Apolipoprotein (apo) E is one of the major protein constituents of very-low-density lipoprotein and high-density lipoprotein (HDL). Its main function is to serve as a receptor ligand for the uptake of lipoproteins from the circulation. Because of its key role in lipoprotein metabolism, it has an important influence on the pathophysiology of atherosclerosis. This is supported by experimental animal models showing that injection of apoE lowers plasma cholesterol, accelerates the clearance of lipoproteins, and prevents progression of atherosclerosis, whereas lack of apoE causes spontaneous development of atherosclerosis.

In humans, the gene locus for apoE is polymorphic: three common alleles, designated e2, e3, and e4, code for three major apoE isoforms in plasma. This polymorphism has been extensively studied in various populations, and evidence has accumulated that it is a major determinant of individual susceptibility to coronary heart disease (CHD) in the population at large.
seasonal variation in the risk factor levels, all subjects were examined in the 5-month period from October 1990 to February 1991.

### Lipid and Apolipoprotein Analyses

Venous blood was collected after an overnight fast by using standardized equipment and protocols. Blood anticoagulated with potassium EDTA was centrifuged at 4°C, and 11 mL aliquots of plasma were collected and snap-frozen on dry ice within 30 minutes of sample collection. Leukocytes were harvested from the blood in two aliquots and snap-frozen. The plasma and leukocytes were sent from all recruitment centers deep-frozen on dry ice to a central laboratory in Nancy, France.

Plasma total cholesterol, total triglycerides, and HDL cholesterol (HDL-C) were measured in Glasgow according to the Lipid Research Clinic's Manual of Laboratory Operations standardized according to the Centers for Disease Control and Prevention, Atlanta, Ga. The low-density lipoprotein cholesterol (LDL-C) was calculated by using Friedewald’s formula.

The apoA-I and apoB concentrations were measured in Lille by immunonephelometry on a Behring BNA nephelometer by using the Behring antisera and standards. ApoE and apoA-IV were measured in Brugge on a Technicon RA-1000 analyzer by using the Behring antisera and standards. ApoA-II was measured in Brugge by enzyme-linked immunosorbent assay (ELISA) according to published procedures. The apoA-I-containing lipoprotein (Lp-A-I) particles were measured in Lille by rocket immunoelectrophoresis using kits and reagents of Sebia. Lipoprotein(a) [Lp(a)] was measured in Brugge with an Lp(a) ELISA kit [Innotest Lp(a); Innogenetics] as described.\(^\text{11}\)

### ApoE Phenotyping

ApoE phenotyping was performed in Innsbruck, Helsinki, and Leiden by isoelectric focusing of delipidated plasma followed by immunoblotting.\(^\text{12,13}\) The reliability of laboratory performance was tested by the analysis of blinded 1 in 20 duplicate samples. The \(k\) coefficient of concordance\(^\text{14}\) between duplicate samples was 0.83. The rate of discordances (due either to error in sample identification or to error in apoE phenotyping) was 0.09.

### Statistical Analysis

The database was stored in Paris on an IBM Risc 6000 computer. Statistical analysis was performed with the SAS statistical software (SAS Institute Inc.). In order to have sufficient power in analyses, the 14 recruitment centers were grouped into five regions on the basis of ischemic heart disease (IHD) mortality rates, geography, and language: Finland (Helsinki, Oulu), Great Britain (Glasgow, Bristol), and northern (Göteborg, Aarhus, Hamburg), middle (Ghent, Innsbruck, Zurich), and southern (Bordeaux, Barcelona, Reus, Naples) Europe.

Allele frequencies of apoE polymorphism were estimated by gene counting. Hardy-Weinberg (HW) equilibrium was tested among case and control subjects in each region by using an exact test.\(^\text{15}\) Allele frequencies were compared between regions in the case and control populations by \(x^2\) analysis.

