Conclusions—Young adults originating from eastern Finland have greater carotid IMT and lower brachial FMD than western Finns. Consistent with a hereditable component predisposing to or protecting from atherosclerosis, these differences accentuated when subjects’ family origin was taken into account.

Objective—People living in eastern Finland have ≈40% higher coronary heart disease mortality rates than western Finns. Whether this is because of genetic or environmental factors is unknown. We examined the effect of geographic family origin on subclinical atherosclerosis among young Finns.

Methods and Results—As part of a longitudinal follow-up study, we measured carotid intima-media thickness (IMT) in 19264 and brachial flow-mediated dilatation (FMD) in 2109 white adults, aged 24 to 39 years. Subjects from eastern Finland had greater IMT and lower FMD compared with western subjects. These differences accentuated when the subjects’ family origin (grandparents’ birthplace) was taken into account and remained significant after adjusting for several environmental factors. Among subjects with all grandparents born in eastern or western Finland, IMTs were (mean±SEM) 0.592±0.003 versus 0.565±0.005 mm (P<0.0001), respectively. The corresponding FMD values were 7.61±0.15% versus 8.75±0.26%; P<0.01. The number of grandparents born in eastern Finland was directly related to IMT (P<0.0001) and inversely to FMD (P<0.05).

Conclusions—Young adults originating from eastern Finland have greater carotid IMT and lower brachial FMD than western Finns. Consistent with a hereditable component predisposing to or protecting from atherosclerosis, these differences accentuated when subjects’ family origin was taken into account. (Arterioscler Thromb Vasc Biol. 2005; 25:392-398.)

Key Words: atherosclerosis ■ intima-media thickness ■ flow-mediated dilatation

Finland has high coronary heart disease (CHD) mortality, but the risk is unequally distributed within the country. People living in eastern Finland have ≈40% higher CHD mortality rates than those living in western Finland. In the Seven Countries Study in the 1960s and in the World Health Organization Monitoring Trends Determinants in Cardiovascular Disease (WHO MONICA) project in the 1980s, eastern Finnish men were leading the world statistics in CHD mortality. Higher rates for hypertension, smoking, and hypercholesterolemia in the eastern parts of the country were considered to explain the excess risk. Therefore, a national program, the North Karelia Project, was launched in the 1970s to influence diet and other lifestyles to lower risk factor levels. The results of this population strategy have been successful. From the 1970s, CHD mortality rates among working-age population have declined by 65% in the whole country. The differences in conventional risk factor levels between eastern and western Finland have become smaller because of adoption of similar lifestyle and diet. Despite these diminishing regional contrasts in risk factor levels and the overall decline in mortality, the gradient between the eastern and western parts of the country has remained virtually unchanged from the 1960s, with persistently higher mortality rates in the east. This may suggest that genetic differences exist in CHD susceptibility between the people of the eastern and western parts of the country. Although the Finnish population has previously been considered ethnically very homogenous, recent genetic analyses have provided evidence in support of 2 independent groups settling in Finland.

In population studies, noninvasive ultrasound methods can be used to assess early vascular changes related to atherosclerosis. Increased carotid intima-media thickness (IMT) is a structural marker of subclinical atherosclerosis. It correlates...
with risk factors,\textsuperscript{9–11} relates to the severity of coronary artery disease,\textsuperscript{12} and predicts cardiovascular events in populations.\textsuperscript{13} The brachial artery flow-mediated dilation (FMD) is a functional marker of endothelial health. It has been shown to occur mainly in response to endothelial release of NO.\textsuperscript{14} Brachial FMD responses correlate with coronary endothelial function\textsuperscript{15} and predict future cardiovascular events in patient groups.\textsuperscript{16}

The Cardiovascular Risk in Young Finns is a follow-up study of atherosclerosis precursors in children and young adults. The study was planned in the 1970s\textsuperscript{17} and a main objective was to provide insight for the east-west difference in cardiovascular risk within Finland.\textsuperscript{18} The latest follow-up study was conducted in 2001\textsuperscript{11,19} and included an ultrasound examination to assess carotid IMT and brachial FMD. We hypothesized that the geographic family origin of young adults in Finland would have influence on these preclinical vascular changes.

