APoE Gene and Gene-Environment Effects on Plasma Lipoprotein-Lipid Levels

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Hagberg, James M., Kenneth R. Wilund, and Robert E. Ferrell. APO E gene and gene-environment effects on plasma lipoprotein-lipid levels. Physiol Genomics 4: 101–108, 2000.—Apolipoprotein E (apo E) is important in plasma lipid metabolism and is a component of several plasma lipoprotein-lipid particles. Three major apo E isoforms are encoded by three common alleles at the APO E locus. The E2 allele is associated with lower and the E4 allele with higher total plasma cholesterol and LDL cholesterol levels compared with the E3 allele. Available data generally indicate that APO E2, and possibly E3, genotype individuals reduce plasma total and low-density lipoprotein (LDL) cholesterol levels more than APO E4 individuals with statin therapy. Some evidence also indicates that APO E2 individuals are more likely to respond favorably to gemfibrozil and cholestyramine. On the other hand, it appears that with probucol, APO E4 genotype individuals may improve plasma lipoprotein-lipid profiles more than APO E3 individuals. APO E2 and E3 genotype perimenopausal women appear to improve plasma lipoprotein-lipid profiles more with hormone replacement therapy than APO E4 women. On the other hand, low-fat diet interventions tend to reduce plasma LDL cholesterol and, perhaps, plasma total cholesterol levels more in APO E4 than in APO E2 or E3 individuals. Both cross-sectional and longitudinal studies generally indicate that APO E2 and E3 individuals improve plasma lipoprotein-lipid profiles more with exercise training than APO E4 individuals. Although these data are hardly definitive, they lend strong support for the possibility that in the near future individuals will be directed to what might be their optimal therapy for improving plasma lipoprotein-lipid profiles and cardiovascular disease risk based partially on APO E genotype.

APO E Gene and Plasma Lipoprotein-Lipid Levels

Intense interest in the genetics of apolipoprotein E (apo E) began with the discovery by Utermann et al. (42–44) of genetically determined structural variation in apo E and the association between apo E variation and type III hyperlipoproteinemia. Subsequent biochemical and physiological studies have defined the role of apo E in lipid metabolism, and genetic studies have examined the relationship between variation at the APO E locus and intermediate risk factors and specific disease end points for cardiovascular (CV) disease in various patient groups and in the general population. These topics have been thoroughly reviewed (5, 6, 9, 20, 24, 36, 45, 46) and will only be summarized here.

The APO E gene, located on human chromosome 19, is 3.7 kb in length and contains four exons. The genomic organization of APO E is similar to that of the APO A and APO C gene families, suggesting that these genes arose from a common ancestor by gene duplication. The primary product of the APO E gene is a 317-amino acid protein that gives rise to the 299-amino acid mature protein by cleavage of an 18-amino acid signal peptide. Apo E is a constituent of triglyceride (TG)-rich chylomicrons, very-low-density lipoprotein (VLDL) particles and their remnants, and a subclass of high-density lipoprotein (HDL). The primary role of apo E in plasma lipid metabolism is to mediate the interaction of chylomicron remnants and intermediate density lipoprotein particles with lipoprotein receptors, including the low-density lipoprotein (LDL) receptor and the chylomicron remnant or apo E receptor. The remnant receptor appears to be the LDL receptor-related protein.

Three major apo E isoforms are coded by three alleles at the APO E locus, designated E2, E3, and E4, giving rise to six common phenotypes. The most common isoform, E3, is characterized by a cysteine at amino acid residue 112 and an arginine at residue 158.
The E2 isoform has a cysteine at residues 112 and 158, whereas the E4 allele product has an arginine at residues 112 and 158. In populations of European origin, the E3 allele ranges in frequency between 0.7 and 0.8, the E4 between 0.10 and 0.15, and E2 between 0.05 and 0.10. In the general population, the E2 allele is consistently associated with lower levels of total plasma cholesterol, LDL cholesterol, and apo B and elevated levels of TG and apo E compared with the E3 allele. Elevated levels of TG and apo E are consistent with impaired clearance of remnant particles containing apo E, presumably due to defective receptor recognition of apo E-containing particles (18). The basis for the reduced apo B and LDL cholesterol levels in APO E2/3 and 2/2 individuals is less clear. Ehnholm et al. (11) suggested that the presence of apo E2 in intestinal VLDL particles impairs their conversion to LDL by interfering with normal lipolytic processing. Conversely, the E4 allele is associated with higher levels of total and LDL cholesterol and apo B and lower levels of apo E. These observations are consistent with the faster rate of catabolism of particles containing apo E compared with those containing apo E3 (14).

