Population-Based Twin Study of the Effects of Migration From Finland to Sweden on Endothelial Function and Intima-Media Thickness


Abstract—Finnish men have higher coronary heart disease (CHD) mortality than Swedish men do. To assess the impact of migration to a country with lower CHD mortality on subclinical atherosclerosis, we measured early functional and structural atherosclerotic vascular changes in twins discordant for migration from Finland to Sweden. Conventional CHD risk factors, flow-mediated dilatation (FMD) of the brachial artery, carotid intima-media thickness, and carotid artery compliance were measured in 74 male twin pairs (20 monozygous, 54 dizygous), aged 42 to 69 years, in which co-one twin had migrated more than 20 years ago permanently to Sweden. There were no significant differences in CHD risk factors except for diastolic blood pressure and body fat percentage, which were higher in Sweden. In all subjects, mean FMD was non-significantly higher in Sweden (5.7±4.3% vs 4.9±4.2%, P=0.22), but in monozygous twins the difference in FMD was highly significant (7.2±4.4 vs 3.7±2.9%, P=0.003). There was no significant difference in intima-media thickness or carotid artery compliance between Sweden and Finland. We conclude that in Finnish monozygous twins the endothelial function is better among the twins that have migrated to a country with lower CHD prevalence. (Arterioscler Thromb Vasc Biol. 2002;33:832-837.)

Key Words: higher coronary heart disease ■ flow-mediated dilatation ■ carotid intima-media thickness

Coronary heart disease (CHD) mortality has been higher among Finnish men than in other Nordic countries. The age-adjusted relative risk of death from ischemic heart disease is 1.5 in Finnish compared with Swedish men. The reason for this difference is unknown. Economic recession in Finland in the 1960s and 1970s resulted in a migrant population of ∼240,000 Finnish-born persons permanently living in Sweden. Among Finnish migrants who have lived more than 20 years in Sweden, the risk of myocardial infarction is near to that in the native Swedish population. In a recent study, overall mortality was significantly lower in male Finnish migrants after 20 years of residency in Sweden compared with mortality rates in Finland. This suggests that environmental factors could explain the changes in mortality rate over time in migrant populations. Migration studies are natural experiments of the effects of how environment influences the risk of developing various diseases. Several studies have shown that migration to a country with higher CHD mortality is associated with an increased incidence of atherosclerotic diseases among migrants. For example, there was a 50% increase in CHD risk in Japanese men after moving to Hawaii and an additional 50% increment in the risk after migration to United States. Furthermore, the adverse effect of westernization and urbanization on CHD risk factors has been observed in populations living in isolated areas where the CHD prevalence has traditionally been low. Within populations, it is also recognized that there is substantial familial aggregation of CHD, and much of this familial aggregation is genetic. Study of twin pairs discordant for a putative exposure is a powerful design for testing the relationship between exposure and CHD, as the genetic component in CHD can be controlled.

This is the first study that has assessed the impact of migration from a country with high CHD prevalence to a country with lower CHD prevalence on subclinical markers of atherosclerosis. As CHD mortality rates are lower in Sweden compared with Finland, we tested the hypothesis that Finnish migrants to Sweden would have less evidence of subclinical atherosclerotic disease than their co-twins in Finland. Another objective was to assess whether the possible differences in subclinical markers of atherosclerosis, ie, endothelial function, intima-media thickness (IMT) and carotid artery compliance (CAC), would be explained by possible differences in conventional CHD risk factors.
Methods

Subjects
The Finnish Twin Cohort includes all pairs (4307 monozygous [MZ] pairs, 9581 same-sex dizygous [DZ] pairs) of adult Finnish twins born before 1958 and alive in 1975. For the present study, the inclusion criteria were the following: male gender, one co-twin had lived permanently in Finland for at least 20 years and the other co-twin had lived permanently in Finland, age ≤70 years, and no history of cancer. In all, there were 194 twin pairs eligible for participation. We aimed to study 100 twin pairs. First, all MZ pairs and pairs originated from east Finland were selected for the study. Additional pairs from west Finland were selected randomly. A total of 122 pairs were selected, of which 19 could not be contacted. In addition, there were two pairs in which at least one in the pair had recently died, and one pair was found not to be biological twins. The remaining 100 pairs were sent a letter of invitation to take part in the physical examination. The final study population consisted of 76 male twin pairs (age, 54±7 years; range, 42 to 69 years; 76% participation rate) of which 21 were MZ pairs (age, 53±7 years; range, 42 to 66 years), and 55 DZ pairs (age, 55±7 years; range, 43 to 69 years). To confirm zygosity, DNA samples from all participants of the present study were typed using 12 highly polymorphic markers at the paternity testing laboratory of the National Public Health Institute.