The comparison of apoE phenotype distributions between case and control subjects was based on the calculation of odds ratios to provide an estimate of the relative risk of having an affected father in groups of subjects with different phenotypes. Odds ratios were estimated by logistic regression analysis adjusted for age and sex (matching criteria) and region (stratification variable). We have shown that in studies comparing offspring with and without parental history of disease, specific relations are expected between the odds ratios: the odds ratio in heterozygotes should be the mean of the two odds ratios in homozygotes. Taking E3/3 as the reference phenotype, ie, \(OR_{3/3}=1\), it follows that \(OR_{4/4}=(OR_{4/4}+1)/2\), \(OR_{2/2}=(OR_{2/2}+1)/2\), and \(OR_{3E}=(OR_{3E}+OR_{2E})/2\). The model specifying these constraints well fitted the data (data not shown).

The apoE phenotype effects were then tested by contrasting this model to a submodel without apoE phenotype effect by means of the likelihood-ratio statistic (\(x^2\) with 2 df).

The association of lipid and apolipoprotein levels with apoE phenotypes was tested by analysis of variance controlling for age, sex, region, and status (covariates) (GLM procedure). For each lipid and apolipoprotein considered, a model assuming additive effects of alleles \(e2\) and \(e4\) with no dominance (codominant model) was fitted to the data, the E3/3 phenotype being taken as reference. As no significant deviation from this hypothesis was observed for any trait (data not shown), the additive model was adopted in subsequent analyses.

The proportion of variance attributable to apoE polymorphism \((R^2)\) was calculated as the ratio of the sum of squares due to allele effects to the covariate-adjusted total sum of squares (total sum of squares minus the covariate sum of squares). Homogeneity of allelic effects according to status, gender, and region was tested by introducing corresponding terms of interaction in the model.

In all analyses, triglyceride and apoB distributions were log transformed to remove positive skewness. A transform by power 0.2 was applied to normalize the Lp(a) distribution.

### Results

Among the 1994 subjects recruited in EARS, 1894 (95%) were phenotyped for the apoE polymorphism (635 case and 1259 control subjects). Descriptive characteristics of the five study populations are presented in Table 1. Case subjects had significantly higher levels of apoB and triglycerides than control subjects. The mean age of MI

### Table 1. Descriptive Characteristics of the Five European Atherosclerosis Research Study Populations

<table>
<thead>
<tr>
<th>Region</th>
<th>Age, y (Mean±SD)</th>
<th>BMI, kg/m²</th>
<th>ApoB, mg/dL*</th>
<th>Triglycerides, mmol/L*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Case</td>
<td>Control</td>
<td>Case</td>
</tr>
<tr>
<td>Finland (n=282)</td>
<td>23.5±1.6</td>
<td>22.2</td>
<td>21.9</td>
<td>90.8</td>
</tr>
<tr>
<td>Great Britain (n=174)</td>
<td>21.2±2.0</td>
<td>22.1</td>
<td>22.3</td>
<td>91.6</td>
</tr>
<tr>
<td>North (n=474)</td>
<td>23.4±1.7</td>
<td>21.8</td>
<td>21.4</td>
<td>91.0</td>
</tr>
<tr>
<td>Middle (n=490)</td>
<td>22.6±2.2</td>
<td>21.6</td>
<td>21.6</td>
<td>93.0</td>
</tr>
<tr>
<td>South (n=474)</td>
<td>21.9±2.2</td>
<td>22.5</td>
<td>22.3</td>
<td>89.8</td>
</tr>
<tr>
<td>All regions (n=1894)</td>
<td>22.7±2.1</td>
<td>22.1</td>
<td>21.9</td>
<td>91.3(\dagger)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; Apo, apolipoprotein. See “Methods” for definition of regions.

*Mean level adjusted for age and sex.