### Methods

For a more detailed description, please see online data supplement, available at http://atvb.ahajournals.org.

#### Subjects

The Young Finns Study was launched in 1980 and has been performed in 5 centers in Finland. The east-west division was made according to the epidemiologic borderline for CHD (Figure 1). A total of 3596 subjects, 1753 from east and 1843 from west, participated in 1980\textsuperscript{18} (80% of those invited). In 2001, we re-examined 2264 of these individuals (now aged 24 to 39 years).\textsuperscript{19} Subjects gave written informed consent, and the study was approved by local ethics committees.

#### Clinical Characteristics

Height and weight were measured, and body mass index (BMI) was calculated. Blood pressure measurement values were obtained from 3-year-olds with an ultrasound device and from the older children and adolescents with a standard mercury sphygmomanometer.\textsuperscript{20} In 2001, a random zero sphygmomanometer was used.

Standard methods were used for serum lipids. Plasma high sensitive C-reactive protein (CRP) concentrations were analyzed by latex turbidometric immunoassay (Wako Chemicals GmbH). Birth weight, socioeconomic status (number of parental school years in 1980, number of own school years in 2001), alcohol use, smoking, physical activity, and diet (butter use, including butter-based mixtures, and daily use of vegetables) were acquired using questionnaires. Physical activity index was calculated by assessing the duration, intensity, and frequency of physical activity. Daily intake of energy and macronutrients were computed based on the 48-hour recall interviews (from half of the cohort). Details of methods have been presented previously.\textsuperscript{11,19,21}

#### Ultrasound Imaging

Ultrasound studies were performed using Sequoia512 ultrasound mainframes (Acuson). Carotid IMT was measured in 2264 subjects as described previously.\textsuperscript{11} The between-visit coefficient of variation (CV) of IMT measurements was 6.4%.\textsuperscript{11}

Brachial artery studies were performed successfully for 2109 subjects as reported.\textsuperscript{22} The 3-month between-visit CV was 3.2% for brachial artery diameter and 26.0% for FMD.

#### Analysis Design

Eastern and western subjects were first compared according to their baseline origin (1980) and current residency (2001). Then, the effect of family origin was assessed by comparing subjects with all 4 grandparents born in eastern or western Finland (n=1131). Finally, we correlated IMT and FMD values with the number of grandparents born in eastern Finland (n=1720; Figure I, available online at http://atvb.ahajournals.org).

Grandparents’ birthplaces were inquired in a questionnaire in 1980. Internal migration in Finland was sparse in the beginning of the 20th century and has increased since the 1920s.\textsuperscript{23} Therefore, we used grandparents’ birthplace to assess subjects’ geographic family origin.

#### Statistical Methods

Comparisons in clinical characteristics were performed using $t$ test for continuous variables and $\chi^2$ test for categorical variables. The comparisons in ultrasound variables were performed with linear regression analysis adjusted for age (and for brachial diameter when comparing FMD). To study whether the east-west difference is independent of current risk factors and childhood risk factors identified 21 years earlier, we performed stepwise multivariate regression analysis with age and sex forced into the models. The relationships between the number of grandparents born in east and ultrasound variables were examined with linear regression analysis adjusted for age and sex (in FMD also for baseline brachial diameter).

Values for carotid IMT, triglycerides, and CRP were log\textsubscript{10}-transformed before analyses because of skewed distributions. To ease the interpretation of the results, mean and $\beta$-values are shown for nontransformed values. Statistical tests were performed with SAS, and statistical significance was inferred at a 2-tailed $P$ value $<0.05$.  

---

**Figure 1.** The 5 cities participating in the study and the east-west division of Finland according to CHD risk (thick line). Age-standardized mortality rates for CHD between 1997 to 2001 are given for the various provinces of Finland. The figures express the indices based on a national average rate of 100.

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In 1980, smoking habits were inquired of subjects 12 years of age. In adulthood, eastern women had significantly lower smoking rates in childhood. In adulthood, eastern men had higher total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, blood pressure levels, but the difference in total cholesterol level was no longer significant. Compared with western women, eastern women had higher total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, blood pressure levels, and lower smoking rates in childhood. In adulthood, eastern women had higher high-density lipoprotein (HDL) cholesterol and blood pressure levels compared with western women.

