Apolipoprotein E Genotype: epsilon32 Women Are Protected While epsilon43 and epsilon44 Men Are Susceptible to Ischemic Heart Disease

The Copenhagen City Heart Study

Ruth Frikke-Schmidt, MD,* Anne Tybjærg-Hansen, MD, DMSc,*† Rolf Steffensen, MD,‡ Gorm Jensen, MD, DMSc,† Børge G. Nordestgaard, MD, DMSc†§

Herlev, Copenhagen, and Glostrup, Denmark

OBJECTIVES We tested the hypothesis that risk of ischemic heart disease (IHD) differs as a function of apolipoprotein E (APOE) genotype in women and men.

BACKGROUND Apolipoprotein E genotype influences lipids and lipoproteins and, therefore, possibly the risk of IHD.

METHODS We genotyped 9,241 white women and men from the general population and 940 white women and men with IHD.

RESULTS Test of interaction suggested that APOE genotype may influence risk of IHD differently in women and men (p = 0.07). After age adjustment, the odds ratio (OR) for IHD for epsilon32 versus epsilon33 women was 0.57 (95% confidence interval [CI]: 0.35 to 0.94) while epsilon43 and epsilon44 versus epsilon33 men had ORs of 1.16 (0.96 to 1.41) and 1.58 (1.01 to 2.45). After adjustment for age and other conventional cardiovascular risk factors, the equivalent ORs were for epsilon32 women 0.38 (0.18 to 0.79), for epsilon43 men 1.35 (1.02–1.78) and for epsilon44 men 1.58 (0.80 to 3.08). Equivalent ORs for epsilon43 and epsilon44 versus epsilon33 women and for epsilon32 versus epsilon33 men were all close to 1.0 and nonsignificant. Of the total risk of IHD relative to the epsilon33 genotype, the fraction attributed to epsilon32 in women was −9%, while the fractions attributed to epsilon43 and epsilon44 in men were +8% and +2%.

CONCLUSIONS Relative to epsilon33 individuals, epsilon32 women are protected while epsilon43 and epsilon44 men are particularly susceptible to IHD. (J Am Coll Cardiol 2000;35:1192–9) © 2000 by the American College of Cardiology

The apolipoprotein E (APOE) polymorphism consists of three alleles (epsilon2, epsilon3 and epsilon4) on the long arm of chromosome 19 (1–3), coding for three protein isoforms, APOE-2, APOE-3 and APOE-4. The APOE-2 isoform differs from APOE-3 by a cysteine for arginine substitution at amino acid residue 158, while APOE-4 differs from APOE-3 by an arginine for cysteine substitution at residue 112. Apolipoprotein E mediates interaction with lipoprotein receptors of mainly triglyceride-rich lipoproteins, the affinity of which depend on the APOE isoform (1).

Previous studies suggest that effects of the APOE polymorphism on lipids and lipoproteins differ in women and men (4–8). It remains unknown, however, whether effects of the APOE polymorphism on risk of ischemic heart disease (IHD) also differ by gender (1,9–12).

We tested the hypothesis that risk of IHD differs as a function of the six APOE genotypes in women and men. For this purpose, 9,241 individuals sampled from a white general population, the Copenhagen City Heart Study, and 940 patients with IHD were genotyped.

METHODS

Subjects. The Copenhagen City Heart Study (third examination, 1991 through 1994) includes an almost equal number of women (55%) and men stratified into 10 year age...
groups from 20 to 80 years and above, drawn randomly from the Copenhagen Central Population Register with the aim to obtain a representative sample of the Danish general population (13–19). For this study 9,241 individuals were genotyped; of these, 557 subjects suffered from IHD (13,19). Patients with IHD were identified among 992 consecutive patients from the Greater Copenhagen Area referred for coronary angiography in the period 1991 through 1993 (13,14). All 992 patients were evaluated by experienced cardiologists at the Department of Cardiology, Copenhagen University Hospital (Rigshospitalet), and 948 patients (26% women) had IHD (18,20). Of these 948 patients, 940 were genotyped. In both samples about 99% were white. The study was approved by Danish ethical committees: no. 100.2039/91 Copenhagen and Frederiksborg committee and no. KA 93125 Copenhagen County committee.

