ACE gene and physical activity, blood pressure, and hypertension: a population study in Finland

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—The study evaluated the association of the insertion/deletion polymorphism of the angiotensin-converting enzyme gene (ACE I/D) with self-reported moderate-intensity leisure time physical activity (MILTPA), arterial blood pressure (BP) and history of hypertension (HT). A representative population-based sample of 721 middle-aged adults (358 women) from two areas of Finland was genotyped for the ACE I/D. After exclusion criteria were applied, 455 subjects (288 women) were selected for the analysis. The distribution of the ACE I/D genotypes did not differ significantly among frequent vs. nonfrequent MILTPA groups ($\chi^2 = 2.556; df = 2, P = 0.279$). The main predictors of BP were male gender, age, body mass index, and arterial pulse. Additionally, tobacco smoking and alcohol consumption also had a significant main effect on diastolic BP. HT was significantly more frequent in subjects with obesity, family history of cardiovascular disease, or lower educational level. As for BP, neither ACE I/D nor MILTPA was associated with HT. The study confirmed recent reports from population-based studies of no association between ACE I/D and physical fitness. The study also confirmed a lack of association between ACE I/D and BP or HT.

variance of serum ACE (26, 31) and that the ACE/DD genotype, which is associated with higher levels of serum ACE, is also a risk factor for myocardial infarction, especially in subjects normally considered to be at low risk (3). Recent reports additionally suggest that the ACE I/D may be associated to the anabolic response and the left ventricular growth induced by physical training (15–17, 36), maximal oxygen consumption (10), and elite athletic performance (1, 7, 18). Thus it could be possible that, given an ACE I/D genotype, subjects might be more likely to become physically active during adulthood. The aims of this study were to evaluate the association of the ACE I/D with self-reported moderate-intensity leisure time physical activity (MILTPA), arterial blood pressure (BP), and history of HT in a population-based sample of Finnish middle-aged adults participants of the 1992 FINRISK survey.

METHODS

The World Health Organization (WHO) initiated the MONICA Project (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) in 1982 to assess the extent to which trends in CHD and cardiovascular disease (CVD) are related to changes in known risk factors. FINMONICA (renamed FINRISK from 1992 onward) was the Finnish part of this project, which included the provinces of North Karelia and Kuopio in eastern Finland and the region of Turku-Loimaa in southwestern Finland. This study presents results based on the sample of the FINRISK survey carried out in 1992. In that survey, a random sample was chosen from the national population register with an age range of 25–64 yr. The sample was stratified so that at least 250 persons for each gender and 10-yr age group were chosen in the areas. The total number of respondents was 6,051 (3,202 women), and the participation rate ranged from 72% in men to 81% in women. A representative subsample of 357 participants (176 women) from the region of North Karelia and 364 participants (182 women) from the region of Turku-Loimaa was drawn among participants aged 35–64 yr to undergo ACE I/D genotyping. Subjects who reported to be 55 yr or older and/or to be unable to practice leisure time
physical activity (LTPA) because of disease or disability and/or to have angina pectoris/heart failure/rheumatoid arthritis and/or to be pregnant were excluded from this study. Altogether, 266 subjects (130 women) were excluded, leaving 455 participants (288 women) available for the analysis. The 1992 FINRISK survey followed the WHO MONICA project protocol, including a self-administered questionnaire on socioeconomic status, health status, and lifestyles; blood sampling; and physical measurements (19). MILTPA was defined as the practice of at least 20–30 min of physical exercise during leisure time so that the person is at least a little out of breath and sweating. It was assessed through the following question: How often do you practice physical exercise during leisure time for at least 20–30 min so that you are a little out of breath and sweating? The possible answers to this question were: 1) daily, 2) 2–3 times a week, 3) once a week, 4) 2–3 times a month, 5) few times a year or less, 6) I can’t do it because of disease or disability. Subjects who answered 1 or 2 were classified as having frequent MILTPA. Subjects who answered 3, 4, or 5 were classified as having nonfrequent MILTPA, and those who answered 6 were excluded from the study. Weight was measured with subjects dressed in light indoor clothes without shoes by use of a digital scale with an accuracy of 0.1 kg. Height was measured by stadiometer of barefoot subjects with an accuracy of 0.1 cm. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). BP was measured twice on the right arm of subjects in a sitting position after 5 min of rest by using a mercury sphygmomanometer with an accuracy of 2 mmHg. The cuff bladder used for the measurements was 13 cm wide and 42 cm long. Systolic BP (SBP) and diastolic BP (DBP) were recorded at the first and fifth phases of Korotkoff sounds, respectively. The average of the two measurements was used in the analysis. BP measurements were taken by a small number of well-trained nurses who were rotated between the study areas at regular intervals. Serum total cholesterol, high-density lipoprotein cholesterol, and triglycerides (CHOD-PAP Monotest, Boehringer Mannheim, Germany) were measured enzymatically in fresh serum samples by use of a Staaris III photometer (Gilford Instrument Laboratories, Oberlin, OH) after a minimum 4-h fasting period. DNA was extracted from EDTA-anti-coagulated whole blood in accordance with standard procedures. ACE I/D genotyping was carried out as previously described by Perola et al. (22). ACE I/D genotypes were in Hardy-Weinberg equilibrium in both subsamples. The association of ACE I/D with MILTPA was evaluated through $\chi^2$ test. To account for the possible effect of confounders, an adjusted $\chi^2$ test was obtained by using a multinomial logistic regression model in which MILTPA was included as the dependent variable; ACE I/D was included as the main factor; and living area, gender, age group, educational level, obesity status, tobacco smoking, alcohol consumption, and family history of CVD were included as covariates. The main predictors of HT were also evaluated through a multinomial logistic regression model in which HT was included as the dependent variable; ACE I/D and MILTPA were included as the main factors; and living area, gender, age group, educational level, obesity status, tobacco smoking, alcohol consumption, and family history of CVD were included as covariates. History of HT was used in this analysis because it is based on a diagnosis made by a physician on the basis of blood pressure measurements taken at least on three subsequent occasions, which is more reliable than HT classification based on casual blood pressure measurements. However, an analysis using HT classification based on the present blood pressure measurements and the antecedent of HT drug treatment did not give different results. Results were considered as statistically significant with $P$ value < 0.05. All the statistical analyses were carried out by use of the SPSS program version 10. Informed, written consent was obtained from all participants, and the research protocol was approved by a locally appointed ethics committee.