### Results

#### Biological Risk Markers

Adult (year 2001) and childhood (year 1980, baseline) characteristics of study subjects are shown in Table 1 according to their baseline origin. Compared with western men, eastern men had higher total cholesterol and diastolic blood pressure levels in childhood. In adulthood, there was a significant difference in blood pressure levels, but the difference in total cholesterol level was no longer significant. Compared with western women, eastern women had higher total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, blood pressure levels, and lower smoking rates in childhood. In adulthood, eastern women had higher high-density lipoprotein (HDL) cholesterol and blood pressure levels compared with western women.

#### Table 1. Characteristics of Study Subjects According to Baseline Origin

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>East</td>
<td>West</td>
</tr>
<tr>
<td>n</td>
<td>499</td>
<td>519</td>
</tr>
<tr>
<td>Baseline risk factors (1980)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>10.6±5.1</td>
<td>10.7±4.9</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.08±0.83</td>
<td>4.97±0.79*</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>3.25±0.75</td>
<td>3.16±0.69</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.49±0.30</td>
<td>1.47±0.29</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.76±0.28</td>
<td>0.75±0.30</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>17.8±2.85</td>
<td>18.1±3.41</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>114.3±13.4</td>
<td>113.2±12.8</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>70.8±9.4</td>
<td>67.2±10.0****</td>
</tr>
<tr>
<td>Current risk factors (2001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>31.6±5.1</td>
<td>31.7±4.9</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.30±1.03</td>
<td>5.22±1.05</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>3.45±0.93</td>
<td>3.38±0.93</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.17±0.29</td>
<td>1.15±0.27</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.52±0.85</td>
<td>1.54±1.11</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.7±3.89</td>
<td>25.8±4.22</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>123.2±11.9</td>
<td>120.0±12.5****</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>74.6±10.8</td>
<td>72.0±11.3***</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>1.49±2.83</td>
<td>1.53±3.76</td>
</tr>
<tr>
<td>Daily smokers (%)</td>
<td>33.3</td>
<td>26.8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>178.5±6.21</td>
<td>180.4±6.72****</td>
</tr>
<tr>
<td>School years</td>
<td>14.4±3.2</td>
<td>14.1±3.1</td>
</tr>
<tr>
<td>Physical activity index</td>
<td>13.4±4.3</td>
<td>12.9±4.3</td>
</tr>
<tr>
<td>Alcohol consumption (doses per week)</td>
<td>8.7±11.1</td>
<td>8.8±9.4</td>
</tr>
<tr>
<td>Vegetable use (daily eaters, %)</td>
<td>29.0</td>
<td>35.0*</td>
</tr>
<tr>
<td>Butter users (%)</td>
<td>74.2</td>
<td>57.7****</td>
</tr>
</tbody>
</table>

Plus-minus values are mean±SD.

In 1980, smoking habits were inquired of subjects ≥12 years of age.

*P<0.05; **P<0.01; ***P<0.001; ****P<0.0001.
Lifestyle
Eastern men and women used butter more frequently and ate vegetables less frequently in childhood. In adulthood, the difference in vegetable consumption was observed only in women, and butter usage was more common among western than eastern women in 2001 (Table 1). In childhood, eastern men had greater daily intake of saturated (20.3±3.9% versus 19.5±3.9% of daily energy [E%]; \( P = 0.01 \)) and smaller intake of polyunsaturated fat (4.2±1.8 E% versus 4.8±1.9 E%; \( P = 0.0002 \)). In adulthood, these differences were no longer observed, but eastern men had higher carbohydrate intake (45.5±7.4 E% versus 44.0±7.5 E%; \( P = 0.03 \)). Among women, eastern subjects had smaller intake of polyunsaturated fat (4.0±1.5 E% versus 4.4±1.8 E%; \( P = 0.002 \)) in childhood, but in adulthood, no differences in nutrient intake were observed.

