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(54) CETP TAQIB POLYMORPHISM AS RISK FACTOR FOR DEVELOPMENT OF CORONARY HEART DISEASE

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(57) **ABSTRACT**

Disclosed is method for assessing risk for the development of cardiovascular disease in an individual. The method includes isolating nucleic acid from the individual, analyzing the nucleic acid for the presence of the TaqIB polymorphism of the cholesteryl ester transfer protein gene, determining from the analysis whether the individual is homozygous for the TaqIB polymorphism; is heterozygous for the TaqIB polymorphism; or does not possess the TaqIB polymorphism. Risk for the development of cardiovascular disease is assessed in the individual on the basis of these determinations. Additional determinations of one or more known factors of cardiovascular disease risk may also be assessed. Methods for analysis of genomic DNA for the presence of the TaqIB polymorphism are provided. Also disclosed is a kit for assessing risk for the development of cardiovascular disease in an individual. The kit contains useful reagents, such as oligonucleotide primers for the amplification of a suitable section of the first intron of the cholesteryl ester transfer protein gene encompassing the TaqI restriction site of the B1 allele of the CETP gene. Optionally, the kit also contains indicators for additional known factors of cardiovascular disease risk.

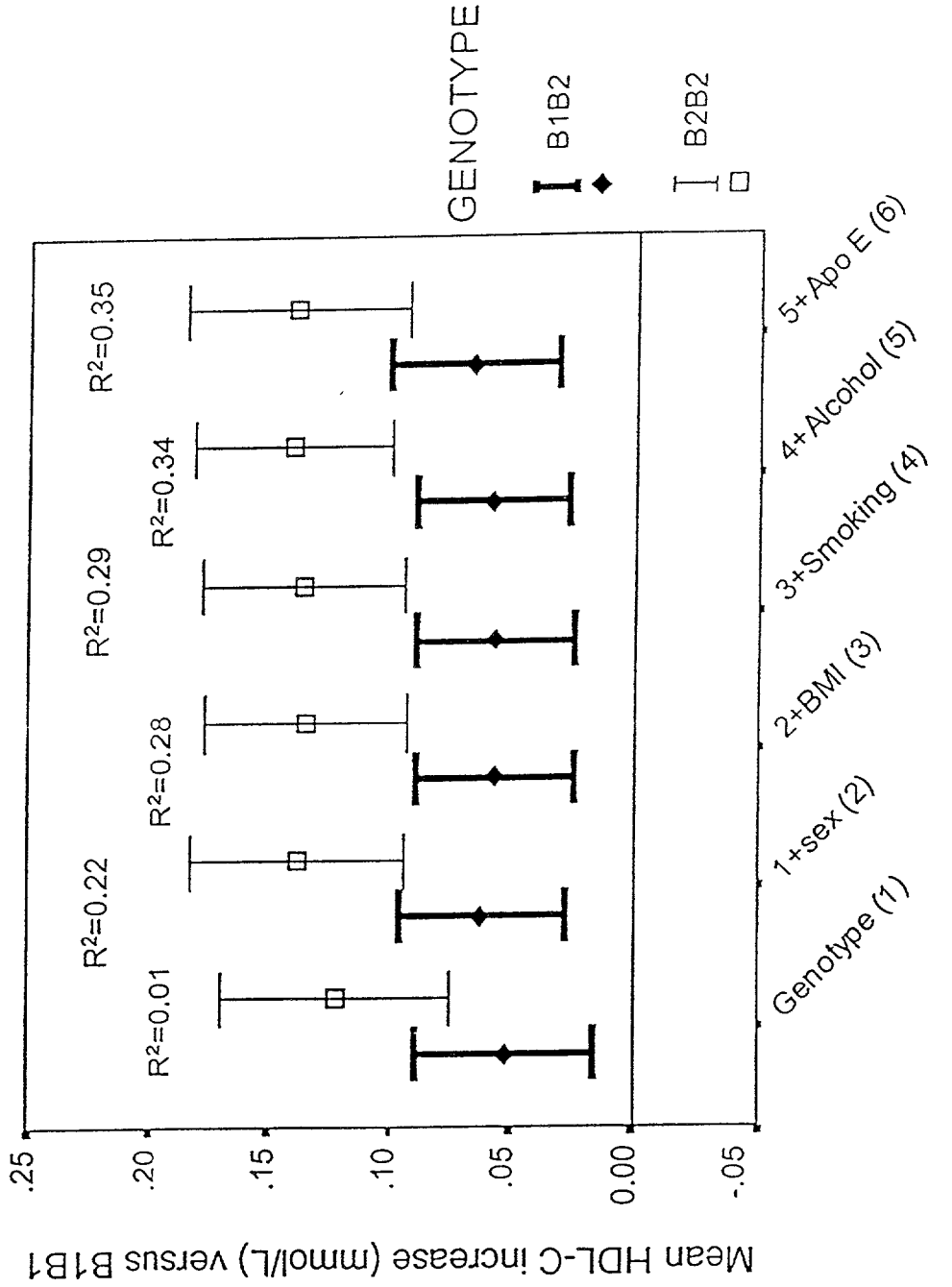
GENOTYPE
B1B2
B2B2
R²=0.01
R²=0.22
R²=0.28
R²=0.29
R²=0.34
R²=0.35
Genotype (1)
1+sex (2)
2+BMI (3)
3+Smoking (4)
4+Alcohol (5)
5+Apo E (6)
Regression models
Mean HDL-C increase (mmol/L) versus B1B1
.25
.20
.15
.10
.05
0.00
-.05

