($P=0.02$), and adulthood systolic blood pressure ($P<0.0001$), insulin ($P=0.0009$), and triglycerides ($P=0.003$). Reduction in the number of risk factors ($P<0.0001$) and a favorable change in obesity status ($P=0.0002$) from childhood to adulthood were associated with lower pulse wave velocity in adulthood. Conventional risk factors in childhood and adulthood predict pulse wave velocity in adulthood. Favorable changes in risk factor and obesity status from childhood to adulthood are associated with lower pulse wave velocity in adulthood. These results support efforts for a reduction of conventional risk factors both in childhood and adulthood in the primary prevention of atherosclerosis. (*Hypertension*. 2010;55:806-811.)

Key Words: cardiovascular health ▪ risk factors ▪ elasticity ▪ epidemiology ▪ pulse wave velocity

It is well recognized that atherosclerosis has its roots in childhood. Risk factors identified in childhood predict the occurrence of preclinical carotid atherosclerosis in adulthood. Risk factors have also been associated with decreased arterial elasticity in cross-sectional studies. We have demonstrated previously a link between youth risk factor exposure and decreased carotid elasticity in adulthood. Arterial pulse wave velocity (PWV) is commonly used as a marker of arterial stiffness. In various patient categories, including patients with hypertension, end-stage renal failure, and diabetes mellitus, PWV is an independent predictor of all-cause and cardiovascular mortality. Furthermore, aortic PWV is associated with higher cardiovascular mortality, coronary heart disease, and stroke among generally healthy older adults.

Previous observations concerning the relationship between risk factors identified in childhood/adolescence and arterial PWV in adulthood have been controversial. Li et al reported a direct correlation between childhood blood pressure and PWV in adulthood, whereas Oren et al did not find an association between adolescent blood pressure and adult PWV. To gain more insight on determinants of arterial PWV in adulthood, we measured PWV in 1691 white adults aged 30 to 45 years. These individuals were participants of the prospective Cardiovascular Risk in Young Finns Study for whom risk factor data were available since their childhood. In the present study, we have analyzed the associations of risk factors measured in childhood and adulthood with PWV assessed in adulthood.

Methods

Subjects
The first cross-sectional survey was conducted in 1980 for 3596 subjects aged 3 to 18 years. They were randomly selected from the national register. Four follow-up studies were conducted in 1983,
Clinical Characteristics
Height and weight were measured, and body mass index (BMI) was calculated. Skinfold thicknesses (in 1980, 1983, and 1986) were measured as described previously.7 Blood pressure was measured from the brachial artery with standard methods, as described previously.7 The mean of 3 measurements was used in the analysis. Smoking habits were ascertained with a questionnaire in subjects aged ≥12 years. Smoking was modeled as a dichotomous variable (smoking or nonsmoking). Smoking was defined as regular cigarette smoking on a weekly basis or more often in adolescents and adults.

Biochemical Analyses
Venous blood samples were taken after fasting for 12 hours. Standard methods were used for serum total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, insulin, and glucose concentrations (glucose only in 1986, 2001, and 2007). Low-density lipoprotein (LDL) cholesterol concentration was calculated by the Friedewald formula. Childhood C-reactive protein (CRP) was analyzed in 2005 from serum samples that were taken in 1980 and stored at −20°C. Details of all of the methods and analytic procedures have been reported previously.7,15–17

Arterial PWV Studies
We used a whole-body impedance cardiography device (CircMon, JR Medical Ltd) to determine PWV. CircMon includes whole-body impedance cardiography channel (ICG), distal impedance plethysmogram channel (IPG), and an ECG channel (Figure 1A). When the pulse pressure wave enters the aortic arch and the diameter of the aorta changes, the whole-body impedance decreases. The CircMon software measures the time difference between the onset of the decrease in impedance in the whole-body impedance signal and, later, the popliteal artery signal. The PWV can be determined from the distance and the time difference between the 2 recording sites (Figure 1B). The repeatability index and the reproducibility index were good (99% and 87%, respectively).18 A detailed description of the method and the validation study has been reported previously.19

Statistical Methods
Values for triglycerides, insulin, glucose, and CRP were log-transformed before analyses, because of skewed distributions. The comparisons between study participants and nonparticipants (subjects lost to follow-up or excluded) were performed using regression analysis adjusted with age for continuous variables and with the χ² test for categorical variables.