\(\dagger\) Case/control difference, \(P<.0001\).
TABLE 2. Phenotype Distribution and Allele Frequency of ApoE Polymorphism Among Case and Control Subjects in the European Atherosclerosis Research Study

<table>
<thead>
<tr>
<th>Group</th>
<th>Total</th>
<th>E2/2</th>
<th>E3/2</th>
<th>E3/3</th>
<th>E4/2</th>
<th>E4/3</th>
<th>E4/4</th>
<th>e2</th>
<th>e3</th>
<th>e4</th>
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<td></td>
</tr>
<tr>
<td>Finland</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case</td>
<td>90</td>
<td>0</td>
<td>7</td>
<td>48</td>
<td>1</td>
<td>31</td>
<td>3</td>
<td>0.044</td>
<td>0.744</td>
<td>0.211</td>
</tr>
<tr>
<td>Control</td>
<td>192</td>
<td>0</td>
<td>17</td>
<td>115</td>
<td>7</td>
<td>46</td>
<td>7</td>
<td>0.063</td>
<td>0.763</td>
<td>0.175</td>
</tr>
<tr>
<td>Great Britain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case</td>
<td>60</td>
<td>0</td>
<td>2</td>
<td>33</td>
<td>1</td>
<td>22</td>
<td>2</td>
<td>0.025</td>
<td>0.750</td>
<td>0.225</td>
</tr>
<tr>
<td>Control</td>
<td>114</td>
<td>1</td>
<td>8</td>
<td>68</td>
<td>3</td>
<td>29</td>
<td>5</td>
<td>0.057</td>
<td>0.759</td>
<td>0.184</td>
</tr>
<tr>
<td>North</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case</td>
<td>159</td>
<td>0</td>
<td>7</td>
<td>100</td>
<td>1</td>
<td>46</td>
<td>5</td>
<td>0.025</td>
<td>0.796</td>
<td>0.179</td>
</tr>
<tr>
<td>Control</td>
<td>315</td>
<td>3</td>
<td>37</td>
<td>184</td>
<td>8</td>
<td>75</td>
<td>8</td>
<td>0.081</td>
<td>0.762</td>
<td>0.157</td>
</tr>
<tr>
<td>Middle</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case</td>
<td>163</td>
<td>1</td>
<td>17</td>
<td>96</td>
<td>3</td>
<td>42</td>
<td>4</td>
<td>0.068</td>
<td>0.770</td>
<td>0.163</td>
</tr>
<tr>
<td>Control</td>
<td>327</td>
<td>3</td>
<td>42</td>
<td>200</td>
<td>5</td>
<td>67</td>
<td>10</td>
<td>0.081</td>
<td>0.778</td>
<td>0.141</td>
</tr>
<tr>
<td>South</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case*</td>
<td>163</td>
<td>7</td>
<td>15</td>
<td>108</td>
<td>2</td>
<td>30</td>
<td>1</td>
<td>0.095</td>
<td>0.801</td>
<td>0.104</td>
</tr>
<tr>
<td>Control</td>
<td>311</td>
<td>4</td>
<td>30</td>
<td>214</td>
<td>4</td>
<td>57</td>
<td>2</td>
<td>0.068</td>
<td>0.828</td>
<td>0.105</td>
</tr>
</tbody>
</table>

Apo indicates apolipoprotein. See "Methods" for definition of regions.

*Significant deviation from Hardy-Weinberg equilibrium (exact test, P<.001).

occurrence of case fathers was 52.6±0.3 years, and the mean age of control fathers was 53.5±0.2 years (P<.01).

Comparison of ApoE Polymorphism Between Case and Control Subjects and Across Regions

The distributions of phenotypes among case and control subjects in the five regions ranked according to decreasing IHD mortality rates are given in Table 2. No significant deviation from HW equilibrium was detected in any group except among case subjects of the south region, where an excess of phenotype E2/2 was observed (exact test, P<.001). Allele frequencies in control subjects were significantly different between the five regions in case (*^2=30.7, 8 df; P<.001) and control (*^2=17.6, 8 df; P<.05) subjects. The difference primarily reflected a decreasing frequency of allele e4 from Finland to the south, as shown in Fig 1 for control subjects.