Both twins of a pair were examined on the same day. The twin resident in Sweden arrived in Finland by plane the night before the examination. Both twins spent the night before the examination in the dormitory (Social Insurance Institution, Turku, Finland). After an overnight fast, venous blood samples were drawn, and a clinical examination was performed. After an oral glucose tolerance test was performed, the subjects ate an early light lunch containing approximately 450 kcal. The meal varied daily but was always the same for both twin brothers. One to 2 hours after the lunch, endothelial function, IMT, and CAC were measured, and thereafter, an exercise capacity test and stress echocardiography were performed. Because there is a 1-hour time zone difference between Sweden and Finland, the co-twin living in Finland was in every case examined first and the co-twin living in Sweden was studied approximately 1 hour later.

The studies were conducted according to the guidelines of the Helsinki declaration, and the study protocol had been approved by the local Ethics Committee. All subjects gave their informed consent.

Clinical Examination
Weight was measured with a digital scale, with an accuracy of 0.1 kg, and height was measured by a wall-mounted stadiometer with a 0.5-cm accuracy. Waist and hip circumferences were measured twice with the accuracy of 1.0 mm, and the mean of two measurements was used. Body mass index (BMI) was calculated as weight/height$^2$. The amount of body fat was determined by bioelectric impedance method (BIA-101A/S, Clemens). Blood pressure was measured at every load increment stage. Mean workload attained during the last 4 minutes of the test ($W_{max}$) was used as an indicator of exercise capacity. Transthoracic echocardiography was performed to detect myocardial ischemia (for detailed description of the ultrasound methods please see http://atvb.ahajournals.org). History of CHD was considered positive if a subject had a history of myocardial infarction or if a subject reported that he had been previously diagnosed with CHD. The subjects were grouped as having CHD if they had either a positive history of CHD or an ischemic finding on stress echocardiography. Four subjects with no history of CHD were defined as having CHD after stress echocardiography. Only two subjects had typical angina pectoris during the bicycle test, and they both had positive history of CHD.

Leisure time physical activity was assessed by using a questionnaire that included questions on average intensity (in categories equivalent to walking, jogging, or running), frequency, and duration of leisure time physical activities. From these data, a combined index to estimate metabolic equivalents (METs) was calculated. Leisure time physical activity index correlated directly ($r=0.24, P=0.01$) with the exercise capacity assessed in the treadmill test.

Statistical Methods
The results are expressed as mean±SD, unless stated otherwise. Because the data were derived from twin pairs discordant for migration, statistics for pairwise data were used. Thus, the equality of means and proportions between brothers was tested by using a paired $t$ test for continuous variables and McNemar’s test for dichotomous variables. All data analyses were done with SAS (SAS Institute) and STATA (STATA).

Because twin samples have traditionally been used to estimate the relative roles of genetic factors and environment, heritability ($h^2$) or the proportion of variance attributed to genetic variance was approximated according to the following formula: $h^2=2×(r_{MZ}−r_{DZ})$, where $r_{MZ}$ is the intraclass correlation for MZ pairs and $r_{DZ}$ for DZ pairs. Formal genetic modeling was not undertaken due to limited sample size and the selection procedures.

Results
The characteristics are presented in Table 1 (all twins) and Table 2 (MZ pairs). When analyzed for either all men together or MZ pairs separately, there were no differences in study variables, except in fat percentage and diastolic blood pressure, which were higher in co-twins living in Sweden.
TABLE 2. Background Data and Biochemical Markers of 20 Identical Twin Pairs Discordant for Migration