In general, the lower plasma total cholesterol levels observed in subjects carrying the E2 allele correlate with reduced coronary and peripheral artery atherosclerosis, and the higher cholesterol levels seen in E4 carriers are associated with a higher prevalence of CV disease. However, the effect of APO E variation on clinical atherosclerosis is not completely explained by its impact on risk factor levels, as recent studies have demonstrated associations between carotid atherosclerosis (4, 7, 40) and coronary artery calcification (23) in asymptomatic adults.

There is convincing evidence that the relationship between APO E genotype and plasma lipoprotein-lipid levels is context dependent, being significantly influenced by age (49), sex (33–35), and body weight distribution (34). Recent evidence also indicates that the responses of plasma lipoprotein-lipid levels to different lipid-lowering interventions may be affected by an individual’s APO E genotype, indicating the significance of gene-environment interactions.

In this review “APO E2 individuals” will refer to those with at least one APO E2 allele, “APO E4 individuals” are those with at least one APO E4 allele, and “APO E3 individuals” are those homozygous for the APO E3 allele.

**APO E Genotype and Plasma Lipoprotein-Lipid Changes with Cholesterol-Lowering Medications**

The effectiveness of many common lipid-lowering medications varies greatly between individuals. Twelve studies have investigated the association between polymorphic APO E variation and plasma lipoprotein-lipid changes with lipid-lowering medications (1, 3, 8, 12, 13, 25, 27–30, 32, 37). Nine of these studies used hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors as the intervention, two used probucol, three used gemfibrozil, and one used cholestyramine.

**HMG-CoA reductase inhibitors.** Four studies have found a significant interaction between an individual’s APO E genotype and plasma lipoprotein-lipid changes with statin therapy (3, 27, 32). Nestel et al. (27) found that combined hyperlipoproteinemic subjects with at least one APO E2 allele were more likely to respond favorably to simvastatin therapy (plasma total cholesterol decrease >25% or plasma TG decrease >40%) than either APO E3 homozygous or APO E4 individuals. Ordonez et al. (32) investigated the effects of pravastatin therapy in 97 patients with hypercholesterolemia of unknown etiology and found that individuals with at least one APO E2 allele, despite having lower initial plasma LDL cholesterol levels, reduced LDL cholesterol significantly more (−36%) than APO E3 homozygous individuals (−27%) or those with at least one APO E4 allele (−26%). APO E2 individuals also reduced their plasma total cholesterol significantly more (−25%) than both APO E3 and E4 individuals (−18% each). There were no genotype-dependent differences in the plasma HDL cholesterol or TG level changes. Carmena et al. (3) investigated the lipid-lowering response to lovastatin in 94 men and women with heterozygous familial hypercholesterolemia (FH). When data from all subjects were considered together, the plasma total and LDL cholesterol reductions were significantly greater in the APO E3 (−36% and −41%, respectively) and APO E2 subjects (−44% and −47%, respectively) compared with APO E4 individuals (−31% and −37%, respectively). However, this differential response was mainly due to genotype-dependent responses in men, as plasma total and LDL cholesterol reductions were significantly greater and plasma HDL cholesterol changes were significantly less in APO E3 (−36%, −41%, and +13%, respectively) and APO E2 men (−44%, −47%, and +17%, respectively) compared with APO E4 men (−26%, −32%, and +29%, respectively). Plasma lipoprotein-lipid changes did not differ between APO E genotype groups in women.