FIG. 1

CETP TAQIB POLYMORPHISM AS RISK FACTOR FOR DEVELOPMENT OF CORONARY HEART DISEASE

GOVERNMENT SUPPORT

[0001] This work was supported by grants HL54776 and NIH/NHLBI, contract NO1-38038 and contract 53-K06-5-10, from the US Department of Agriculture Research Service, and as such the U.S. Government owns certain rights in the invention.

BACKGROUND OF THE INVENTION

[0002] Cholesteryl ester transfer protein (CETP) facilitates the exchange of triglycerides and cholesteryl esters between lipoprotein particles. In humans, CETP mRNA encodes a polypeptide of MR 53,000, which is n-glycosylated at four sites, giving rise to the mature form of CETP of MR 74,000 (Drayna et al., *Nature* 327: 632-634 (1987)). CETP is expressed primarily in liver, spleen and adipose tissue, and lower levels have been detected in the small intestine, adrenal gland, heart, kidney and skeletal muscle (Drayna et al., *Nature* 327: 632-634 (1987); Bruce and Chouinard Jr., *Annu. Rev. Nutr.* 18: 297-330 (1998)). The CETP gene encompasses 16 exons, and it has been localized on chromosome 16q21 adjacent to the LCAT gene. Several mutations at the CETP locus have been identified resulting in absence of detectable CETP mass and/or activity (Yamashita et al., *Curr. Opin. Lipidol.* 8: 101-110 (1997)). These mutations are common in Japanese populations (Inazu et al., *N. Engl. J. Med.* 323: 1234-1238 (1990); Koizumi et al., *Atherosclerosis* 90: 189-196 (1991); Takegoshi et al., *Atherosclerosis* 96: 83-85 (1992); Inazu et al., *J. Clin. Invest.* 94: 1872-1882 (1994)) although some have been recently reported in Caucasian subjects (Hill et al., *Clin. Biochem.* 30: 413-418 (1997); Tamminen et al., *Atherosclerosis* 124: 237-247 (1996)). CETP deficiency is associated with hyperalphalipoproteinemia, primarily due to an increase of cholesteryl ester-enriched large size HDL. Conversely, the triglyceride rich lipoproteins and the LDL are smaller and triglyceride enriched, reflecting its role in neutral lipid exchange (Yamashita et al., *Curr. Opin. Lipidol.* 8: 101-110 (1997).

[0003] Several common restriction fragment length polymorphisms (RFLPs) have been reported in the CETP gene locus (Drayna and Lawn, *Nucleic Acids Res.* 15: 4698 (1987); Freeman et al., *Nucleic Acids Res.* 17: 2880 (1989); Zuliani and Hobbs, *Nucleic Acids Res.* 18: 2834 (1990)). The most studied RFLP to date has been the TaqIB, which has been shown to be a silent base change affecting the 277th nucleotide in the first intron of the gene (Drayna and Lawn, *Nucleic Acids Res.* 15: 4698 (1987)). The B2 allele (absence of the TaqI restriction site) at this polymorphic site has been associated in normolipemic subjects with increased HDL-C levels and decreased CETP activity and levels (Kondo et al., *Clin. Genet.* 35: 49-56 (1989); Freeman et al., *Arterioscler. Thromb.* 14: 336-344 (1994); Hannuksela et al., *Atherosclerosis* 110: 35-44 (1994); Kuivenhoven et al., *Arterioscler. Thromb. Vasc. Biol.* 17: 560-568 (1997)), thus, resembling a mild form of CETP deficiency. It has been suggested that this association may be population specific (Tenkanen et al., *Hum. Genet.* 87: 574-578 (1991); Mitchell et al., *Human Biology* 66: 13-25 (1994)) and highly influenced by environmental factors such as alcohol consumption and tobacco smoking (Hannuksela et al., *Atherosclerosis* 110: 35-44 (1994); Fumeron et al., *J. Clin. Invest.* 96: 1664-1671 (1995); Kauma et al., *Hum. Genet.* 97: 156-162 (1996)). Moreover, Kuivenhoven et al. (*N. Engl. J. Med.* 338: 86-93 (1998)) has shown an interaction between the TaqIB genotype and the progression of coronary heart disease following therapy. These observations could be of significant relevance, since low plasma HDL levels are associated with an increase in coronary artery disease risk (Gordon et al., *Am. J. Med.* 62: 707-714 (1977); Gordon and Rifkind, *N. Engl. J. Med.* 321: 1311-1316 (1989)). Moreover, clinical evidence suggests that an increase of 1% in the plasma HDL-C levels is associated with a reduction in cardiovascular morbidity and mortality of 2-3% (Manninen et al., *JAMA* 260: 641-651 (1988)). Therefore, CETP could have a relevant role in atherogenesis through its effects on HDL metabolism.