To study the effects of risk variables on PWV, we calculated age- and sex-specific z scores for each risk variable in each study year. Childhood risk variable load was assessed by calculating the average of z scores from years the 1980, 1983, and 1986. In these analyses, only measurements conducted at ages 3 to 18 years were used. Adulthood risk variable load was assessed by calculating the average of z scores in 2001 and 2007.

The univariate relationships between load variables and PWV in childhood and adulthood were examined by regression analysis. To examine whether sex modifies the associations between risk variables and PWV, we included sex×risk variable interaction terms in the regression models. To evaluate which childhood or adulthood risk variables were independently associated with PWV, we used stepwise multivariable regression analysis. In regression analysis we used a heart rate–specific z score for PWV.20

To examine the effect of multiple risk factors on PWV, we calculated a risk score, determined as the number of risk factors. Risk factors were defined as values at or above the age- and sex-specific 80th percentile for LDL cholesterol, systolic blood pressure (SBP), and BMI; at or below the 20th percentile for HDL cholesterol; and smoking (assessed in subjects ≥12 years of age). One-way ANOVA was used to compare the PWV values in the various groups.

In addition, we studied whether changes in the risk factor score and obesity status between childhood and adulthood were associated with PWV. In these analyses, the presence of ≥1 risk factor was considered an unfavorable risk factor status, and a cutpoint of age- and sex-specific 80th percentile for BMI was used in determining favorable or unfavorable obesity status. We used t tests to assess whether subjects with unfavorable status in childhood and favorable status in adulthood, favorable status in childhood and unfavorable in adulthood, and favorable status both in childhood and adulthood differed from those having an unfavorable status in childhood and in adulthood.

All of the analyses were performed with the SPSS for Windows (release 16.0.1, SPSS Inc). Statistical significance was inferred at a 2-tailed P value <0.05.
Results

The representativeness of the present study cohort was studied by comparing the characteristics at the original baseline study (1980) between the participants of the present study (n=1691) and nonparticipants (n=1905). There were more males than females among nonparticipants (P<0.0001) and they had higher SBP, BMI, and combined skinfold thickness than participants (P=0.0001, P=0.04, and P=0.049, respectively). There were no statistically significant differences in the levels of total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, insulin, and CRP between participants and nonparticipants (Table 1). The characteristics of the study subjects in 1980 and in 2007 are shown in Table 2.

Table 2. Baseline (1980) and Current (2007) Characteristics of Study Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>1980</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>10.5±5.0</td>
<td>37.5±5.0</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.28±0.87</td>
<td>5.01±0.9</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.56±0.30</td>
<td>1.20±0.43</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.42±0.79</td>
<td>3.22±0.85</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>112±12</td>
<td>120±14</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>17.8±2.9</td>
<td>25.7±4.5</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.60 (0.45 to 0.79)</td>
<td>1.32 (0.85 to 1.56)</td>
</tr>
<tr>
<td>Insulin, IU/L</td>
<td>7.74 (5.00 to 13.00)</td>
<td>6.46 (4.20 to 10.40)</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>0.29 (0.11 to 0.56)</td>
<td>0.87 (0.39 to 1.77)</td>
</tr>
<tr>
<td>Smoking prevalence, %*</td>
<td>17.7</td>
<td>23.0</td>
</tr>
<tr>
<td>PWV, m/s</td>
<td>8.13±1.5</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SD or geometric mean (25th to 75th percentiles) or percentages of subjects.

*In 1980, smoking data were gathered on subjects aged 12 to 18 years defined as regular cigarette smoking on a weekly basis or more often. Smoking was defined as smoking on a weekly basis or more often.
In childhood, as well as SBP, insulin, and triglycerides in adulthood, are independent predictors of PWV in adulthood. We also demonstrated that the number of risk factors identified in childhood and adulthood correlated directly with adult PWV. Moreover, we found that favorable changes in risk factor status and obesity status in adulthood were associated with lower PWV in adulthood.