<table>
<thead>
<tr>
<th>Country of Residence</th>
<th>Finland</th>
<th>Sweden</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of CHD</td>
<td>2 (10)</td>
<td>1 (5)</td>
<td>0.56</td>
</tr>
<tr>
<td>Echo estimated CHD</td>
<td>0</td>
<td>2 (10)</td>
<td>0.16</td>
</tr>
<tr>
<td>CHD</td>
<td>2 (10)</td>
<td>2 (10)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (25)</td>
<td>5 (25)</td>
<td>1.0</td>
</tr>
<tr>
<td>Any medication</td>
<td>6 (30)</td>
<td>8 (40)</td>
<td>0.32</td>
</tr>
<tr>
<td>Cholesterol medication</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 (10)</td>
<td>2 (10)</td>
<td>1.0</td>
</tr>
<tr>
<td>Leisure time physical activity (METs)</td>
<td>1.01±0.95</td>
<td>1.58±1.99</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Smoking

Non-smoker | 2 (10) | 3 (15) | ... |
Ex-smoker  | 9 (45) | 9 (45) | ... |
Occasional smoker | 1 (5)  | 2 (10) | ... |

Smoker | 8 (40) | 6 (30) | ... |

BMI, kg/m² | 25.4±3.5 | 25.5±3.1 | 0.86|
Waist circumference, cm | 92.8±10.2 | 93.3±7.4 | 0.82|
Waist-to-hip ratio | 0.961±0.065 | 0.971±0.046 | 0.48|
Fat percentage, % | 21.6±4.9 | 23.6±3.3 | 0.06|
Systolic BP, mm Hg | 130±19 | 132±13 | 0.66|
Diastolic BP, mm Hg | 79±10 | 84±8 | 0.004|
Exercise capacity, Wlast4 | 166±32 | 178±53 | 0.40|
Cholesterol, mmol/L | 5.67±0.76 | 5.63±1.11 | 0.83|
HDL-cholesterol, mmol/L | 1.48±0.41 | 1.42±0.36 | 0.58|
LDL-cholesterol, mmol/L | 3.54±0.75 | 3.49±1.01 | 0.79|
Triglycerides, mmol/L | 1.41±0.34 | 1.59±0.87 | 0.32|
Fasting glucose, mmol/L | 5.83±1.13 | 6.29±2.18 | 0.27|
Glucose after 2 hours, mmol/L | 6.91±3.14 | 6.59±1.65 | 0.57|
Fasting insulin, mU/L | 11.5±12.7 | 12.3±16.8 | 0.90|
Alcohol consumption, g/d | 21.2±36.8 | 19.0±22.3 | 0.81|

Values are mean±SD or N (%).
*Pairwise t test after logarithmic transformation.

Among MZ pairs, those living in Sweden had significantly higher FMD compared with their Finnish co-twins (7.24±4.36% vs 3.70±2.93%, P=0.003, Table 3, Figure). There was no difference in IMT, carotid plaques, or carotid artery compliance between co-twins living in Sweden and Finland, either in all subjects (Table 4) or among MZ pairs (Table 3).

In all subjects, FMD correlated significantly with age (r = -0.17, P = 0.04), waist (r = -0.16, P = 0.05), systolic blood pressure (r = -0.21, P = 0.01), and diastolic blood pressure (r = -0.17, P = 0.04). IMT correlated with age (r = 0.48, P = 0.0001), systolic blood pressure (r = 0.24, P = 0.004), waist-to-hip ratio (r = 0.27, P = 0.0009), and exercise capacity (r = -0.36, P = 0.0001).

In subjects with coronary artery disease (n=16), FMD was lower (3.20±2.88% vs 5.60±4.31%, P=0.03) compared with those without CHD. The respective difference in IMT was of borderline significance (0.847±0.204 vs 0.747±0.192 mm, P=0.053, unpaired t test).

To study the heritability of endothelial function and carotid IMT, we correlated FMD and IMT values within twin pairs. FMD did not correlate between co-twins, (rMZ=0.23, P=0.34; rDZ=0.11, P=0.43), suggesting that the genetic component in FMD is very modest in this sample with a heritability (h²) estimate of 0.23 (2×[0.23−0.11]=0.46). In contrast to FMD, IMT values correlated between twin pairs (rMZ=0.64, P=0.002; rDZ=0.46, P=0.0006), with a heritability (h²) estimate of 0.36. (2×[0.64−0.46]). This suggests IMT in the common carotid arteries has a greater genetic component than FMD.

**Discussion**

In migrant populations, the risk of disease tends to shift toward the risk prevailing in the population of the new home.