One additional study, by Ojala et al. (29), found a significant interaction between APO E genotype and plasma lipoprotein-lipid changes with statin therapy only in subsets of their study population. They assessed the effects of 20 and 40 mg/day of lovastatin in 232 subjects, some of whom had FH while the remainder had non-FH hypercholesterolemia. When all subjects were analyzed together, no significant interactions with APO E2, E3, or E4 genotype were evident. However, for the non-FH subjects on the 20 mg/day dose, APO E3 homozygous individuals had slightly, but significantly, larger plasma LDL cholesterol reductions than APO E4 individuals (−28% vs. −20%), but significantly smaller increases in plasma HDL cholesterol levels (+1% vs. +11%). In addition, APO E3 homozygous FH patients on the 40 mg/day dose had significantly larger plasma total cholesterol and plasma TG reductions (−27% for both) than APO E4 patients (−23% and −11% for total cholesterol and TG, respectively).
In contrast to these significant findings, five other statin therapy studies did not find significant interactions between APO E genotype and plasma lipoprotein-lipid changes. However, in two of these studies, there was a trend for greater LDL cholesterol reductions in APO E2 and E3 genotype individuals. De Knijff et al. found that LDL cholesterol levels were reduced 41% in subjects with at least one APO E2 allele, 39% in APO E3 homozygotes, and 35% in those with at least one APO E4 allele. A similar trend was seen by O’Malley and Illingworth. In contrast to these significant findings, five other statin therapy studies did not find significant interactions between APO E genotype and plasma lipoprotein-lipid changes. However, in two of these studies, there was a trend for greater LDL cholesterol reductions in APO E2 and E3 genotype individuals. De Knijff et al. (8) found that LDL cholesterol levels were reduced 41% in subjects with at least one APO E2 allele, 39% in APO E3 homozygotes, and 35% in those with at least one APO E4 allele. A similar trend was seen by O’Malley and Illingworth (30) as LDL cholesterol levels were reduced somewhat more in APO E2 and E3 individuals (36 and 37%, respectively) compared with those with at least one APO E4 allele (31% reduction). Although no such trend was seen by Sanlehy et al. (37), their subjects had been on and remained on a lipid-lowering diet during drug therapy. Because dietary interventions have been found to reduce plasma total and LDL cholesterol more in APO E4 individuals (see below), these two therapies may counteract each other and result in similar responses in all APO E genotype groups. In the last study not reporting a significant interaction between APO E genotype and plasma lipoprotein-lipid changes with pravastatin therapy, no data were provided concerning the plasma total or LDL cholesterol changes, so it cannot be determined whether nonsignificant trends similar to those observed by De Knijff et al. (8) and O’Malley and Illingworth (30) were evident.

A recent study provides further evidence that the APO E genotype may not exert its entire effect on CV pathologies by altering plasma lipoprotein-lipid profiles. In a followup of 966 myocardial infarction survivors from the Scandinavian Simvastatin Survival Study (the “4S Trial”), untreated APO E4 individuals had an 80% greater risk of dying within 5.5 yr than untreated APO E2 or E3 individuals. However, simvastatin therapy reduced the risk of dying somewhat more in APO E4 than in E2 or E3 individuals, and although these genotype-dependent differences in risk reduction were not significant, the excess mortality evident in APO E4 individuals was eliminated with simvastatin therapy. This occurred despite the fact that simvastatin therapy reduced plasma LDL cholesterol levels to the same extent in APO E4 and E2/E3 individuals.

One problem with most of these studies is that, with the exception of the study by Nestel et al. (27), the APO E genotype distributions were extremely skewed. In contrast to these significant findings, five other statin therapy studies did not find significant interactions between APO E genotype and plasma lipoprotein-lipid changes. However, in two of these studies, there was a trend for greater LDL cholesterol reductions in APO E2 and E3 genotype individuals. De Knijff et al. (8) found that LDL cholesterol levels were reduced 41% in subjects with at least one APO E2 allele, 39% in APO E3 homozygotes, and 35% in those with at least one APO E4 allele. A similar trend was seen by O’Malley and Illingworth (30) as LDL cholesterol levels were reduced somewhat more in APO E2 and E3 individuals (36 and 37%, respectively) compared with those with at least one APO E4 allele (31% reduction). Although no such trend was seen by Sanlehy et al. (37), their subjects had been on and remained on a lipid-lowering diet during drug therapy. Because dietary interventions have been found to reduce plasma total and LDL cholesterol more in APO E4 individuals (see below), these two therapies may counteract each other and result in similar responses in all APO E genotype groups. In the last study not reporting a significant interaction between APO E genotype and plasma lipoprotein-lipid changes with pravastatin therapy, no data were provided concerning the plasma total or LDL cholesterol changes, so it cannot be determined whether nonsignificant trends similar to those observed by De Knijff et al. (8) and O’Malley and Illingworth (30) were evident.