**DNA analyses.** Apolipoprotein E genotypes were identified by polymerase chain reaction (PCR) followed by restriction enzyme digestion of the amplified DNA (244 bp) with HhaI as previously described (21), except that, due to the large sample size, we used a 5% agarose gel instead of a polyacrylamide gel. However, on the agarose gel we could not always detect the 48 base pair (bp) band that distinguished between the epsilon22 and the epsilon32 genotypes; we, therefore, retyped all epsilon22 and epsilon32 genotypes, using a second PCR (sense primer: 5′ACGCGGC-CCTGTTCCACCA′3; antisense primer: 5′ACATGGAG-GACGTGTGCGG′3) followed by digestion of the PCR product (250 bp) with HaeII (epsilon22 homozygotes: 2 × 187 bp; epsilon32 heterozygotes: 1 × 187 bp, 1 × 152 bp, 1 × 35 bp, and common bands of 32, 18 and 13 bp). The 187 bp band and 152 bp band (epsilon32) were clearly distinguishable on an agarose gel.

**Other analyses.** Blood samples were drawn in the fasting state in patients with IHD but in the nonfasting state in participants of the Copenhagen City Heart Study. Colorimetric and turbidimetric assays measured levels of total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, apoB, apoAI (all Boehringer Mannheim, Mannheim, Germany) and lipoprotein(a) total mass (DAKO A/S, Glostrup, Denmark). Height, weight, systolic and diastolic blood pressure were measured in the Copenhagen City Heart Study as described (16). Criteria for hypertension and diabetes mellitus were those previously used (13–15,17,18). Body mass index was weight divided by height² (kg/m²).

**Statistical analyses.** A p value < 0.05 was considered significant. All data were analyzed in each gender separately using the SPSS program (22). Kruskal-Wallis analysis of variance compared levels of lipids and lipoproteins as a function of APOE genotype; two-genotype comparisons and tests of interaction are reported elsewhere (R. Frikke-Schmidt et al. 1999, in preparation). Results were similar when we used a case-referent study design (cases vs. all individuals sampled from the general population), a case-control study design (cases vs. individuals from the general population without IHD) or a pooled case-control study design (cases plus individuals with IHD from the general population vs. individuals from the general population without IHD). We have chosen to present results from the case-referent study design, as done previously (13,14,17,18). Results were also similar whether we excluded individuals taking lipid lowering medication or not and whether we allowed for use of antihypertensive medication or not. We have chosen to present results on all individuals without adjustment for use of these medications. Logistic regression (23,24) was used to explore the impact of APOE genotype, hypertension, diabetes mellitus, smoking and tertiles of total cholesterol, apoB, HDL cholesterol, apoAI and triglycerides on risk of IHD. Lipids and lipoproteins as risk factors for IHD were evaluated as continuous covariates, in tertiles or in quartiles; all showed similar results, and for simplicity we chose to present results based on tertiles. Analysis on APOE genotype adjusted for

1) age only,

2) age and known cardiovascular risk factors (total cholesterol, HDL cholesterol, apoAI, triglycerides, lipoprotein(a), body mass index, hypertension, diabetes mellitus and smoking for both men and women and, in addition, for menopausal status and use of hormonal replacement therapy [HRT] in women), or

3) age and apoB levels.

Interaction between APOE genotype and lipid and non-lipid covariates were explored in logistic regression models including APOE genotype, the risk factor in question and, in addition, an interaction term for these two factors.

Population attributable risk was calculated as: f(R – 1)/(1 + f[R – 1]), where f is the frequency of the risk factor in the population and R is the odds ratio (OR) for IHD (25).

**RESULTS**

Basic characteristics of participants in this study are given in Table 1 and genotype frequencies in Table 2. Genotype frequencies in the sample from the general population did
not differ significantly from those predicted by the Hardy-Weinberg equilibrium (chi-square: 0.20, p < 0.30).