**RESULTS**

Subjects with frequent MILTPA, in general, showed a better profile of CVD risk factors than subjects with nonfrequent MILTPA, although only arterial pulse and DBP were significantly lower in the former group (Table 1). The distributions of the ACE DD, ID, and II genotypes did not differ significantly among the MILTPA groups ($\chi^2 = 2.556; df = 2; P$ value = 0.279) (Table 2). The adjustment for confounders did not change this result. The D allele was common, and its frequency did not differ significantly between the MILTPA groups ($\chi^2 = 1.217; df = 1; P$ value = 0.269). The main predictors of BP were male gender, age, BMI, and arterial pulse (Table 3). Additionally, tobacco smoking and alcohol consumption also had a significant main

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonfrequent (n = 254)</th>
<th>Frequent (n = 200)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Living area, % eastern Finland</td>
<td>45.3</td>
<td>54.5</td>
<td>0.059</td>
</tr>
<tr>
<td>Gender, % male</td>
<td>50.4</td>
<td>49.5</td>
<td>0.925</td>
</tr>
<tr>
<td>Age, yr</td>
<td>44.5</td>
<td>44.0</td>
<td>0.346</td>
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<tr>
<td>Education, yr</td>
<td>11.5</td>
<td>11.0</td>
<td>0.109</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.4</td>
<td>25.8</td>
<td>0.140</td>
</tr>
<tr>
<td>Arterial pulse, per 30 s</td>
<td>36.1</td>
<td>33.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>135.2</td>
<td>134.0</td>
<td>0.497</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>84.5</td>
<td>81.7</td>
<td>0.013</td>
</tr>
<tr>
<td>Tot-chol, mmol/l</td>
<td>5.7</td>
<td>5.6</td>
<td>0.123</td>
</tr>
<tr>
<td>HDL-chol, mmol/l</td>
<td>1.4</td>
<td>1.4</td>
<td>0.139</td>
</tr>
<tr>
<td>TRG, mmol/l</td>
<td>1.6</td>
<td>1.4</td>
<td>0.111</td>
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<tr>
<td>Tobacco smoking, %</td>
<td>35.8</td>
<td>31.0</td>
<td>0.317</td>
</tr>
<tr>
<td>Alcohol consumption, %</td>
<td>90.2</td>
<td>90.5</td>
<td>0.234</td>
</tr>
<tr>
<td>Obesity, %</td>
<td>18.5</td>
<td>13.0</td>
<td>0.124</td>
</tr>
<tr>
<td>History of hypercholesterolemia, %</td>
<td>34.8</td>
<td>29.5</td>
<td>0.302</td>
</tr>
<tr>
<td>History of IGT or diabetes, %</td>
<td>3.9</td>
<td>2.5</td>
<td>0.441</td>
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<tr>
<td>History of hypertension, %</td>
<td>31.1</td>
<td>25.6</td>
<td>0.211</td>
</tr>
<tr>
<td>Family history of CVD, %</td>
<td>31.9</td>
<td>31.5</td>
<td>0.999</td>
</tr>
</tbody>
</table>