In four of the five regions, the frequency of allele e4 appeared higher in case subjects than control subjects, while the inverse trend was observed for allele e2. Odds ratios associated with the different phenotypes were estimated by logistic regression analysis (Table 3). In the analysis including all the regions, the global significance of the apoE effects was borderline (*^2=4.98, 2 df; P<.05). Because of the unexpected excess of E2/2 subjects among cases in the south, analysis was repeated without this region. The apoE effects were significant (*^2=12.36, 2 df; P<.01), and the population-adjusted odds ratios reflected a lower risk associated with phenotypes E2/2, E3/2, and E4/2 and a higher risk for phenotypes E4/3 and E4/4 by reference to E3/3.

Association of ApoE Polymorphism With Lipid and Lipoprotein Concentrations

Table 4 shows the allelic effects on lipid and apolipoprotein concentrations and the proportion of the variance of each trait explained by these effects after adjustment for the stratification variables. As expected, the apoE polymorphism was primarily implicated in the modulation of plasma apoE level, explaining 18.7% of the variability of this trait. It also accounted for a substantial amount of the variance of apoB (8.6%), LDL-C (8.2%), and total cholesterol (4.7%) levels. The effect of e2 was to raise the apoE level and to lower apoB, LDL-C, and total cholesterol levels, whereas the effect of e4 was the opposite. The association, although significant, was weaker for HDL-C (1.8%), apoA-I (1.3%), and LpA-I (2.4%) levels. The effects of e2 and e4 on these traits were parallel to those on the apoE level. The e2 and e4 alleles equally increased the mean

![Fig 1. Bar graph showing allele frequencies of apolipoprotein E polymorphism in the five control populations of the European Atherosclerosis Research Study. Solid bars indicate allele e4; shaded bars, allele e2.](http://atvb.ahajournals.org/Downloaded from http://atvb.ahajournals.org/ by guest on May 8, 2017)
triglyceride level. Only the e2 allele had a significant lowering effect on Lp(a) concentration.

The homogeneity of the e2 and e4 effects by status, gender, and region was tested for each variable associated with the apoE polymorphism. There was no significant heterogeneity according to status for any of the traits. With regard to gender, the e2 effect was higher in women than in men for apoE (P<.05), HDL-C (P<.001), apoA-I (P<.001), LpA-I (P<.001), and Lp(a) (P<.01) concentrations. There was a great homogeneity of the effects on apoB, apoE, and triglyceride levels across populations, but less cross-population consistency for apoA-I levels (Fig 2).

**Contribution of ApoE Polymorphism to the Case-Control Differences of ApoB and Triglyceride Concentrations**

One of the major findings of EARS concerned the independent elevation of apoB and triglyceride concentrations among offspring of affected fathers compared with control subjects. As both traits are modulated by apoE phenotypes which, in turn, differ between case and control subjects, we investigated the source of the contribution of the polymorphism to the case-control differences of apoB and triglyceride levels. In a logistic regression analysis in which status was the dependent variable, the coefficients associated with apoB and triglycerides were compared before and after adjusting for the apoE effects (Table 5). In the analysis that included all regions, the coefficients of apoB and triglycerides were both significant when the apoE polymorphism was not included in the model, reflecting the case-control difference for these traits. These coefficients were barely modified after taking into account the apoE effects because of the nonsignificant association of apoE polymorphism with case-control status in the analysis including all regions. However, when the south was omitted, the coefficient of apoB markedly decreased and was no longer significant, indicating that the case-control difference of apoB level was largely attributable to the different frequencies of apoE phenotypes between case and control subjects. In contrast, the triglyceride coefficient increased as a consequence of the raising effect of e2 allele on triglyceride level and the opposite influence of these two factors on risk.