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One problem with most of these studies is that, with the exception of the study by Nestel et al. (27), the APO E genotype distributions were extremely skewed. In addition, these studies include subjects with genetically determined hypercholesterolemia (FH) and subjects with hypercholesterolemia of unknown etiology. Studies are needed that enroll subjects more homogeneous with respect to the cause of their hyperlipidemia and that prospectively screen and select subjects on the basis of their APO E genotype to achieve a balanced study design with respect to APO E genotypes.

In summary, four studies using HMG-CoA reductase inhibitors have found significantly greater plasma lipoprotein-lipid reductions in APO E2 and possibly APO E3 genotype individuals compared with those with at least one APO E4 allele. Furthermore, of the five studies that did not report significant APO E genotype-dependent differences in plasma lipoprotein-lipid changes with statin therapy, two actually showed trends similar to those in the four studies with significant genotype-dependent changes. Thus the data are generally consistent in supporting the conclusion that APO E2, and perhaps also APO E3, genotype individuals respond more favorably in terms of plasma total and LDL cholesterol than APO E4 individuals to statin therapy. Some evidence indicates that this interaction may be sex specific, with the interaction being most evident in men, and there is also evidence that the entire effect of APO E genotype on CV disease may not be mediated by its impact of plasma lipoprotein-lipid profiles.

**Possible Mechanisms.** HMG-CoA reductase inhibitors reduce plasma cholesterol levels by inhibiting this rate-limiting enzyme in cholesterol biosynthesis. This inhibition is believed to increase the hepatic production of LDL receptors, thus increasing hepatic LDL uptake and reducing plasma LDL cholesterol levels. Individuals carrying the APO E4 allele tend to have lipoproteins enriched with apo E, which results in an enhanced binding capacity of these lipoproteins to the LDL receptor. This enhanced binding increases the removal rate of these lipoproteins by hepatocytes, increasing the intracellular concentration of cholesterol in the liver and causing a downregulation in the production of HMG-CoA reductase and LDL receptors. On the other hand, lipoproteins containing apo E2 have a reduced binding affinity for the LDL receptor; thus their plasma clearance rate is reduced. This lowers intracellular cholesterol levels and upregulates HMG-CoA reductase synthesis. Consequently, it is reasonable to expect that HMG-CoA reductase inhibitors would be less effective in reducing cholesterol levels in APO E4 individuals, as they may already have relatively low-HMG-CoA reductase activities. Data from the studies presented here provide some indirect support for this hypothesis.

**Probucol.** Two studies have investigated the interaction between APO E genotype and plasma lipoprotein-lipid changes following treatment with probucol. Nestruck et al. (28) compared the plasma total cholesterol changes in response to probucol in 89 hypercholesterolemic individuals, 34 of whom had FH while the remainder had hypercholesterolemia of unknown etiology. When both FH and non-FH subjects were considered together, those with the APO E4 genotype reduced plasma total cholesterol levels significantly more (−61 mg/dl) than APO E3 homozygous individuals (−46 mg/dl). However, when the two groups were compared separately, a significant genotype-dependent effect on plasma lipoprotein-lipid changes was seen in the FH (APO E4 = −70 mg/dl vs. APO E3 = −45 mg/dl) but not in the non-FH subjects.
and VLDL cholesterol and TG reductions were all significantly greater in APO E4 subjects compared with APO E3 homozygous individuals (Table 1). However, there were no differences in plasma HDL cholesterol changes with probucol between the two APO E genotype groups (Table 1). Thus the differences in the changes in total cholesterol were mainly due to differential LDL cholesterol changes following treatment.

One shortcoming of both of these studies is that APO E2 genotype individuals were not included. However, both studies provided some evidence that APO E4 genotype individuals respond more favorably in terms of plasma lipoprotein-lipid profiles than APO E3 homozygous individuals to probucol therapy.