Previous studies concerning the relationship between conventional risk factors in childhood/adolescence and PWV have been limited, and the results were partly controversial. In the Bogalusa Heart Study, Li et al. reported that SBP, BMI, and HDL cholesterol (inverse correlation) in childhood correlated with PWV in adulthood. They also showed that SBP, HDL cholesterol (inverse association), triglycerides, and smoking were cross-sectionally associated with PWV in young adulthood. In another cross-sectional study, Im et al. showed that mean blood pressure, BMI, sex, and total homocysteine levels were independently associated with PWV. In the Atherosclerosis Risk in Young Adults Study, no association between adolescent blood pressure and adult PWV was observed. This controversial result could be at least partly explained by differences in blood pressure measurement methods. Oren et al used only single measurement from school health records, whereas Li et al. and Im et al. measured blood pressure using the same protocol in the entire cohort.

In the present study, SBP load in childhood was an independent predictor of PWV in adulthood. This is consistent with reports mentioned earlier showing an association between arterial stiffness and cumulative burden of SBP since childhood. The acceleration of atherosclerosis, vascular smooth muscle hyperplasia, and hypertrophy, as well as the induction of oxidative stress in the arterial wall caused by elevated blood pressure, are probable underlying pathophysiological mechanisms behind this association. In addition to SBP, glucose in childhood was an independent predictor of PWV. This is in line with a previous finding that impaired fasting glucose had a strong association with high intima-media thickness, a marker of early atherosclerosis, in overweight children. In adulthood, SBP, insulin, and triglyceride levels were independent predictors of PWV. These risk factors have been shown to be directly associated with arterial PWV and elasticity in adults and are independent risk factors for ischemic heart disease.

Our findings show that the number of risk factors identified in childhood was significantly associated with increased PWV in adulthood. The present results are in line with earlier observations showing that the presence of multiple risk factors may lead to the acceleration of atherosclerosis in young people. In this study, we also demonstrated that the number of risk factors identified in adulthood correlated directly with adult PWV. Notably, the difference of adult PWV between subjects with no risk factors and subjects with ≥3 risk factors was 0.87 m/s. This difference is worthy of mention because Blacher et al. observed an all-cause mortality-adjusted odds ratio of 1.39 for each PWV increase of 1 m/s in patients with end-stage renal failure.

Observations from this analysis suggest that early life atherosclerotic effects can be modified by low risk factor levels in adulthood. In this study, high risk factor levels in
childhood were related to significantly decreased PWV in adulthood if combined with low risk factor levels in adulthood. Moreover, obese youths who became lean adults had slower PWV compared with persistently obese subjects. These observations support the concept that the vascular changes in childhood may improve over time with appropriate intervention.

A limitation of this study is the PWV measurement method, which is not yet widely used in epidemiological settings, apparently limiting comparability of the present finding with the observations from other cohorts. However, PWV values measured by CircMon are highly comparable to those measured by Doppler ultrasound method, indicating the generalizability of the present findings. In addition, ICG is very useful in epidemiological studies, because the method is easy, fast, operator independent and highly repeatable and reproducible, and the observed variability of the measured parameters is mainly physiological. Reference values for PWV measured with this method have also been published previously. Another potential limitation is the nonparticipation in the follow-up study. However, baseline risk factors in 1980 were mainly similar among participants and nonparticipants, with the exception of SBP, BMI, and combined skinfold thickness, which were slightly higher in nonparticipants. Thus, the present study cohort appears to be fairly representative of the original study population. Because our study cohort was racially homogenous, the generalizability of our results is limited to white European subjects. It is also important to remember that both the impact of baseline values and the impact of follow-up changes in risk factors could have been underestimated or overestimated because of possible regression dilution bias. Finally, observational studies cannot establish causality between cardiovascular risk factors and arterial stiffness.

**Perspectives**

There is accumulating and consistent evidence showing that conventional risk factors are predictive of cardiovascular risk later in life. However, favorable changes in risk factor status from childhood to adulthood may decrease the cardiovascular risk. These results provide support for the reduction of conventional risk factors both in childhood and adulthood.

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**Figure 3.** A, Relations between risk score in childhood (ages 3 to 18 years) and adulthood (ages 24 to 45 years) with PWV in adulthood (2007). Subjects having 0 risk factors were considered to have favorable status and those with ≥1 risk factors unfavorable status. B, Relations between BMI in childhood (ages 3 to 18 years) and adulthood (ages 24 to 45 years) with PWV in adulthood (2007). A cutpoint of the 80th percentile was used, classifying BMI as favorable or unfavorable status. P values from t tests. Bars represent mean ±95%CI. Values inside columns indicate the number of subjects in each group.
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Disclosures
None.

References
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