**APOE genotype and lipids and lipoproteins.** When age was adjusted for, APOE genotype from epsilon22 to epsilon32 to epsilon42 to epsilon33 to epsilon43 to epsilon44 was associated with a stepwise increase in cholesterol and apolipoprotein B (apoB) in both genders and a stepwise decrease in HDL cholesterol in women (Fig. 1). In both genders epsilon33 individuals had the lowest levels of nonfasting triglycerides, while the highest levels were found in individuals with epsilon22 and epsilon44 genotypes. The results in women were similar when premenopausal women, untreated postmenopausal women and postmenopausal women on HRT were examined separately (Fig. 2), except that HRT seemed to abolish the effect of APOE genotype on HDL cholesterol and triglycerides in postmenopausal women. Two-genotype comparisons and tests of interaction between APOE genotype and conventional cardiovascular risk factors in predicting these lipid and lipoprotein traits are reported elsewhere (R. Frikke-Schmidt et al. 1999, in preparation).

**Lipids, lipoproteins and risk of IHD.** When age was adjusted for, risk of IHD disease in both women and men increased as a function of levels of apoB and triglycerides and decreased as a function of levels of HDL cholesterol, while levels of total cholesterol did not confer any major change in risk (Fig. 3); however, non-HDL cholesterol (i.e., mainly low density lipoprotein [LDL] cholesterol) was a predictor of IHD risk in both genders (data not shown). When in addition the logistic regression analysis adjusted for other known cardiovascular risk factors, the results were similar to those shown in Figure 3 (data not shown).

### Table 1. Basic Characteristics of Participants

<table>
<thead>
<tr>
<th></th>
<th>General Population</th>
<th>Patients With Ischemic Heart Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>No. of individuals*</td>
<td>5,112</td>
<td>4,129</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>58 ± 0.2</td>
<td>57 ± 0.2</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>6.3 ± 0.02</td>
<td>6.0 ± 0.02</td>
</tr>
<tr>
<td>Apolipoprotein B (mg/dL)</td>
<td>86 ± 0.3</td>
<td>86 ± 0.3</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.7 ± 0.01</td>
<td>1.4 ± 0.01</td>
</tr>
<tr>
<td>Apolipoprotein A1 (mg/dL)</td>
<td>151 ± 0.4</td>
<td>130 ± 0.4</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)†</td>
<td>1.7 ± 0.01</td>
<td>2.1 ± 0.03</td>
</tr>
<tr>
<td>Lipoprotein(a) (mg/dL)</td>
<td>32 ± 0.6</td>
<td>29 ± 0.6</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25 ± 0.1</td>
<td>26 ± 0.1</td>
</tr>
<tr>
<td>Ischemic heart disease (%)</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Smokers (%)‡</td>
<td>69</td>
<td>82</td>
</tr>
<tr>
<td>Postmenopausal (%)</td>
<td>71</td>
<td>—</td>
</tr>
<tr>
<td>Hormonal replacement therapy (%)</td>
<td>20</td>
<td>—</td>
</tr>
</tbody>
</table>

*Number of individuals genotyped; the number for each characteristic varies slightly according to availability of data; †Nonfasting in the general population, but fasting in patients with IHD; ‡Smokers were ex-smokers and current smokers combined. Values in the upper part of the table are means ± SEM.

HDL = high density lipoprotein.

### Table 2. Apolipoprotein E Genotype Frequencies in a Sample From the General Population and in Patients With IHD

<table>
<thead>
<tr>
<th></th>
<th>General Population</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>Frequency</td>
</tr>
<tr>
<td>epsilon22</td>
<td>28</td>
<td>0.005</td>
</tr>
<tr>
<td>epsilon32</td>
<td>655</td>
<td>0.128</td>
</tr>
<tr>
<td>epsilon42</td>
<td>127</td>
<td>0.025</td>
</tr>
<tr>
<td>epsilon33</td>
<td>2,855</td>
<td>0.558</td>
</tr>
<tr>
<td>epsilon43</td>
<td>1,298</td>
<td>0.254</td>
</tr>
<tr>
<td>epsilon44</td>
<td>149</td>
<td>0.029</td>
</tr>
<tr>
<td>All</td>
<td>5,112</td>
<td>247</td>
</tr>
</tbody>
</table>
APOE genotype and risk of IHD. On logistic regression analysis adjusting for age, female carriers of the epsilon32 genotype versus epsilon33 had an OR for IHD of 0.57 (95% confidence interval [CI]: 0.35 to 0.94), while no other genotype conferred altered risk (Fig. 4, women, age-adjustment). When, in addition, the analysis adjusted for other known cardiovascular risk factors, including all lipids and lipoproteins except apoB, female epsilon32 versus epsilon33 carriers had an OR of 0.38 (95% CI: 0.18 to 0.79) (Fig. 3, women, multifactorial adjustment). When premenopausal women, untreated postmenopausal women and postmenopausal women on HRT were examined separately (Fig. 5), the protective effect of epsilon32 was statistically significant in untreated postmenopausal women, while a nonsignificant trend was observed in the two other smaller groups of women.