Gemfibrozil. Three studies have assessed the interaction between APO E genotype and plasma lipoprotein-lipid changes with gemfibrozil treatment (25, 27, 37). Nestel et al. (27) found that subjects with at least one APO E2 allele were more likely to respond favorably to gemfibrozil therapy (plasma total cholesterol decrease >25% or plasma TG decrease >40%) than either APO E3 homozygous or APO E4 individuals. However, the greatest plasma HDL cholesterol increases were seen in APO E3 homozygous individuals. Manttari et al. (25) treated 230 dyslipidemic men from the Helsinki Heart Study with a combination of gemfibrozil and diet therapy. No difference was found in the response of genotype groups to the gemfibrozil treatment in this study. However, this may indicate that the gemfibrozil treatment was actually less effective in the E4 individuals, because all subjects underwent dietary therapy and APO E4 individuals generally respond more favorably to dietary interventions (see below). In the third study, by Sanlehy et al. (37), after long-term adherence to a lipid-lowering diet, hyperlipidemic men and women with the APO E2, E3, or E4 genotype all improved plasma lipoprotein-lipid profiles to the same extent with gemfibrozil therapy.

Thus, with respect to gemfibrozil therapy, one study indicates that APO E2 individuals are more likely to respond favorably, one other study reported results potentially consistent with this finding, and the final study found no effect of APO E genotype on plasma lipoprotein-lipid alterations.

Cholestyramine. Berglund et al. (1) found that APO E genotype did not affect the plasma total or LDL cholesterol reductions with cholestyramine therapy in 120 FH patients. However, plasma TG decreased with cholestyramine only in FH patients with the APO E2 genotype. Thus these data provide some evidence APO E2 individuals may respond more favorably to cholestyramine therapy.

Summary. A majority of the studies that have investigated the interaction between APO E genotype and plasma lipoprotein-lipid changes with medications have involved HMG-CoA reductase inhibitors. The results indicate there was a strong tendency for APO E2 and possibly APO E3 genotype individuals to respond more favorably to HMG-CoA reductase inhibitors than those with at least one APO E4 allele. However, the effect of APO E genotype may not solely be a result of its effect on plasma lipoprotein-lipids, as very recent evidence indicates that HMG-CoA reductase inhibitor therapy decreased the risk of dying more in APO E4 individuals than E2 or E3 individuals despite similar LDL cholesterol reductions in all genotype groups. In addition, there is some evidence that the responses of men may be more APO E genotype dependent. In contrast, studies using probucol indicate that APO E4 individuals respond with greater plasma lipoprotein-lipid profile improvements than APO E3 individuals. Of the three studies that assessed the effect of gemfibrozil, two found no significant genotype-dependent effects, but one found that plasma total cholesterol and TG levels were reduced significantly more in APO E2 than E3 or E4 individuals. The one study that investigated cholestyramine found some evidence that APO E2 individuals may respond more favorably, in terms of plasma lipoprotein-lipid levels, than APO E3 or E4 individuals. Thus the available data indicate that APO E4 individuals may respond more favorably to HMG-CoA reductase inhibitors than APO E3 individuals.

APO E Genotype and Plasma Lipoprotein-Lipid Changes with Hormone Replacement Therapy

A recent study indicates that APO E genotype appears to affect the plasma lipoprotein-lipid changes that occur with hormone replacement therapy in perimenopausal women (19). With 5 yr of continuous estrogen and cyclic progestin therapy, only women with APO E3 or E2 alleles decreased plasma total (−8.1%) and LDL cholesterol levels (−17.1%) and increased plasma HDL cholesterol levels (+3.1%), whereas no plasma total, LDL, or HDL cholesterol changes were evident in women with at least one APO E4 allele. Plasma TG levels increased significantly and to the same degree (16 vs. 27%) in both genotype groups.

Table 1. Plasma lipoprotein-lipid changes with probucol treatment as a function of APO E genotype

<table>
<thead>
<tr>
<th>APO E Genotype</th>
<th>APO E3</th>
<th>APO E4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔTotal cholesterol</td>
<td>-41</td>
<td>-90*</td>
</tr>
<tr>
<td>ΔLDL cholesterol</td>
<td>-34</td>
<td>-70*</td>
</tr>
<tr>
<td>ΔVLDL cholesterol</td>
<td>+8</td>
<td>-37*</td>
</tr>
<tr>
<td>ΔHDL cholesterol</td>
<td>-9</td>
<td>-9</td>
</tr>
<tr>
<td>ΔTG</td>
<td>+2</td>
<td>-8*</td>
</tr>
</tbody>
</table>

LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; Δ is defined as the respective lipoprotein-lipid level in mg/dl before treatment subtracted from the value after treatment. Data are from Eto et al. (12). *Significantly different from the Δ value in the APO E3 genotype group, P < 0.05.
The effect of tamoxifen, a nonsteroidal estrogen antagonist used for breast cancer prevention in high-risk women and as an adjuvant hormonal therapy in primary breast cancer, on plasma lipoprotein-lipid changes as a function of APO E genotype has also been assessed (22). Initial case reports indicated that APO E3 women might be more susceptible to abnormal plasma lipoprotein-lipid elevations with tamoxifen (2, 21). However, in a followup study by Hozumi et al. (22) in a larger sample of women, both APO E3 and E4 women increased plasma TG to the same extent with tamoxifen treatment, and neither group changed plasma cholesterol levels.