BRIEF DESCRIPTION OF THE FIGURES

[0004] **FIG. 1** is a graphical representation of data from sensitivity analysis of six different models. Regression coefficients and 95% confidence intervals for B1B2 and B2B2 genotypes, respectively, are compared with B1B1 when each indicated variable was progressively included into the linear regression models. The respective models include the following: Model 1: CETP genotype; Model 2: Model 1+gender; Model 3: Model 2+body mass index (BMI); Model 4: Model 3+tobacco smoking; Model 5: Model 4+alcohol consumption; Model 6: Model 5+ApoE genotype. R-squared were included in the figure to show the variability accounted for each regression model.

SUMMARY OF THE INVENTION

[0005] The present invention relates to a method for assessing risk for the development of cardiovascular disease in an individual. The method comprises isolating nucleic acid from the individual, analyzing the nucleic acid for the presence of the TaqIB polymorphism of the cholesteryl ester transfer protein gene, determining from the analysis whether the individual is homozygous for the TaqIB polymorphism; is heterozygous for the TaqIB polymorphism; or does not possess the TaqIB polymorphism. Risk for the development of cardiovascular disease is assessed in the individual on the basis of these determinations. In one embodiment, additional determinations of one or more known factors of cardiovascular disease risk are also assessed. In a preferred embodiment, the genomic DNA is analyzed for the presence of the TaqIB polymorphism by restriction analysis of an amplified fragment for the presence of a TaqI restriction site at a position corresponding to nucleotide 277 of the first intron. Useful primers for PCR amplification of a suitable fragment are provided.

[0006] Another aspect of the present invention relates to a kit for assessing risk for the development of cardiovascular disease in an individual. The kit comprises oligonucleotide primers for the amplification of a suitable section of the first intron of the cholesteryl ester transfer protein gene encompassing the TaqI restriction site of the B1 allele of the CETP gene. The kit optionally further comprises indicators for additional known factors of cardiovascular disease risk.

DETAILED DESCRIPTION OF THE INVENTION

[0007] Cholesteryl ester transfer protein (CETP) facilitates the exchange of triglycerides and cholesteryl esters between lipoprotein particles, a key step in reverse cholesterol transport in humans. Variations at the CETP locus have previously been shown to be determinants of the levels and activity of CETP and high density lipoprotein plasma concentration. One common variation of the CETP locus is the CETP gene polymorphism, TaqIB (referred to herein as the TaqIB polymorphism) which is located in intron 1. The present invention is based on the identification of a statistically significant correlation of the absence of the TaqIB polymorphism with the frequency, phenotypic expression and potential modulation of coronary heart disease (also referred to herein as cardiovascular disease) development in the general population.

[0008] Detailed in the Exemplification section below is an analysis of the association of the TaqIB polymorphism with interindividual variability in lipid levels, lipoprotein subclass profiles, CETP activity, and cardiovascular disease risk, examined in a population-based sample of 1411 men and 1505 women from the Framingham Offspring Study. The findings reveal a correlation of the absence of the TaqIB polymorphism (denoted as the homozygous presence of the B1 allele) with the development of cardiovascular disease/coronary heart disease. Absence of the TaqIB polymorphism (presence of the B1 allele) also correlates with decreased HDL-C levels in men and women, and also with decreased apoA-I levels in men. The presence of the TaqIB polymorphism (denoted as presence of the B2 allele) correlates with about 30% lower risk of developing coronary heart disease.

[0009] These findings are directly applicable to methods for ascertaining predisposition to disease development. One aspect of the present invention relates to a method for assessing risk for the development of cardiovascular disease in an individual by examination of the individual for the presence or absence of the TaqIB polymorphism. The term cardiovascular disease as used herein includes, without limitation, conditions such as coronary artery disease, myocardial infarction, angina pectoris, coronary insufficiency and coronary death.

[0010] The method involves isolation of nucleic acid from an individual, followed by analysis of the nucleic acid for the presence or absence of the TaqIB polymorphism. This analysis is used to determine if the individual is homozygous for the TaqIB polymorphism (B2B2), is heterozygous for the TaqIB polymorphism (B1B2), or does not possess the TaqIB polymorphism (B1B1). Once the genotype of the individual is determined, the risk for the development of cardiovascular disease in the individual is assessed on the basis of this genotype determination utilizing the correlations presented in the Exemplification section below.