After adjusting for age, male carriers of the epsilon43 and epsilon44 genotypes versus epsilon33 had ORs for IHD of 1.16 (95% CI: 0.96 to 1.41) and 1.58 (95% CI: 1.01 to 2.45), while the other APOE genotypes did not confer altered risk (Fig. 4, men, age-adjustment). When, in addition, the analysis adjusted for other known cardiovascular risk factors, including all lipid and lipoproteins except apoB, male epsilon43 and epsilon44 versus epsilon33 carriers had ORs of 1.35 (95% CI: 1.02 to 1.78) and 1.58 (95% CI: 0.80 to 3.08) (Fig. 4, men, multifactorial-adjustment).

When the logistic regression analysis adjusted for both age and apoB levels, the epsilon22 genotype versus epsilon33 had ORs for IHD of 5.1 (95% CI: 1.1 to 23.4) and 1.16 (95% CI: 0.96 to 1.41) and 1.58 (95% CI: 1.01 to 2.45), while the other APOE genotypes did not confer altered risk.
The above-mentioned results of APOE genotype on risk of IHD were similar when we used: 1) a case-referent study design, 2) a case-control study design or 3) a pooled case-control study design (see “Methods,” “Statistical analyses” sections). For simplicity we have chosen only to present results from the case-referent study.

Interactions of APOE genotype with lipid and nonlipid cardiovascular risk factors. Of 24 interactions tested, only one was significant (men, HDL cholesterol, p = 0.01). In this case, APOE genotype effects on risk of IHD showed irregular, rather than consistent, biologically plausible patterns in different strata of HDL cholesterol and, thus, suggested chance observations.

There was, however, as one should expect because of the apparent gender specific effects on risk of IHD, a borderline statistically significant interaction (p = 0.07) between APOE genotype and gender in predicting risk of IHD when women and men were combined.

Fraction of IHD attributed to APOE genotype. Of the total risk of IHD in the general population, the fraction attributed to epsilon32 versus epsilon33 in women was –9% (Table 3). The fractions attributed to epsilon43 and epsilon44 versus epsilon33 in men were +8% and +2%, equivalent to fractions attributed to hypertension and diabetes mellitus combined in men.

DISCUSSION

This study demonstrates that female carriers of the APOE epsilon32 genotype versus epsilon33 have a 62% (multifactorial-adjustment; 95% CI, 21%–81%) reduction in risk of IHD, while male carriers of epsilon43 and epsilon44 versus epsilon33 have a 35% (multifactorial adjustment; 95% CI, 2%–78%) and 58% (age adjustment; 95% CI, 1%–145%) increase in risk, respectively; after multifactorial-adjustment, the 58% increase in risk in epsilon44 men did not reach statistical significance (95% CI, 220%–208%).
attributed to the epsilon32 genotype versus epsilon33 in women while +8% and +2% can be attributed to epsilon43 and epsilon44 versus epsilon33 in men.