TABLE 1. Background Data and Biochemical Markers of 74 Twin Pairs Discordant for Migration

<table>
<thead>
<tr>
<th>Country of Residence</th>
<th>Finland</th>
<th>Sweden</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of CHD</td>
<td>7 (9.5)</td>
<td>5 (6.8)</td>
<td>0.53</td>
</tr>
<tr>
<td>Echo estimated CHD</td>
<td>6 (8.1)</td>
<td>4 (5.4)</td>
<td>0.53</td>
</tr>
<tr>
<td>CHD positive</td>
<td>10 (13.5)</td>
<td>6 (8.1)</td>
<td>0.25</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23 (31.1)</td>
<td>29 (39.2)</td>
<td>0.20</td>
</tr>
<tr>
<td>Any medication</td>
<td>26 (35.1)</td>
<td>29 (39.2)</td>
<td>0.55</td>
</tr>
<tr>
<td>Cholesterol medication</td>
<td>6 (8.1)</td>
<td>7 (9.5)</td>
<td>0.74</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8 (10.8)</td>
<td>14 (18.9)</td>
<td>0.08</td>
</tr>
<tr>
<td>Leisure time physical activity (METs)</td>
<td>1.37±1.41</td>
<td>1.39±1.65</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Smoking

Non-smoker | 18 (24.3) | 19 (25.7) | ... |
Ex-smoker  | 24 (32.4) | 31 (41.9) | ... |
Occasional smoker | 5 (6.8) | 3 (4.1) | ... |
Smoker | 27 (36.5) | 21 (28.4) | ... |
BMI, kg/m² | 26.2±4.4 | 26.8±4.0 | 0.22|
Waist circumference, cm | 93.0±10.8 | 95.1±10.5 | 0.13|
Waist-to-hip ratio | 0.961±0.064 | 0.972±0.064 | 0.21|
Fat percentage, % | 22.1±5.7 | 23.7±5.3 | 0.03|
Systolic BP, mm Hg | 135±19 | 138±21 | 0.17|
Diastolic BP, mm Hg | 82±11 | 86±11 | 0.002|
Exercise capacity, Wlast4 | 164±46 | 171±48 | 0.35|
Cholesterol, mmol/L | 5.70±1.09 | 5.78±1.08 | 0.59|
HDL-cholesterol, mmol/L | 1.46±0.42 | 1.49±0.44 | 0.54|
LDL-cholesterol, mmol/L | 3.54±0.94 | 3.58±0.90 | 0.73|
Triglycerides, mmol/L | 1.56±0.95 | 1.57±0.90 | 0.75|
Fasting glucose, mmol/L | 5.92±1.56 | 6.07±1.51 | 0.45|
Glucose after 2 hours, mmol/L | 6.72±2.62 | 6.88±3.32 | 0.28|
Fasting insulin, mU/L* | 10.2±8.6 | 11.5±10.9 | 0.25|
Alcohol consumption, g/d | 20.4±27.2 | 16.7±18.5 | 0.26|

Values are mean±SD or N (%).
*Pairwise t test after logarithmic transformation.
country. We studied, for the first time, the effect of migration from a country with high CHD prevalence to a country with lower CHD prevalence on subclinical atherosclerosis. We found no significant differences in traditional risk factors in favor of Finnish migrants to Sweden; however, the endothelial function was better among migrant MZ twins.

Endothelial function may be tested noninvasively in the brachial artery, by using external vascular ultrasound. The brachial arterial dilator response to shear stress has been shown to be due mainly to endothelial release of nitric oxide and to correlate with coronary endothelial function, as well as with the severity of coronary atherosclerosis. Endothelial dysfunction may be the earliest functional expression of systemic atherosclerotic disease process. Most traditional risk factors have been associated with endothelial dysfunction. In a recent report, a population of healthy immigrants from India in Great Britain had significantly lower endothelial function compared with European whites. This was not explained by traditional risk factors, possibly changes in dietary habits, lifestyle, and other factors, including similar upbringing, lifestyle, friends, and hobbies. The observed effect of migration on FMD, it is possible that some unmeasured psychosocial factors may play a role. These may include stronger social coherence and a socially more open atmosphere in Sweden.