Carotid IMT and Brachial FMD
Subjects with baseline origin in eastern Finland had greater IMT than western subjects (Table 1; Figure 2). This difference accentuated when family origin was taken into account. When subjects were compared according to their current residency, the east-west difference was slightly attenuated (Figure 2). The effects of baseline and family origin on IMT remained significant after adjustments for childhood and current environmental factors (Table 2). A direct dose-response relationship was seen between the number of grandparents born in eastern Finland and carotid IMT (Figure 3).

A significant east-west difference was seen in brachial FMD when subjects were compared according to their baseline origin, and the difference accentuated when family origin was taken into account (Figure 2). The effect of family east-west origin on FMD remained significant after adjustments for childhood and current risk factors (Table 2). An inverse relationship was seen between the number of grandparents born in eastern Finland and brachial FMD (Figure 3).

During the ischemic phase of the FMD test, vasoconstriction may occur in subjects at risk, whereas in normal subjects, there may be a trend toward vasodilatation. In our cohort as a whole, a minor vasodilatation of the brachial artery was observed during cuff occlusion (Table 1), with no east-west difference in absolute or relative diameter change during the ischemic phase (\( P \) for both >0.05).

There is a loss of \( \leq 17\% \) of individuals in multivariate models adjusted for childhood risk factors (Table 2). The main reason for this is that data on birth weight (n=1913) were collected in the second follow-up in 1983. Therefore, the multivariate models were examined in 3 different ways: (1) as shown in table 2; (2) in the same cohort as in Table 2 but without birth weight data; and (3) in the total cohort without birth weight data. In all 3 different analyses, the east-west differences in IMT and FMD remained essentially similar.

Effect of Blood Pressure on East-West Difference in IMT and FMD
Because eastern subjects have higher blood pressure values, and blood pressure is a correlate for IMT and FMD, we made a further subgroup analysis to examine whether the east-west difference in ultrasound variables is influenced by blood pressure values. To study this, IMT and FMD data were analyzed after exclusion of subjects with high blood pressure levels (above age- and sex-specific 75th percentile). The east-west difference between subjects with all grandparents from east or west remained highly significant in IMT (\( P = 0.0002 \)) and FMD (\( P = 0.0003; P = 0.0008 \) after adjustment for brachial diameter) in this subgroup without significant differences in blood pressure values between eastern and western subjects (\( P = 0.23; \) Table I, available online at http://atvb.ahajournals.org).

Discussion
We found significant differences among healthy young adults in markers of subclinical atherosclerosis between east and west.
TABLE 2. Multivariate Model of the Relationships Between Baseline Origin (Place of Living in 1980) or Family Origin (all Grandparents Born in East or West Finland) With Carotid IMT and Brachial FMD, Adjusted for Current or Childhood Environmental Factors

<table>
<thead>
<tr>
<th>Explanatory variable</th>
<th>Childhood Risk Factors</th>
<th>Current Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Origin</td>
<td>Family Origin</td>
</tr>
<tr>
<td></td>
<td>n=1879</td>
<td>n=948</td>
</tr>
<tr>
<td>Carotid IMT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eastern origin</td>
<td>0.020±0.004***</td>
<td>0.021±0.006***</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.020±0.004***</td>
<td>0.022±0.006***</td>
</tr>
<tr>
<td>Age (years)</td>
<td>−0.001±0.001</td>
<td>0.003±0.001***</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.008±0.002***</td>
<td>0.012±0.003***</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>0.005±0.003*</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.007±0.003*</td>
<td>0.011±0.002***</td>
</tr>
<tr>
<td>Height</td>
<td>0.023±0.007***</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td>0.010±0.005*</td>
</tr>
<tr>
<td>Birth weight</td>
<td>−0.007±0.002**</td>
<td></td>
</tr>
<tr>
<td>Butter use</td>
<td>0.008±0.004*</td>
<td></td>
</tr>
<tr>
<td>R² whole model (eastern origin)</td>
<td>14% (1.5%)</td>
<td>11% (1.6%)</td>
</tr>
<tr>
<td>Brachial FMD</td>
<td>n=1769</td>
<td>n=879</td>
</tr>
<tr>
<td>Explanatory variable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eastern origin</td>
<td>−0.38±0.20</td>
<td>−0.82±0.30**</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.94±0.30**</td>
<td>0.47±0.41</td>
</tr>
<tr>
<td>Age (years)</td>
<td>−0.03±0.03</td>
<td>−0.02±0.04</td>
</tr>
<tr>
<td>Brachial diameter</td>
<td>−1.93±0.15**</td>
<td>−1.51±0.21***</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>0.20±0.10*</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.56±0.14***</td>
<td>0.60±0.19**</td>
</tr>
<tr>
<td>Birth weight</td>
<td>0.29±0.10**</td>
<td>0.35±0.14*</td>
</tr>
<tr>
<td>School years</td>
<td>−0.25±0.09**</td>
<td>−0.40±0.13**</td>
</tr>
<tr>
<td>Butter use</td>
<td></td>
<td>0.46±0.21*</td>
</tr>
<tr>
<td>R² whole model (eastern origin)</td>
<td>14% (0.2%)</td>
<td>13% (0.9%)</td>
</tr>
</tbody>
</table>