[0011] To determine risk of disease development in an individual, one applies statistically significant correlations made in a population between disease development and presence of a given factor or factors, to the individual. Risk, as the term is used herein, refers to the likelihood of disease development. Risk is determined by consideration of one or more disease factors present in, or associated with, the individual. A factor, or risk factor, is a specific condition of an individual (e.g., genotype, physiologic state, behavior, and environmental condition) which has a documented, statistically significant correlation with development of the disease in question. The factor may be known to contribute to disease progression or merely known associated with disease development. Risk is generally used to describe an increased likelihood of disease development, but may also describe a decreased likelihood (e.g., protection). A determination of decreased likelihood, generally referred to as decreased risk, is often made with respect to consideration of other known (increased) risk factors. As an application of statistical analysis to real life predispositions, risk is conceptually determined relative to an otherwise similar individual having a different complement of all factors being considered (e.g., genetic or behavioral/environmental).

[0012] The TaqIB polymorphism exhibits codominance for the observed phenotypes. A determination that the individual does not possess the TaqIB polymorphism indicates a high increased risk for the development of cardiovascular disease, relative to a determination that the individual is homozygous for the TaqIB polymorphism. A determination that the individual is heterozygous for the TaqIB polymorphism indicates a moderate increased risk for cardiovascular disease development relative to a determination that the individual is homozygous for the TaqIB polymorphism. A determination that the individual is homozygous for the TaqIB polymorphism indicates no increased risk for the cardiovascular disease development. Indeed, such a determination may actually indicate decreased risk in the form of protection from the disease when considered with other known factors of cardiovascular disease development.

[0013] Preferably, the risk for the development of cardiovascular disease in the individual is assessed on the basis of the presence or absence of the TaqIB polymorphism in combination with additional determinations of one or more known factors of cardiovascular disease risk. Because the development of cardiovascular disease is influenced by a variety of factors, both genetic and environmental, the risk for disease development is optimally determined by consideration of as many factors as possible. Other known genetic factors include, without limitation, apolipoprotein E, lipoprotein lipase, and the low density lipoprotein (LDL) receptor of the individual. Mutations in the individual's angiotensin-converting enzyme gene have also been identified as factors in the development of cardiovascular disease. Specific mutations and methods for their identification is disclosed in Raynolds et al., U.S. Pat. No. 5,800,990 (1998), the contents of which are incorporated herein by reference. Environmental factors include, without limitation, diet (e.g., fat and cholesterol), level of exercise, alcohol consumption, and smoking. Each of these factors contributes to the susceptibility or protection of the individual from cardiovascular disease. Therefore, the overall risk of the individual is best assessed by taking as many known factors into account as possible.

[0014] In addition, several physiologic factors (caused by either genetic or environmental factors) also play a significant role in the development of cardiovascular disease. Examples of such are age, weight, blood pressure (systolic and diastolic), lipid parameters (e.g., total cholesterol, triglycerides, low and high density lipoproteins), and glycemic parameters (glucose and/or insulin). Elevated plasma homocysteine levels are also used to indicate substantially increased risk of coronary heart disease. Assays for measuring homocysteine levels in biological fluids are known in the art. For example, specific assays are disclosed by Tan et al., U.S. Pat. No. 5,998,191 (1999), the contents of which are incorporated herein by reference.

[0015] Techniques for calculating risk of cardiovascular disease from a plurality of factors are known in the art. One example is the "Cardiovascular Risk Manager" of D. Cuypers (U.S. Pat. No. 5,396,886 (1995)), the contents of which are incorporated herein by reference. Additional examples are provided by the American Heart Association in Anderson et al. (*Circulation* 83: 356-362 (1991)) and the World Health Organization (Erica Research Group, *The Second European Heart Journal* 12: 291-297 (1991)).

[0016] Both male and female individuals may be analyzed for risk of cardiovascular disease by the presence or absence of the TaqIB polymorphism. Due to the small number of coronary heart disease events in the group of female individuals in the Framingham Offspring Study, a statistically significant correlation of the association of cardiovascular disease with the absence of the TaqIB polymorphism were made in male individuals only. However, the findings made in this study are also applicable to female individuals.

[0017] Detection of the TaqIB polymorphism is accomplished by examination of both copies of the CETP gene in an individual. The TaqIB polymorphism is characterized by the absence of a TaqI restriction endonuclease site in the first intron of the CETP gene. One reliable detection method is to isolate genomic nucleic acid from the individual and examine relevant sequences of the first intron of the CETP gene. The relevant sequences may be isolated by PCR amplification of a suitable section of the first intron of the CETP gene. These sequences can be analyzed by restriction analysis of the fragment for the presence or absence of a TaqI restriction site at the position which corresponds to nucleotide 277 of the first intron of the gene. A suitable section of the first intron is characterized as containing nucleotide 277 and sufficient surrounding nucleotides, such that if the relevant TaqI site were present, the resulting amplified nucleotide would serve as substrate for cleavage. Preferably, the suitable section is between 100 and 1000 base pairs in length, with the putative restriction site located in a central, asymmetrical position within the section, such that cleavage at that site generates two bands which are easily and accurately discernable from each other, and from an undigested band when size fractionated (e.g., on a DNA gel).