MILTPA, moderate-intensity leisure time physical activity: at least 20–30 min of physical exercise during leisure time so that the person is at least a little out of breath and sweating; frequent MILTPA, regular practice of MILTPA for at least 2–3 times/week; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Tot-chol, serum total cholesterol; HDL-chol, serum high-density lipoprotein cholesterol; TRG, serum triglycerides; IGT, impaired glucose tolerance; Obesity, BMI $\geq$ 30 kg/m²; Family history of cardiovascular disease (CVD), parental history of acute myocardial infarction or stroke.
Effect on DBP. Neither ACE I/D nor MILTPA had a significant main effect on arterial blood pressure. The only significant predictor of arterial pulse was MILTPA. Subjects with frequent MILTPA showed a significantly lower arterial pulse than subjects with nonfrequent MILTPA. Finally, HT was significantly more frequent in subjects with obesity (adjusted $\chi^2 = 24.57; P = 0.001$), family history of CVD (adjusted $\chi^2 = 5.92; P = 0.015$), or lower educational level (adjusted $\chi^2 = 7.64; P = 0.054$). As for BP, neither ACE I/D nor MILTPA was associated with HT.

**DISCUSSION**

Between 1982 and 1992, the Finnish adult population showed a significant decline in total energy expenditure, mainly because of a decrease in energy expenditure at work, which has not been counterbalanced by the favorable increase of energy expenditure during leisure time (6). Because the total energy intake in the Finnish adult population decreased during the same time period, the lower energy expenditure at work has been suggested as one the contributors to the increment of BMI in the Finnish adult population during the last decades (11, 25). Because an increase of energy expenditure at work is not expected, the promotion of LTPA has been proposed as a feasible and effective approach to increase the total energy expenditure at the population level. This national epidemiological scenario and the intrinsic health benefits of physical fitness make self-evident the importance of studying the determinants of LTPA in the Finnish population.

We found no association between ACE I/D and MILTPA. This lack of association can be ascribed to factors related to the study population, the definition of the phenotype under study, and the genotype itself. The Finnish population is well known by its condition of a genetically isolated population with a common cultural background. Additionally, morbidity and mortality related to CVD and related risk factors are still high in the population, although significant improvements have occurred during the past three decades. Overall, the Finnish population represents an ideal setting to evaluate the contribution of genetic factors to the development of CVD. Moreover, in our study we used representative samples of adult populations from eastern and southwestern Finland in which the ACE I/D genotypes were in Hardy-Weinberg equilibrium and the proportion of the participants with frequent MILTPA was similar to the national figures reported for the years 1991–1992 (20). Thus the characteristics of the population and the sampling procedures carried out in this study should not weaken any association between the genotype and the phenotype being evaluated.

In population studies, physical activity usually is assessed by questionnaire, either filled out by the respondent or collected by interview (28). Information on the amount, the intensity, and the response of the individual to the activity is gathered, and analyses of absolute energy expenditure and vigorous quality can be done. The main objective is to learn about the behavior (physical activity) among different sections of the adult population. LTPA has been the component of

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Nonfrequent (n = 254), %</th>
<th>Frequent (n = 200), %</th>
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<tbody>
<tr>
<td>DD</td>
<td>29.5</td>
<td>36.5</td>
</tr>
<tr>
<td>ID</td>
<td>50.0</td>
<td>46.0</td>
</tr>
<tr>
<td>II</td>
<td>20.5</td>
<td>17.5</td>
</tr>
</tbody>
</table>