**Discussion**

The usual approach for studying the association between disease and genetic polymorphisms is to compare affected and unaffected individuals. The design of EARS provided an indirect method of investigating this association by comparing offspring having a paternal history of MI with control subjects. Such an approach allowed us to determine whether affected parents transmit more (or less) frequently some specific alleles to their offspring. The use of multiple populations allowed us to determine whether affected and unaffected individuals are more (or less) frequently some specific alleles to their offspring.
their offspring than do unaffected parents. Since mothers in the case group are expected to transmit each allele with the same frequency as mothers in the control group (unless there is assortative mating with respect to the apoE genotype), the case-control difference in allele frequencies is then entirely attributable to the presence or absence of paternal MI. Compared with the classic case-control study, this approach has two main drawbacks: the decrease of power due to the dilution of genes at the second generation and the fact that no information about the dominance pattern of genotype-disease association can be inferred. On the other hand, classic case-control studies are generally restricted to survivors of disease, a limitation that is likely to cause an underestimation of the association. Such a restriction does not happen in studies of offspring. In EARS, for instance, the proportion of fathers who had died from their infarction was 30%. Another advantage of the EARS design was the possibility of investigating the early expression of biological risk factors before the onset of modifications caused by prolonged lifestyle habits, medical treatments, and preexisting disease.

The choice of university students as study populations was inspired by methodological considerations regarding homogeneity of the study group, comparability between case and control subjects and between centers, and practical feasibility in a large international study. Although these samples are not representative of the population within the same range of age, the selection bias should be the same in both case and control groups and should not seriously affect the association between genetic factors and the disease. The participation rate of control subjects was low (24%), which again raises the question of possible selection bias. However, the frequencies of apoE alleles in the control populations of the five regions were comparable to those reported for healthy populations of the same countries.

In previous studies of the association between the apoE polymorphism and quantitative phenotypes, results have generally been presented in terms of average effects of alleles, which is a combined measure of the absolute phenotypic effects weighted by the phenotype frequencies. Since one of the main objectives of EARS was to test the effects of each allele, the choice of university students allowed for a more detailed examination of the allele-specific associations. The results presented here support the hypothesis that the apoE polymorphism has a significant influence on the risk of coronary disease, with allele E4 being associated with a higher risk than allele E2.
the homogeneity of genetic effects between regions, absolute effects rather than average effects were given here. For all the traits investigated in this study, phenotypic means were compatible with a codominant model assuming additive effects of alleles at the apoE locus. The associations of apoE polymorphism with plasma cholesterol, LDL-C, apoB, and apoE levels were consistent with the now well-identified effects of e2 and e4 alleles on these traits.\textsuperscript{21-32} A unifying hypothesis to explain the mechanisms whereby the apoE locus modulates the metabolism of apoB-containing lipoproteins has been proposed in the review of Davignon et al.\textsuperscript{3} More interesting was the great homogeneity of these effects according to status, gender, and region. The fact that the apoE locus modulates cholesterol levels in a relatively uniform manner was already indicated by the similarity of effects among populations of various ethnic origins,\textsuperscript{36,37} between parents and offspring,\textsuperscript{22} and on the longitudinal changes of lipid profiles.\textsuperscript{27,33} The apoE gene apparently acts on the metabolism of lipoproteins relatively independent of environment, as also reported in a study of monozygotic twins.\textsuperscript{34}

Unlike the previous traits, the association of apoE polymorphism with triglyceride levels is still a matter of controversy. The recent meta-analysis of Dallongeville et al\textsuperscript{19} combining the data of 45 samples from 17 countries brings new insight to this question. They noted a significant elevation of triglyceride levels in subjects with the e2 allele or phenotype E4/3. The results of EARS also provided evidence that both e2 and e4, acting codominantly, significantly affect triglyceride levels. The meta-analysis also conclusively shows that HDL-C levels were significantly decreased in E4/3 subjects.\textsuperscript{35} The data of EARS indicated not only that e4 lowered HDL-C, apoA-I, and LpA-I levels but also that e2 raised them. However, these effects were apparently restricted to women and did not seem consistent in all regions.