epsilon32 genotype. In this study we find a reduction in IHD risk associated with the epsilon32 genotype versus epsilon33 only in women, which is plausible from the gender specific effects on lipids and lipoproteins; while both epsilon32 women and men have lower cholesterol and apoB levels when compared with epsilon33 individuals, epsilon32 women, in addition, have higher HDL cholesterol levels, a factor that may reduce risk even further; an impact of APOE alleles on HDL cholesterol levels in women only, epsilon32 and epsilon44 genotypes. The present demonstration of increased risk of IHD in male carriers of the epsilon43 and epsilon44 genotypes versus epsilon33 is in accordance with results from a study including 574 white men (26) and are, furthermore, indirectly supported by numerous studies estimating a risk increasing effect of the epsilon4 allele relative to the epsilon3 allele mainly in men (1,9,10). Also on this issue, a recent meta-analysis included 181 women and 1,971 men with IHD from nine studies (27); in spite of the overall impression that the epsilon4 allele increased risk of IHD in both women and men, the data were not convincing for women. Only four studies included women, and only one of these showed a significant OR associated with the epsilon4 allele. Female cases in this particular study and in two other studies were compared with a common control group not stratified by gender, which could mask potential gender specific effects.

Although both women and men with epsilon43 and epsilon44 versus epsilon33 have higher levels of cholesterol and apoB, only men with these genotypes have major increases in triglycerides relative to epsilon33 individuals (Fig. 1). If epsilon4 women compared with men lipolyze very low density lipoprotein to LDL better, there would be

Figure 5. Odds ratio and 95% CI for risk of ischemic heart disease as a function of apolipoprotein E genotype relative to the common epsilon33 genotype as the reference in premenopausal women (n = 1,451), untreated postmenopausal women (n = 2,908) and in HRT treated postmenopausal women (n = 689). Logistic regression models adjusted for 10 year age groups. The size of the squares reflects the number of individuals with each genotype. The epsilon22 genotype in premenopausal women and the epsilon22, epsilon42 and epsilon44 genotypes in HRT treated postmenopausal women were too few to calculate reasonable odds ratios. CI = confidence interval; HRT = hormone replacement therapy.

Table 3. Fractions of IHD in the General Population Attributed to APOE Genotypes (Relative to the epsilon33 Genotype) and to Conventional Cardiovascular Risk Factors

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>epsilon22</td>
<td>0.2%</td>
<td>0.8%</td>
</tr>
<tr>
<td>epsilon32</td>
<td>-9%</td>
<td>-0.5%</td>
</tr>
<tr>
<td>epsilon42</td>
<td>3%</td>
<td>0.6%</td>
</tr>
<tr>
<td>epsilon43</td>
<td>-2%</td>
<td>8%</td>
</tr>
<tr>
<td>epsilon44</td>
<td>-1.0%</td>
<td>2%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18%</td>
<td>4%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>Smoking</td>
<td>15%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Attributable fraction = f(R - 1)/(1 + f(R - 1)).
more LDL in epsilon4 women, but a better and faster removal of epsilon4 remnants in men might downregulate LDL receptors severely and lead to higher LDL levels in men. This could be what is happening, although apoB levels were similar in women and in men (Fig. 1). If this is the mechanism for epsilon4 men versus women, and the same mechanism is operating in the epsilon32 situation, epsilon32 men should also be at an increased risk relative to epsilon32 women. And they are, although it comes out as less protective than more risk. Alternatively, a simplistic view could be that epsilon43 and epsilon44 genotypes may increase risk of IHD in men only because triglyceride-rich lipoproteins may be trapped preferentially to LDL in the arterial intima to promote accelerated atherosclerosis (28). In this, as in previous, studies (29), triglycerides conferred a higher OR for IHD in women than in men. This may seem paradoxical because the triglyceride raising epsilon43 and epsilon44 genotypes only raised IHD risk in men. However, it is important to note that a major triglyceride raising effect of these genotypes was lacking in all groups of women (Fig. 1 and 2). It is also possible that the lack of an association between the epsilon43 and epsilon44 genotypes versus epsilon33 and IHD in women in our study is due to lack of power. It should be emphasized that our evidence for interaction between APOE genotype and gender on IHD risk only was at the p = 0.07 level. We can, therefore, not totally exclude that APOE genotype affects risk of IHD similarly in women and men.

epsilon22 genotype. It is well known that a subgroup of carriers of the epsilon22 genotype have the propensity to develop type III hyperlipoproteinemia, characterized by severely elevated levels of both triglycerides and cholesterol, tuberous xanthomas, xanthomas of the palmar creases and premature IHD (1). In the present population based study, we could demonstrate that epsilon22 individuals, after adjustment for low apoB levels, had a three- to five-fold increase in risk of IHD, probably reflecting an even higher risk of IHD in a subset of epsilon22 individuals with type III hyperlipoproteinemia. However, since there were only two women and five men among patients with IHD with the epsilon22 genotype, it is also possible that this association is due to a few extreme cases.