[0018] In a preferred embodiment, the suitable section of the first intron is 535 base pairs in length. This section may be amplified using the forward primer 5'-CACTAGCCCAGAGAGAGGAGTGCC -3' and the reverse primer 5'-CTGAGCCCAGCCGCACACTAAC -3'. It is within the abilities of one of skill in the art to devise additional primers which will amplify sections of the nucleic acid suitable for use in the present invention.

[0019] The presence of the sequence unique to the TaqIB polymorphism can alternatively be identified, or ruled out, by other methods common in the art. One such method is direct sequencing of the relevant nucleotides. Another method is probing the relevant nucleic acid sequences with labeled oligonucleotide probes which specifically hybridize to one or the other allele, followed by detection of the label to identify allele presence. These and additional methods of detection of a polymorphism are commonly known in the art and within the ability of one of average skill, and as such the present invention encompasses their use.

[0020] The mechanism by which the TaqIB polymorphism affects CETP activity is not known. Without wishing to be bound by theory, it is unlikely that the nucleotide sequence change at the location of the TaqI site represents a functional mutation. The most plausible explanation is that the polymorphism is in linkage disequilibrium with a still unknown functional mutation in the CETP gene. Once this functional mutation is identified, the B1 and B2 alleles can alternatively be determined by identification or absence of the functional mutation.

[0021] Another aspect of the present invention relates to the use of the TaqIB polymorphism as a marker for decreased atherogenic lipid profile in an individual. The presence of the TaqIB polymorphism correlates with decreased HDL-C levels in men and women, and also for decreased apoA-I levels in men. Statistically relevant correlations of the TaqIB polymorphism with decreased HDL-C levels and decreased apoA-I levels in the individuals of the study are detailed in the Exemplification section below. These results indicate that the CETP gene locus plays a significant role in determining HDL-C variability, apoA-I levels, and LDL size. These associations translate into a less atherogenic lipid profile in individuals of both genders which possess the TaqIB polymorphism. Identification of the TaqIB polymorphism in an individual by the above described methods can therefore also be applied to determining risk for decreased HDL-C levels and for decreased apoA-I levels, to ascertain risk of developing other such pathologies which result from or correlate with such decreases.

[0022] Another aspect of the present invention relates to a diagnostic kit for determining susceptibility to the development of cardiovascular disease in an individual. The kit comprises components required for the performance of the above indicated methods for assessing risk for the development of cardiovascular disease in an individual. This includes, without limitation, components for the identification of the TaqIB polymorphism in an individual. Preferably, the components allow the discernment between heterozygosity and homozygosity in the individual. In one embodiment, the kit comprises oligonucleotide primers for the amplification of a suitable section of the first intron of the CETP gene encompassing the TaqI restriction site of the TaqIB polymorphism of the CETP gene, specific examples of which are described above. In another embodiment, the kit comprises alternate means for identifying the TaqIB polymorphism. Other components for the PCR and restriction digestion analysis may optionally be included in the kit. Preferably, the kit of the present invention also contains components for assessment (referred to herein as indicators) of other known factors in cardiovascular disease development. Such factors are also discussed in detail above. The form of the indicators will depend on the factors which are assessed, and can be determined by a practitioner of average skill in the art.

Exemplification

[0023] Subject Characteristics

[0024] To investigate the frequency and phenotypic association of the TaqIB CETP polymorphism at the population level, a total of 2876 subjects (1411 males and 1505 females) who participated in the Framingham Offspring Study, and who had lipid values available off lipid altering medication, were analyzed. Table 1 provides a summary of the demo-

graphic, genotypic and biochemical characteristics of the participants according to gender. The mean age of men and women at examination was 51.6 and 51.2 years, respectively. Although a similar proportion of men and women were smokers (23.4% and 22.8%, respectively), male subjects smoked more cigarettes per day (5.8±12.5) than the female subjects (4.7±10.3; p<0.016), and over half of the female participants (54.2%) were post-menopausal. There was no significant difference in the frequency of the B2 allele between men and women and the distribution of alleles was consistent with Hardy-Weinberg equilibrium. Alcohol consumption, body mass index (BMI), plasma LDL-C, total apoB, triglyceride and glucose levels were significantly higher in men compared to women, and total HDL-C, HDL_2-C and HDL_3-C concentrations were significantly higher in female participants. The ApoE genotype distribution was similar in men and women (P=0.398).