Increased IMT of the common carotid artery measured with ultrasound is a structural marker of subclinical atherosclerosis. It correlates with traditional vascular risk factors, the extent of coronary artery disease, and predicts the likelihood of cardiovascular events in population groups. Increased carotid IMT has been observed in urbanized Chinese subjects and in Chinese migrants to Australia compared with rural Chinese subjects. This increment in IMT was not explained by traditional CHD risk factor levels, which were in fact more favorable among migrants and urban Chinese subjects. Despite the more desirable risk factor profile, urban and migrant Chinese subjects seemed to have greater susceptibility to the pro-atherogenic effects of traditional risk factors, suggesting a protective factor or factors in the rural Chinese environment against atherosclerosis. As CHD mortality rates are lower in Sweden, we hypothesized that IMT would be smaller among Finnish migrants to Sweden. There was, however, no significant difference in IMT. Structural atherosclerotic changes appear due to the absence of confounding from genetic factors in this analysis. Most twins have shared childhood environment, including similar upbringing, lifestyle, friends, and hobbies. Thus, the possible differences between twin pairs later in life can be thought to due to the differences in their adult life environment. Therefore, environmental effects can be most effectively studied by examining MZ twins with identical genes and similar childhood environments. A relative risk of a magnitude of 8.1 has been reported in MZ twins when one’s twin dies of coronary heart disease. For DZ twins the relative risk is 3.8. These relative risks are strongly age dependent, being highest in middle-aged men, and decreasing with age. The differences observed between MZ twins can be thought to be purely accounted for by environmental factors, whereas differences in the DZ pairs can arise also from genetic differences between brothers. Endothelial function is affected by many environmentally related factors, including acute changes in mental stress, high-fat meals and cigarette smoke, short-term interventions with antioxidants, and statins. As traditional risk factors did not explain the observed effect of migration on FMD, it is possible that some unmeasured psychosocial factors may play a role. These may include stronger social coherence and a socially more open atmosphere in Sweden.

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| TABLE 3. Ultrasound Data of 20 Identical Twin Pairs Discordant for Migration |
|---------------------------------|------------------|------------------|---|
|                                | Finland          | Sweden           | P  |
| FMD, %                         | 3.70±2.93        | 7.24±4.36        | 0.003 |
| Vessel size, mm                | 3.94±0.40 (3.34–4.54) | 3.79±0.64 (2.95–5.68) | 0.23 |
| Baseline VTI, m/s×s            | 0.19±0.09        | 0.15±0.05        | 0.08 |
| Hyperemia VTI, m/s×s           | 0.76±0.16        | 0.95±0.56        | 0.27 |
| Hyperemia percentage, %        | 374±193 (137–709) | 571±436 (121–1936) | 0.24 |
| Glycerin trinitrate–mediated dilatation, % | 12.5±6.6       | 16.3±9.6         | 0.21 |
| Carotid artery compliance, %/10 mm Hg | 3.65±1.63      | 3.65±1.81        | 0.99 |
| Prevalence of plaques, %       | 5%               | 5%               | 1.0 |
| IMT, mm                        | 0.758±0.135      | 0.732±0.159      | 0.36 |

Values are mean±SD (range). VTI indicates velocity time integral.
to change very slowly, even after vigorous risk factor modifications.37 Therefore, our study may not have been powerful enough to detect differences in IMT even if there had been a slight difference in the progression rate between twin pairs. In addition, subjects with presumably similar structural changes in their coronary arteries may be at different risk of coronary events due to differences in endothelial function as suggested by clinical studies showing a favorable effect of early statin treatment in acute coronary syndromes.28 Thus, our findings on similar IMTs but improved FMD in co-twins migrated to Sweden would be in concordance with previous studies showing decreased incidence of myocardial infarction in male migrants from Finland to Sweden.

Despite the small number of MZ twin pairs, we could clearly see a difference in FMD between the twins. The migration itself is a possible psychosocial risk factor for coronary heart disease causing distress in the sense of having to make social adjustments in relation to changing the living surroundings, learning a new language, finding new friends, and longing for the homeland. There might be a selection bias in the study population so that only the survivors of the migration took part in the study. The possible negative influence of the migration itself may dilute our expected findings in various risk factors caused by beneficial change in environment.

We conclude that those identical co-twins who have moved permanently from Finland to Sweden have better endothelial function independently of traditional CHD risk factors. This is the first study demonstrating that migration to a country with lower CHD prevalence can beneficially influence endothelial function among migrants. The result is consistent with decreasing CHD mortality rates among Finnish migrants to Sweden.

Acknowledgments

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References


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