Initial stepwise regression models included current or childhood LDL-cholesterol, HDL-cholesterol, triglycerides, systolic blood pressure, BMI, height, study years (parents in childhood, own in current models), vegetable consumption, and butter use. In addition, smoking, physical activity index, and alcohol consumption were included in current models and birth weight in childhood model. Age and sex were forced into models.

†Values are regression coefficients±SE expressed in millimeters (IMT) or percent units (FMD) for an SD change in continuous variables.

*P<0.05; **P<0.01; ***P<0.001.

west Finland. These differences were independent of environmental factors and accentuated when taking into account the subjects’ family origin. Our results thus suggest that hereditable factors have a role in explaining the east-west difference in CHD mortality within Finland.

Regional differences in subclinical markers of atherosclerosis have been studied previously by Jartti et al., who found that middle-aged men born in eastern Finland had greater carotid IMT compared with men born in western Finland. Our study showing higher IMT in young adults originating from east Finland confirms these findings. We could also demonstrate lower FMD, indicating reduced endothelial function in eastern subjects. Vascular endothelium protects arteries against development of atherosclerosis, therefore, these regional phenotype differences in FMD may provide insight for the variations in the atherosclerosis susceptibility between eastern and western subjects.

Our findings are also interesting in light of the previous pathological studies that have shown greater intimal thickening in coronary arteries in infants who have died and whose families originated from eastern Finland. These early morphological alterations seen in infants of eastern origin may thus represent a difference in the vulnerability on the vascular wall to extrinsic deleterious factors and point to a morphological manifestation of hereditary predisposition to CHD. Together, these findings support the theory that eastern and western Finns have a different genetic origin. A number of considerations have led to a suggestion that genetic differences might exist between the people of the western and eastern parts of the country. Besides CHD mortality distribution, this dualism is supported by anthro-
In the present study, traditional risk factors did not correlate very strongly with brachial FMD. We reported recently in detail the interrelations between traditional risk factors and FMD in the Young Finns cohort. We found that FMD was directly related to HDL-cholesterol and BMI and inversely with systolic blood pressure. We could not demonstrate a significant correlation between FMD and LDL-cholesterol, nor between FMD and smoking. The direct correlation between FMD and BMI was an unexpected finding. During closer examination, this relationship seemed to be curvilinear, so that BMI was directly related to enhanced FMD only within nonobese range. The relationship was not explained by brachial artery diameter or any measured risk factor.

In childhood, eastern subjects had higher cholesterol and blood pressure levels compared with western subjects. In adulthood, the east-west difference in serum cholesterol concentration was clearly diminished, but the difference in blood pressure levels was similar as in childhood. The diminishing regional contrast in serum cholesterol concentration is consistent with the changes in the dietary preferences between east and west Finland also observed in the present study (eg, reduction in butter use and saturated fat intake in the eastern subjects). Genetic differences have been suggested to partly explain regional differences in serum cholesterol concentrations within Finland. Therefore, the present observations may be in line with the notion that changes in environmental conditions may mask the effect of the genetic determinants.

**Study Limitations**

Subjects’ family origin was assessed according to their grandparents’ birthplaces acquired by questionnaire. However, because most of the grandparents were born around 1920 and the migration between areas as large as the division used in this study was scarce before the 1920s, we believe that grandparents’ birthplaces reflect reliably the origin of the ancestors of the study subjects.