TABLE 1

Demographic, Genotypic, and Biochemical Characteristics of Framingham Offspring Study Participants According to Sex

	Men (n = 1411)	Women (n = 1505)	P (Men vs Women)
TaqIB-CETP genotype			
B1B1, %	428 ± 30.3	477 ± 31.7	—
B1B2, %	713 ± 50.6	754 ± 50.1	—
B2B2, %	270 ± 19.1	274 ± 18.2	—
B2 allele frequency	0.444	0.433	—
ApoE alleles			
E2, %	12.0	14.7	—
E3, %	67.2	62.9	—
E4, %	20.8	22.4	—
Age, y	51.6 ± 10.1	51.2 ± 9.7	0.247
BMI, kg/m^2	27.6 ± 3.9	25.9 ± 5.3	<0.001
TC, mmol/L	5.28 ± 0.96	5.30 ± 1.01	0.394
LDL-C, mmol/L	3.47 ± 0.85	3.28 ± 0.93	<0.001
HDL-C, mmoL/L	1.12 ± 0.29	1.45 ± 0.39	<0.001
HDL_2-C, mmol/L	0.13 ± 0.10	0.26 ± 0.15	<0.001
HDL_3-C, mmol/L	0.99 ± 0.23	1.20 ± 0.28	<0.001
TG, mmol/L	1.54 ± 1.12	1.23 ± 1.14	<0.001
ApoA-I, g/L	1.34 ± 0.24	1.55 ± 0.31	<0.001
ApoB, g/L	1.02 ± 0.24	0.95 ± 0.26	<0.001
TC/HDL ratio	5.00 ± 1.50	3.90 ± 1.50	<0.001

TABLE 1-continued

Demographic, Genotypic, and Biochemical Characteristics of Framingham Offspring Study Participants According to Sex

	Men (n = 1411)	Women (n = 1505)	P (Men vs Women)
Glucose, mmol/L	5.41 ± 1.48	5.03 ± 1.26	<0.001
Alcohol, oz/wk	4.0 ± 5.3	1.8 ± 2.9	<0.001
Cigarettes/d (in smokers)	5.8 ± 12.5	4.7 ± 10.3	0.016
Postmenopausal, %	—	54.2	—
On estrogen therapy,* %	—	12.9	—

Values are mean ± SD or percentages: TC indicates total cholesterol; TG, triglycerides.
*Includes hormonal replacement therapy and the use of oral contraceptives.

[0025] Association of the TaqIB Polymorphism with Variations in Plasma Levels of Lipids, Lipoproteins, Apolipoproteins and CETP Activity

[0026] In men and women, the three genotype groups were equivalent with respect to age and BMI, as indicated in Table 2. Male homozygotes for the B1 allele had lower HDL-C levels (1.07"0.27 mmol/L) as compared with B1B2 (1.14"0.28 mmol/L) and B2B2 subjects (1.18"0.34 mmol/L); p<0.001. Likewise, female homozygotes for the B1 allele had lower HDL-C levels (1.40" 0.38 mmol/L) as compared with B1B2 (1.46" 0.39 mmol/L) and B2B2 subjects (1.53" 0.40 mmol/L); p<0.001. Similar associations were noted for apoA-I values. The higher HDL-C levels associated with the B2 allele were due to increases in both HDL_2-C and HDL_3-C subfractions. A significant association was noted between the TaqIB genotype and CETP activity. Both men and women carriers of the B2 allele had significantly lower CETP activity than those homozygotes for the B1 allele. In both genders, there were no statistically significant differences among the genotype groups in the plasma levels of total cholesterol, LDL-C and apoB. These results were confirmed by the variance component approach and revealed that TaqIB accounts for about 1% of the variability in HDL-C.

TABLE 2

Plasma Levels of Lipids, Lipoproteins, and Apollpoproteins of Framingham Offspring Study Subjects According to TaqIB-CETP Genotypes

	B1B1	B1B2	B2B2	P*	P†
Men					
n	428	713	270		
Age, y	51.2 ± 10.3	52 ± 10.0	51.3 ± 10.1	0.313	
BMI, kg/m^2	27.9 ± 4.0	27.50 ± 3.80	27.6 ± 3.8	0.169	
TC. mmol/L	5.28 ± 0.93	5.25 ± 0.96	5.22 ± 0.96	0.639	0.889
LDL-C, mmol/L	3.49 ± 0.83	3.47 ± 0.88	3.41 ± 0.85	0.288	0.363
HDL-C, mmol/L	1.07 ± 0.27	1.14 ± 0.28‡	1.18 ± 0.34§	<0.001	<0.001
HDL_2-C, mmol/L	0.12 ± 0.09	0.14 ± 0.10	0.15 ± 0.11§	<0.001	0.033
HDL_3-C, mmol/L	0.95 ± 0.21	1.00 ± 0.22‡	1.03 ± 0.26§	<0.001	<0.001
TG, mmol/L	1.63 ± 1.16	1.52 ± 1.14	1.45 ± 0.95	0.059	0.098
ApoA-I, g/L	1.32 ± 0.25	1.35 ± 0.23	1.37 ± 0.24§	0.017	0.025
ApoB, g/L	1.03 ± 0.25	1.02 ± 0.24	1.00 ± 0.25	0.135	0.662
HDL-C/ApoA-I	0.81 ± 0.14	0.84 ± 0.13	0.86 ± 0.13	<0.001	<0.001
TC/HDL, ratio	5.3 ± 1.5	4.9 ± 1.5‡	4.8 ± 1.6§	<0.001	0.011