**Table 3. Linear regression model for SBP, DBP, and arterial pulse***

- **Main effect**
- **SBP, mmHg**
  - Constant: 46.85 (P < 0.001)
  - Living area: 1.77 (0.281)
  - Gender: 5.53 (0.001)
  - Age, yr: 0.72 (0.001)
  - BMI, kg/m²: 1.12 (0.001)
  - Educational level: −0.88 (0.256)
  - Arterial pulse: 0.53 (0.001)
  - Tobacco smoking: −1.18 (0.491)
  - Alcohol consumption: 5.45 (0.066)
  - Family history of CVD: 2.52 (0.148)
  - ACE I/D genotype: −1.61 (0.155)
  - MILTPA: 1.17 (0.477)
- **DBP, mmHg**
  - Constant: 20.41 (0.001)
  - Living area: −0.75 (0.435)
  - Gender: 5.21 (0.001)
  - Age, yr: 0.45 (0.001)
  - BMI, kg/m²: 0.76 (0.001)
  - Educational level: 0.06 (0.884)
  - Arterial pulse: 0.43 (0.001)
  - Tobacco smoking: −2.24 (0.031)
  - Alcohol consumption: 6.36 (0.001)
  - Family history of CVD: 1.31 (0.213)
  - ACE I/D genotype: 0.07 (0.913)
  - MILTPA: −0.90 (0.363)
- **Arterial Pulse**
  - Constant: 32.74 (P < 0.001)
  - Living area: −0.94 (0.080)
  - Gender: −0.84 (0.123)
  - Age, yr: 0.02 (0.755)
  - BMI, kg/m²: 0.09 (0.156)
  - Educational level: −0.06 (0.823)
  - Arterial pulse: −0.21 (0.581)
  - Tobacco smoking: 0.99 (0.085)
  - Alcohol consumption: 0.55 (0.581)
  - Family history of CVD: −0.08 (0.889)
  - ACE I/D genotype: 0.21 (0.581)
  - MILTPA: −2.01 (P < 0.001)

*Excluding subjects under hypertension drug treatment (n = 33). Living area: 0 = southwestern Finland, 1 = eastern Finland. Gender: 0 = female; 1 = male. Educational level: 0 = primary, lower secondary school; 1 = vocational school; 2 = high school, college; 3 = university. Tobacco smoking: 0 = no; 1 = yes. Alcohol consumption: 0 = no; 1 = yes. Family history of CVD: 0 = no; 1 = yes. ACE I/D genotype: 0 = DD; 1 = ID; 2 = II. MILTPA: 0 = non-frequent; 1 = frequent. b, Unstandardized linear regression beta.

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total physical activity most extensively studied in cardiovascular research, and in Finland, given the above scenario, it has not been the exception (8, 9, 14, 32). However, recent reports have suggested that physical fitness may be a better predictor of mortality than physical activity itself (6) and that the association of LTPA with physical fitness may not be consistent (13). Also, whereas the validity of question or single-question self-assessment of LTPA has been found acceptable to consider and recommend their use in population studies (4, 34, 27), there are reports that have questioned it (12, 35). There are issues related to the validity of single-question self-assessment to measure LTPA in particular and to estimate physical activity and physical fitness in general that may bias the study of the association of a given genotype and physical activity in population studies.

The studies that have found a significant positive association between ACE I/D and physical fitness have either compared the genotype distribution between a sample of elite athletes and some control group or have evaluated the association of the genotype with physical fitness measured in army recruits before and after a period of intensive physical training (1, 7, 15). Fitness measured in army recruits before and after a period of intensive physical training (1, 7, 15) and population studies (4, 34, 27), there are reports that have questioned it (12, 35). There are issues related to the validity of single-question self-assessment to measure LTPA in particular and to estimate physical activity and physical fitness in general that may bias the study of the association of a given genotype and physical activity in population studies.

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Our study also found no association between the ACE I/D polymorphism and BP or HT, confirming results of most previously published linkage and association studies (5, 30, 33). Additionally MILTPA did not significantly predict either BP or HT in this cross-sectional study. This lack of association persisted in further analyses using HT classification that were based on the present blood pressure measurements and the antecedent of HT drug treatment and/or excluded BMI from the regression models (results not shown). This finding is clearly in disagreement with previous epidemiological and experimental studies showing a significant inverse association between level of physical fitness and BP/prevalence or incidence of HT (8, 9, 14, 21, 32). The validity issues related to the assessment of LTPA in populations discussed above are also pertinent here.

In conclusion, we found no association between ACE I/D and LTPA in the Finnish middle-aged adult population. Although a single-question self-assessment of LTPA was used in our study, the result confirms recent negative reports in which physical fitness has been assessed more thoroughly. The study also confirmed a lack of association between ACE I/D and BP or HT.

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REFERENCES