We found large variation in FMD measurements (CV 26%) but small variation in brachial artery diameter measurements (CV 3%). Thus, much of the long-term variation of FMD is attributable to physiological fluctuation in endothelial function and not to measurement error. We did not measure endothelium-independent nitrate-mediated vasodilatation that is often included as a control test for the FMD test to ensure that the decreased FMD capacity observed is a consequence of endothelial dysfunction not a reflection of underlying smooth muscle dysfunction. However, nitrate-mediated arterial relaxation also seems to attenuate in the process of atherosclerosis.

**Figure 3.**

**a.** Carotid IMT (mean±SEM) according to the number of grandparents born in eastern Finland (n=1720). **b.** Brachial FMD (mean±SEM) according to the number of grandparents born in eastern Finland (n=1600). Linear trend was examined with regression analysis after adjustment for age, gender, and FMD for brachial diameter.

**P for trend < 0.0001**

**P for trend = 0.022**

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Young and healthy individuals with a positive family history of CHD, but without other major risk factors, have evidence of increased IMT and decreased FMD. We found increased IMT and decreased FMD in a population group of young adults originating from a geographic area characterized by excess CHD risk. These observations indicate that a genetic predisposition for CHD influences arterial structure and function before manifestation of CHD. The specific genetic determinants of IMT and FMD are inadequately known. We are currently conducting genetic analysis in this cohort in an attempt to provide more specific insight for the east-west difference.
Conclusions

We conclude that irrespective of risk factors levels, young adults originating from eastern Finland have higher carotid IMT and lower brachial FMD than those originating from western Finland. Consistent with a hereditable component predisposing or protecting from atherosclerosis, these differences accentuated when the subjects’ family origin was taken into account. These results support the dual-origin theory of Finns and suggest that genetic factors have a role in explaining the east-west difference in CHD mortality within Finland.

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References


Geographic Origin as a Determinant of Carotid Artery Intima-Media Thickness and Brachial Artery Flow-Mediated Dilation: The Cardiovascular Risk in Young Finns Study
Pesonen and Olli T. Raitakari

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Geographic origin as a determinant of carotid artery intima-media thickness and brachial artery flow-mediated dilation. The Cardiovascular Risk in Young Finns Study.

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Supplement to be published on-line only

METHODS

Subjects

The Young Finns Study was launched in 1980 and has been carried out in five centers in Finland. The east-west division was made according to the epidemiologic borderline for CHD (Figure 1). Altogether 4,326 children and adolescents aged 3, 6, 9, 12, 15 and 18 years were randomly chosen from the national register in the study areas to include subjects from eastern (N=2,143) and western (N=2,183) parts of the country. A total of 3,596 subjects, 1,753 from east and 1,843 from west, participated in 1980. In 2001, we re-examined 2,264 of these individuals (now aged 24 to 39 years). Between 1980 and 2001, 37 subjects had moved from west to east, and 283 subjects from east to west. Eastern dropouts had higher baseline (in 1980) smoking prevalence than participants. Otherwise, both in eastern and western subjects, baseline risk factor levels in this follow-up cohort were similar to those who had dropped out from the study. Subjects gave written informed consent and the study was approved by local ethics committees.

Clinical characteristics

Height and weight were measured, and body mass index (BMI) was calculated. Due to difficulties in blood pressure measurements in small children, blood pressure values were obtained from 3-year-olds with an ultrasound device, and from the older children and adolescents with a standard
mercury sphygmomanometer\textsuperscript{3}. In 2001, a random zero sphygmomanometer was used. The Arteriosonde 1020 has been found to be a valid device in the assessment of children’s systolic blood pressure values\textsuperscript{4}, which were included in the multivariate models. We also repeated all analysis after exclusion of 3-year-olds from the analyses. As this did not change the results, the blood pressure data have been pooled together.