**APO E Genotype and Plasma Lipoprotein-Lipid Changes with Dietary Interventions**

The ability of dietary interventions to improve plasma lipoprotein-lipid profiles varies greatly among individuals. A number of studies have compared the effects of dietary interventions on plasma lipoprotein-lipid changes in individuals with different APO E genotypes, and this literature has been summarized in recent reviews (10, 31, 41). In general, it appears that low-fat diet interventions tend to reduce plasma LDL cholesterol and, perhaps, plasma total cholesterol levels more in APO E4 individuals than in either APO E2 or E3 individuals. However, these effects are not entirely consistent throughout the literature and may depend on a number of factors, including sex, initial plasma lipoprotein-lipid levels, the dietary modification employed, and whether subjects have a genetically determined dyslipidemia. In contrast, there appears to be little consensus in the literature regarding the interaction between APO E genotype and the effect of dietary modification on plasma HDL cholesterol or TG levels.

**APO E Genotype and Plasma Lipoprotein-Lipid Changes with Exercise Training**

It is generally accepted that exercise training positively affects many of the components of the plasma lipoprotein-lipid profile that influence a person’s CV disease risk (48). When reviewing all of the available data, Wood and Stefanick (48) concluded that long-term endurance exercise training generally results in ~10 mg/dl reductions in plasma total and LDL cholesterol, although these changes are frequently not statistically significant. On the other hand, plasma HDL cholesterol levels appear to increase by ~5 mg/dl when endurance exercise training lasts longer than 12 wk (48). In addition, most evidence indicates that plasma HDL2 cholesterol, the most protective subfraction of HDL cholesterol, also increases by ~3–4 mg/dl with endurance exercise training (48).

However, most studies indicate that there are dramatic interindividual differences in the responses of plasma lipoprotein-lipid levels to even highly standardized endurance exercise training interventions. For example, Williams et al. (47) reported that plasma HDL and HDL2 cholesterol increases with 1 yr of endurance exercise training in middle-aged men averaged 4.2 and 2.9 mg/dl, respectively. However, on an individual basis the HDL cholesterol changes with training ranged from a 20 mg/dl increase to an 8 mg/dl decrease, with at least 20% of the men actually exhibiting reductions in plasma HDL cholesterol with training. Furthermore, HDL2 cholesterol changes ranged from an 18 mg/dl increase to a 5 mg/dl decrease, again with ~26% of the men actually eliciting decreases in plasma HDL2 cholesterol levels with training. Such highly variable responses to a standardized exercise training intervention combined with strict dietary control raise the possibility that genetic factors may be involved in mediating these responses.

The first evidence that plasma lipoprotein-lipid responses to exercise training might be influenced by APO E genotype was provided by Taimela et al. (39). They assessed the plasma lipoprotein-lipid profiles of ~1,500 Finnish children and young adults aged 9–24 yr in whom leisure-time physical activity was assessed by questionnaire. Leisure-time physical activity levels did not affect plasma lipoprotein-lipid profiles in the females. However, in the males, in addition to physical activity levels affecting plasma lipoprotein-lipid profiles, the interaction between apo E phenotype and physical activity also affected plasma lipoprotein-lipid levels. In APO E4/4 men physical activity levels did not affect plasma lipoprotein-lipid levels, whereas in APO E3/4 and 3/3 men, there was an inverse effect of physical activity level on plasma total cholesterol and LDL cholesterol and a positive effect on HDL cholesterol/total cholesterol ratio. In APO E2/3 men there were even stronger relationships between physical activity levels and the same components of the plasma lipoprotein-lipid profile. However, there are a number of inconsistencies between the text and figures in Taimela et al. (39) with respect to these apo E phenotype-physical activity interaction effects on plasma lipoprotein-lipid levels. Thus, bearing in mind these inconsistencies, these data, though cross-sectional, may be consistent with the possibility that exercise training does not affect plasma lipoprotein-lipid levels in APO E4 individuals, has a moderate effect in APO E3 individuals, and has an even greater effect in APO E2 individuals.