TABLE 2-continued

Plasma Levels of Lipids, Lipoproteins, and Apollpoproteins of Framingham Offspring Study Subjects According to TaqIB-CETP Genotypes

	B1B1	B1B2	B2B2	P*	P†
CETP, nmol · L^{-f} · h^{-1}	160 ± 10.0	156 ± 10.0	139 ± 9.0	0.026	0.045
VLDL size, nm	49.12 ± 10.24	48.52 ± 9.23	47.34 ± 8.58	0.054	0.649
LDL size, nm	20.56 ± 0.60	20.69 ± 0.58‡	20.80 ± 0.53§	<0.001	<0.001
HDL size, nm	8.83 ± 0.37	8.92 ± 0.40‡	8.98 ± 0.45§	<0.001	<0.001
Women					
n	477	754	274		
Age, y	51.2 ± 9.7	50.8 ± 9.41	51.3 ± 10.1	0.413	
BMI, kg/m^2	25.6 ± 5.4	25.8 ± 5.12	26.5 ± 5.5	0.081	
TC, mmol/L	5.28 ± 0.98	5.30 ± 1.03	5.33 ± 1.03	0.901	0.794
LOL-C, mmol/L	3.34 ± 0.93	3.28 ± 0.91	3.23 ± 0.98	0.297	0.383
HDL-C, mmol/L	1.40 ± 0.38	1.46 ± 0.39‡	1.53 ± 0.40§‖	<0.001	<0.001
HDL_2-C, mmol/L	0.24 ± 0.15	0.26 ± 0.14	0.28 ± 0.17§‖	0.008	<0.001
HDL_3-C, mmol/L	1.16 ± 0.28	1.20 ± 0.29	1.25 ± 0.29§‖	<0.001	<0.001
TG, mmol/L	1.21 ± 0.86	1.24 ± 1.38	1.23 ± 0.84	0.834	0.646
ApoA-I, g/L	1.52 ± 0.28	1.55 ± 0.32	1.57 ± 0.32	0.040	0.097
ApoB, g/L	0.95 ± 0.24	0.94 ± 0.27	0.95 ± 0.28	0.775	0.648
HDL-C/ApoA-I	0.92 ± 0.15	0.94 ± 0.16	0.97 ± 0.15	0.003	<0.001
TC/HDL ratio	4.0 ± 1.5	3.9 ± 1.50	3.7 ± 1.30§‖	0.006	<0.001
CETP, nmol · L^{-1} · h^{-1}	178 ± 11.0	159 ± 10.0‡	148 ± 11.00§‖	<0.001	<0.001
VLDL size, nm	43.99 ± 8.59	44.11 ± 8.40	45.81 ± 8.89§‖	0.019	0.129
LDL size, nm	21.05 ± 0.52	21.07 ± 0.46	21.09 ± 0.41	0.547	0 194
HDL size, nm	9.35 ± 0.45	9.40 ± 0.43‡	9.44 ± 0.46§	0.027	<0.001

Values are mean ± SD.

*After adjustment for the familial relations.

†After adjustment for the familial relalions, age, BMI, smoking, alcohol intake, use of β-blockers, menopausal status and estrogen therapy (in women), and Apoe.

Shown at significant differences bctween the B1B1 and B1B2 (‡), B1B1 and B2B2 (§), and B1B2 and B2B2 (‖) groups after adjustment for the familial relationships, age, BMI, smoking, alcohol intake, use of β-blockers, menopausal status and estrogen therapy (in women) and Apoe.