Venous blood samples were drawn after an overnight fast. Standard methods were used for serum total cholesterol, triglycerides and HDL-cholesterol. LDL-cholesterol concentration was calculated with Friedewald formula. Plasma high sensitive C-reactive protein concentrations were analyzed by latex turbidometric immunoassay (Wako Chemicals GmbH, Neuss, Germany). Birth weight, socioeconomic status (number of parental school years in 1980, number of own school years in 2001), alcohol use, smoking, physical activity and diet (butter use, including butter based mixtures, and daily use of vegetables) were acquired using questionnaires. Physical activity index was calculated by assessing the duration, intensity and frequency of physical activity. Daily intakes of energy and macronutrients were computed based on the 48-h recall interviews (from half of the cohort). Details of methods have been presented elsewhere\textsuperscript{2,5,6}.

**Ultrasound imaging**

Ultrasound studies were performed using Sequoia512 ultrasound mainframes (Acuson, Mountain View, CA, USA). Carotid IMT was measured in 2,264 subjects, as previously described\textsuperscript{5}. The between-visit coefficient of variation (CV) of IMT measurements was 6.4\%\textsuperscript{5}.

Brachial artery studies were performed successfully for 2,109 subjects, as reported\textsuperscript{7}. To assess FMD, the left brachial artery diameter was measured at rest and during reactive hyperemia. Increased flow was induced by inflation of a blood pressure cuff placed around the forearm to a pressure of 250mmHg for 4.5min, followed by a release. Three measurements of arterial diameter were performed at end-diastole at a fixed distance from an anatomic marker at rest and 40, 60 and
80 seconds after cuff release. The 3-month between-visit CV was 3.2% for brachial artery diameter, and 26.0% for FMD.

**Analysis design**

To examine the east-west difference in the markers of subclinical atherosclerosis, the study subjects were grouped as shown in Figure I. Eastern and western subjects were first compared according to their baseline origin (1980) and current residency (2001). Then, the effect of family origin was assessed by comparing subjects with all four grandparents born in eastern or western Finland (N=1,131). Lastly, we correlated IMT and FMD values with the number of grandparents born in eastern Finland (N=1,720).

Grandparents’ birthplaces were enquired in a questionnaire in 1980. Internal migration in Finland was sparse in the beginning of the 20th century and has increased since 1920’s. Therefore, we used grandparents’ birthplace to assess subjects’ geographic family origin.

**Statistical methods**

The east-west comparisons in clinical characteristics were performed using $t$-test for continuous variables and $\chi^2$-test for categorical variables. The comparisons in ultrasound variables were performed with linear regression analysis adjusted for age (and for brachial diameter when comparing FMD). To study whether the east-west difference is independent of current risk factors and childhood risk factors identified 21 years earlier, we performed stepwise multivariate regression analysis with age and sex forced into the models. In the multivariate analyses, we included risk variables that have been suggested to explaining the east-west difference in CHD mortality. The relationships between the number of grandparents born in east and ultrasound variables were examined with linear regression analysis adjusted for age and sex (in FMD also for baseline brachial diameter).
Values for carotid IMT, triglycerides and CRP were log_{10}-transformed prior to analyses due to skewed distributions. To ease the interpretation of the results, mean and $\beta$-values are shown for non-transformed values. All analyses were repeated after excluding subjects with diabetes (1.0%), and those taking lipid-lowering (0.3%) or antihypertensive medications (3.1%), with similar results. The statistical tests were performed with SAS and statistical significance was inferred at a 2-tailed P-value <0.05.
REFERENCES


Figure I.

Study design and the number of subjects included in analysis.
Table I. Carotid IMT, brachial FMD and systolic blood pressure (SBP) among subjects with age and sex-specific SBP-values at and below 75th percentile. Subjects are grouped by family origin (i.e. all grandparents born in east or west).

<table>
<thead>
<tr>
<th></th>
<th>EAST</th>
<th>WEST</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>580</td>
<td>239</td>
<td></td>
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<tr>
<td>Systolic blood pressure</td>
<td>112.3±9.0</td>
<td>111.5±9.4</td>
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<tr>
<td>Carotid IMT</td>
<td>0.585±0.091</td>
<td>0.560±0.085</td>
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<tr>
<td>Brachial FMD</td>
<td>7.50±4.29</td>
<td>8.74±4.38</td>
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