More recently, in another cross-sectional study St.-Amand et al. (38) concluded that APO E genotype appeared to affect the relationships observed between the different plasma lipoprotein-lipid levels and CV fitness. Increased CV fitness was most closely inversely associated with plasma TG levels in APO E2 men and women ($r = -0.55, P < 0.05$ for both). The relationships between CV fitness and plasma TG levels were also significant in APO E3 men and women ($r = -0.31$ and $r = -0.46$, respectively; both $P < 0.05$). However, CV fitness was not associated with plasma TG levels in APO E4 men or women ($r = 0.31$ and $-0.26$, respectively; both not significant). The relationships between CV fitness and plasma total, LDL, VLDL, HDL, and HDL2 cholesterol were significant in APO E3 women, whereas in APO E2 women only VLDL cholesterol and
in APO E4 women only HDL cholesterol were significantly related to CV fitness. In men the only significant relationships were between CV fitness and HDL and HDL₂ cholesterol levels in APO E3 men. The results of this study may have been influenced by the fact that two to three times as many APO E3 men were studied as APO E2 and E4 men, whereas the number of women in each APO E genotype group was roughly similar. The authors concluded that plasma lipoprotein-lipid profiles of APO E2 individuals appear to be especially affected by increased CV fitness. However, while this does appear to be the case for plasma TG levels, the data are more consistent with the possibility that the overall plasma lipoprotein-lipid profiles of APO E3 men and women appear to affected more by increased CV fitness than those of APO E2 and E4 men and women.

In a third cross-sectional study, we recently reported that APO E genotype was not associated with plasma lipoprotein-lipid levels in sedentary postmenopausal women or postmenopausal women who had undergone 5–6 h/wk of low- to moderate-intensity aerobic activity for the previous 12 yr (Hagberg JM, McCole SD, Ferrell RE, Zmuda JM, Rodgers KS, Wilund KR, and Moore GE, unpublished observations). Furthermore, postmenopausal women athletes with only APO E3 or E4 alleles who ran an average of 30 miles/wk for the preceding 15 yr had plasma lipoprotein-lipid profiles only slightly better, in terms of total, LDL, HDL, and HDL₂ cholesterol and TG levels, than the sedentary or physically active women. Only women distance runners with at least one APO E2 allele had better plasma lipoprotein-lipid profiles than the sedentary and physically active women. Women athletes with at least one APO E2 allele also had better overall plasma lipoprotein-lipid profiles than women distance runners with only APO E3 or E4 alleles, despite the fact that they were otherwise similar in terms of training mileage and history, body composition, diet, and hormone replacement therapy status.

We recently published, to our knowledge, the first longitudinal intervention study assessing the impact of APO E genotype on plasma lipoprotein-lipid responses to exercise training and found that middle-aged and older APO E2 genotype men had larger overall plasma lipoprotein-lipid profile improvements with prolonged endurance exercise training than otherwise comparable APO E3 and E4 genotype men (Table 2) (15). Men in all APO E genotype groups generally reduced body weight and percent body fat to the same degree with exercise training. The APO E2 and E3 men tended to reduce plasma total and LDL cholesterol more with exercise training than E4 men, but the differences were not significant. However, APO E2 genotype men increased plasma HDL cholesterol three to four times more than E3 and E4 genotype men. APO E2 genotype men also increased plasma HDL₂ cholesterol dramatically more with exercise training than APO E3 and E4 genotype men. APO E2 and E3 genotype men both decreased plasma TG more with exercise training than E4 men. The differences in plasma HDL and HDL₂ cholesterol increases with exercise training among APO E genotype groups remained significant after controlling for body weight changes, whereas the reduction in plasma TG in the APO E2 genotype men tended to still be greater than in the APO E4 men after controlling for changes in body weight (P = 0.09). Thus these longitudinal intervention data provide stronger evidence supporting the conclusion that the plasma lipoprotein-lipid profiles of APO E2 individuals may be affected most by prolonged endurance exercise training. Plasma lipoprotein-lipid profiles of APO E4 individuals do not appear to change as a result of exercise training, whereas APO E3 individuals appear to have responses intermediate between those of E2 and E4 individuals.