The main finding of this study was the association of the apoE polymorphism with a parental history of MI, the e4 allele being more frequent and the e2 allele less frequent among offspring of affected fathers than among control subjects. Given the fact that offspring studies have a decreased power to investigate genotype-disease associations, this result provides evidence that the apoE polymorphism is strongly involved in the predisposition to CHD. The association was consistent across regions, except in the south. In this region, there was an unexpected excess of e2 homozygotes among case subjects, although the distribution of the other phenotypes was virtually the same among both case and control groups. The excess of e2 homozygotes ($n_{e2}=7$ versus $n_{e2}=1.5$) might be due to chance alone, since under the hypothesis of HW equilibrium, the probability that among the 10 series tested there is at least one series falling in the critical region is 0.10, for a 1% significance level. However, a selection bias could not be totally excluded (eg, one case subject had a triglyceride concentration of 2.4 mmol/L and possibly had an inherited type III hyperlipoproteinemia, a disease that occurs primarily in association with the E2/2 phenotype). The absence of association between allele e4 and disease in the south is also puzzling in view of the consistent associations observed in the four other regions. This again raises the problem of random fluctuations, but it could also suggest that the link between the apoE locus and CHD involves interactions with other genetic and/or environmental factors in addition to lipids. This could explain some conflicting or nonconclusive results concerning the association of the apoE polymorphism with atherosclerosis and its complications.\textsuperscript{30-40} However, more and more evidence suggests that in the population at large the e4 allele exerts a deleterious effect and, to a lesser extent, the e2 allele exerts a protective effect on risk.\textsuperscript{32,41-49} LDL-C and apoB concentrations have been reported to distinguish offspring with a familial history of MI from control subjects.\textsuperscript{50-53} This finding has been confirmed in EARS,\textsuperscript{18} and the present analysis clearly showed that elevation of apoB levels in offspring of affected fathers was largely attributable to the apoE locus.

The role of apoE in the predisposition to CHD is also supported by the heterogeneity of apoE allele frequencies in various populations around the world.\textsuperscript{9,19,28,54} Of particular interest is the higher frequency of the e4 allele in the northern regions than in the southern regions of Europe,\textsuperscript{34} especially in Finland,\textsuperscript{27,35} where the incidence of MI is the highest.\textsuperscript{17} It should be noted, however, that the difference in sampling designs among studies may have introduced an artificial heterogeneity in the frequencies reported. EARS offered an opportunity of studying the interpopulation variability of apoE polymorphism from samples selected using the same basic protocol. The frequency of e4 followed a clear-cut decreasing gradient from the northern to the southern regions of Europe that paralleled the gradient of IHD mortality rates. A similar gradient was observed in the four populations of the ECTIM study.\textsuperscript{32} Interestingly, the populations of Finland and Great Britain (the latter mainly composed of students from Scotland) also had the lowest prevalence of the e2 allele. Although caution is necessary in interpreting such ecologic correlations, these results provided an additional support to the hypothesis of a predisposing role of e4 and of a protective role of e2 in relation to CHD risk.

In conclusion, this large and comprehensive study in European students showed that offspring of affected fathers had a higher frequency of the e4 allele and a lower frequency of the e2 allele than control subjects; the variation of allele frequencies across Europe followed that of IHD mortality rates; and the effects of apoE polymorphism on quantitative phenotypes were in accordance with a mediation of risk by lipid and apolipoprotein levels. These findings provide a body of evidence that apoE polymorphism contributes to the development of CHD and is one major factor responsible for the familial predisposition to this disease.

Acknowledgments

EARS was supported from EC Concerted Action MRH4-COMAC Epidemiology. The authors wish to thank J. Dallongeville and P. Ducimet\'ere for helpful discussions about this article.

Appendix

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Arterioscler Thromb Vasc Biol. 1994;14:1617-1624
doi: 10.1161/01.ATV.14.10.1617
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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