Attributable fractions. Because 13% of women carry the epsilon32 genotype, the fraction of the total risk of IHD in women attributed to this genotype is as much as ~9%. In other words, if all epsilon32 women carried the epsilon33 genotype instead, the total burden of IHD in women would increase by 9%.

Because 25% and 3% of men carry the epsilon43 and epsilon44 genotypes, the fraction of the total risk of IHD attributed to epsilon43 and epsilon44 is 8% and 2%, respectively. This means that if all male epsilon43 and epsilon44 individuals carried the epsilon33 genotype instead, the total burden of IHD in men would decrease by 10%. Since this is as much as the fraction attributed to hypertension and diabetes mellitus combined, it is very likely that the APOE polymorphism for society as a whole is the quantitatively most important genetic modulator of risk of IHD.

Study limitations. Because we genotyped more than 10,000 individuals, we cannot totally exclude misclassification of a few APOE genotypes; however, genotype frequencies were in accordance with those predicted by the Hardy-Weinberg equilibrium and genotyping as well as database entry was scrutinized by two different researchers. Misclassification of cases is also unlikely, as IHD was diagnosed by experienced cardiologists and verified by coronary angiography, a previous myocardial infarction or a positive exercise electrocardiography test. Bias due to the investigators’ knowledge of IHD status is unlikely because genotyping was performed by technical staff who were unaware of prior knowledge of the effects of the six APOE genotypes. Potential confounders were taken into account by adjusting for age and other cardiovascular risk factors in logistic regression models. Nevertheless, some of our results could still be chance findings; however, all observations are in accordance with previous studies and seem plausible from the effects of APOE genotypes on lipids and lipoproteins. Finally, linkage disequilibrium with other mutations nearby is a possible, but very unlikely, confounder; by now it is very well-established even at the molecular level that differences in APOE genotype result in different protein isoforms that interact differently with lipoprotein receptors, thereby causing different effects on plasma lipids and lipoproteins (1,30–33).

Measurements of plasma lipids and lipoproteins in the nonfasting state in subjects sampled from the general population, but in the fasting state in patients with IHD, could pose a potential problem, particularly for triglycerides. This is because it is conventional to measure triglycerides in the fasting state and because triglycerides increase after a fatty meal. It could be argued, however, that because most humans spend more time in the nonfasting state (up to 8 h after a meal) than in the fasting state (>8 h after a meal), that the nonfasting state is the most relevant to study, like we did on effects of APOE on triglyceride levels. Nevertheless, because nonfasting triglyceride levels are higher than fasting levels, this study probably underestimated the role of triglycerides in predicting IHD.

Conclusion. This study suggested a gender difference of APOE genotype on risk of IHD; epsilon32 versus epsilon33 is protective in women while epsilon43 and epsilon44 versus epsilon33 increase the risk in men. The difference between being an epsilon32 woman and an epsilon43 or epsilon44 man is striking, amounting to up to a four-fold risk difference. The well known propensity of some epsilon22 individuals to develop hyperlipoproteinemia and, thus, increased risk of IHD could also be demonstrated in this study in a sample from the general population. These results, together with previous results, support that APOE geno-
typing is important in assessing risk of IHD in the individual. Because the APOE polymorphism is found in white, black, as well as Asian populations (1), our observations may apply in many parts of the World.

Acknowledgments
We thank Pia T. Petersen, Mette Refstrup and Hanne Damm for their expert technical assistance.

Reprint requests and correspondence: Dr. Børge G. Nordestgaard, Department of Clinical Biochemistry, Herlev University Hospital, DK-2730 Herlev, Denmark. E-mail: brno@herlevhospital.kbhamt.dk.

REFERENCES