Summary. Thus the results of both cross-sectional and longitudinal studies consistently indicate that APO E2 and E3 individuals appear to improve plasma lipoprotein-lipid profiles more than otherwise similar APO E4 individuals with endurance exercise training.

**Overall Summary**

A number of therapeutic options are available for dyslipidemic individuals to improve their plasma lipoprotein-lipid profiles with the ultimate goal of reducing CV disease risk. A substantial amount of data are available assessing the potential interactive effect between APO E genotype and various cholesterol-lowering medications, diet, and exercise training on plasma lipoprotein-lipid levels. These results are generally quite consistent in indicating that APO E2 and possibly E3 individuals appear to respond best to statin, gemfibrozil, exercise training, hormone replacement therapy, and, possibly, cholestyramine treatments. On the other hand, the data also generally consistently indicate that APO E4 individuals appear to respond best to dietary and probucol therapy. While these data are not yet completely definitive, they lend strong support for the possibility that in the near future individuals will be directed to what might be their optimal therapy for improving plasma lipoprotein-lipid profiles and CV disease risk based partially on APO E genotype.

A number of benefits would be afforded by using such a new treatment paradigm. First and foremost is the fact that dyslipidemic patients would have a greater

### Table 2. Plasma lipoprotein-lipid changes with exercise training as a function of APO E genotype

<table>
<thead>
<tr>
<th>APO E Genotype</th>
<th>E2</th>
<th>E3</th>
<th>E4</th>
</tr>
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<tbody>
<tr>
<td>Total cholesterol</td>
<td>−7 ± 1</td>
<td>−12 ± 4</td>
<td>0 ± 5</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>−11 ± 10</td>
<td>−9 ± 4</td>
<td>−2 ± 4</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>8 ± 4</td>
<td>3 ± 1</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>HDL₂ cholesterol</td>
<td>5 ± 3</td>
<td>1 ± 1</td>
<td>−1 ± 1</td>
</tr>
<tr>
<td>HDL₃ cholesterol</td>
<td>3 ± 1</td>
<td>2 ± 1</td>
<td>3 ± 1</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>−32 ± 16</td>
<td>−29 ± 8</td>
<td>1 ± 1</td>
</tr>
</tbody>
</table>

All values are expressed in units of mg/dl and are means ± SE. Data are from Ref. 15. * P < 0.01 and † P < 0.05 vs. APO E4 group. ‡ P < 0.01 vs. APO E3 group.
likelihood of receiving optimal therapy for their abnormal plasma lipoprotein-lipid profiles more rapidly, thus more effectively decreasing their further exposure to this critical CV disease risk factor. Inherent within this benefit is the fact that such a treatment paradigm would also decrease the likelihood of nonresponders, thus reducing the prolonged exposure to an abnormal plasma lipoprotein-lipid profile and its associated increased CV disease risk, while different treatment options are explored. Second, a major determinant of patient adherence to therapeutic interventions is self-efficacy, i.e., the individual’s belief that they can adhere to the intervention and that it will benefit them. It is possible that the knowledge that an individual has a genetic predisposition to respond favorably to a specific intervention is likely to improve their self-efficacy, which is especially important for lifestyle interventions including diet and physical activity. These benefits must be weighed against the negative aspects of such a paradigm. One major concern, especially in the current world of health care, is that of cost. However, genotyping at a single well-defined locus will be a relatively low-cost medical diagnostic test when done commercially in large volumes.

It is also important to remember that the present data provide strong support that genotype at a single chromosomal location, APOE, interacts with various cholesterol-lowering interventions to differentially affect plasma lipoprotein-lipid changes. Also, one other locus, lipoprotein lipase PvuII, appears to interact with exercise training to differentially affect the plasma lipoprotein-lipid improvements, although only minimal data are available to support this as a “candidate” gene locus (16; and Hagberg et al., unpublished observations). To date, studies have attempted to identify only single gene effects, when it is highly likely that these responses are polygenic. With the completion of the sequence of the entire human genome, an overwhelming number of loci will be available to assess as candidate genes affecting these responses. In the future, identifying the optimal therapy to improve plasma lipoprotein-lipid profiles in individuals will undoubtedly require genotyping at loci that are at present unidentified.

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