[**0027**] To test the consistency of the association between the CETP TaqIB genotype and HDL-C levels, a sensitivity linear regression analysis was carried out as described below under the heading of Methods of the Invention. **FIG. 1** shows regression coefficients and 95% confidence intervals for B1B2 and B2B2 genotypes, respectively, as compared with B1B1 when each indicated variable was included into the linear regression models (Models 1 to 6). First, the only variables included were dummies for TaqIB genotype (Model 1). This genetic factor accounted for 1% of the variability of HDL-C ($p<0.001$). The initial regression coefficients for B1B2 and B2B2, after controlling for the gender effect (Model 2), were 0.06 (95% CI: 0.03-0.09) mmol/L; $p<0.001$, and 0.14 (95% CI: 0.09-0.18) mmol/L, respectively; $p<0.001$. When other variables were progressively added to the core model: BMI, tobacco smoking, alcohol consumption and apoE genotypes, only slight variation of the initially estimated values for the regression coefficients were observed, revealing an independent association of the TaqIB polymorphism with HDL-C levels with a strong consistency, whatever additional environmental or genetic factor was considered. The final model explained 35% of the variability of HDL-C in the population, and the regression coefficient for B1B2 and B2B2 were 0.07 (95% CI: 0.03-0.10) mmol/L and 0.14 (95% CI: 0.09-0.18) mmol/l, respectively ($p<0.001$).

[**0028**] To gain better understanding of the metabolic basis of the association of higher HDL-C levels with the B2 allele in men and women, lipoprotein subclass profiles were measured using automated NMR spectroscopy. From these measurements, it was determined that this association was specifically due to a significant increase in the large HDL subfraction (8.8-13.0 nm). In males, the HDL-C concentrations (mmol/L) in this HDL subfraction were 0.31±0.27, 0.37±0.29, and 0.45±0.37 for B1B1, B1B2, and B2B2 subjects, respectively ($p<0.001$). No changes were observed for the small and intermediate size HDL subfractions. These data were consistent with an increase in HDL size in male carriers of the B2 allele as demonstrated by NMR (8.83±0.37; 8.92±0.40 and 8.98±0.45 nm for B1B1, B1B2 and B2B2 subjects, respectively; $p<0.001$) as well as by an increase in the HDL-C/ApoAI values (indicated in Table 2). In addition to the genotype associations seen with the HDL subfractions, a significant association between this polymorphism and LDL subfractions was observed in men. The B2 allele was associated with increased levels of the large LDL subtraction (1.77±0.89 and 1.94±0.88 mmol/L for B1B2 and B2B2, respectively) as compared with B1B1 subjects (1.64±0.86 mmol/L). Conversely, B1B1 men had increased levels of the small LDL fraction (0.86±0.65 mmol/L) as compared with B1B2 (0.79±0.60 mmol/L) and B2B2 (0.80±0.65 mmol/L) ($p=0.031$). Therefore, the B2 allele was associated with increased particle size for both HDL and LDL after adjustment for familial relationships, age, BMI, smoking, alcohol intake, use of beta-blockers, and ApoE genotype. In women, a similar effect was noted with the large HDL subfraction. The concentrations were 0.76±0.43, 0.81±0.42, and 0.87±0.44 for B1B1, B1B2, and B2B2 female subjects, respectively ($p<0.001$). The associations between the B2 allele and LDL size observed in men were not detected in women. Consequently, a genotype/HDL particle size association similar to that shown for men was demonstrated for women after adjustment for the variables

indicated above, as well as for menopausal status and estrogen therapy. However, no genotype differences were observed for LDL size.

[0029] CETP TaqIB Genotype and Risk of Coronary Heart Disease

[0030] To examine the associations of the TaqIB polymorphism with coronary heart disease (CHD) risk, subjects on lipid lowering medications were also included in the analysis. In this analysis, CHD was present in 163 men and 62 women. When CHD prevalence in men was examined at exam 5 with respect to the absence (B1B1) or presence of the B2 allele (B1B2 or B2B2) by chi square analysis, a significantly (p=0.035) lower frequency of carriers of the B2 allele (58.7% vs. 70.6%) among those subjects with positive CHD was demonstrated. Likewise, the odds ratio for CHD associated with the presence of the B2 allele was 0.696 (95% CI: 0.50-0.98; p=0.035). After adjusting for age, BMI, systolic blood pressure, diabetes, smoking, and alcohol consumption, the odds ratio remained at 0.700 (95% CI: 0.46-1.05), but the statistical significance dropped to p=0.090. After additional adjustment for the previous factors plus beta blockers use, cholesterol-lowering drugs, TC and HDL-C, the odds ratio was 0.735 (95% CI: 0.46-1.162; p=0.188). These odds ratios were similar after excluding those subjects on lipid-lowering medications. There were too few CHD cases in the women of the study to draw definitive conclusions about the association between the TaqIB polymorphism and CHD risk in women. No significant association between the presence of the B2 allele and CHD risk was found by chi square analysis (75.8% vs 67.9%, p=N.S.) or by logistic analysis in the women.

[0031] Methods of the Invention

[0032] Subjects

[0033] The details of the design and methods of the Framingham Offspring Study have been presented elsewhere (Feinleib et al., *Prev. Med.* 4: 518-525 (1975)). Starting in 1971, a total of 5124 subjects were enrolled (Kannel et al., *Am. J. Epidemiol.* 110: 281-290 (1979)). Blood samples for DNA were collected between 1987 and 1991. Lipid phenotypes, DNA, and information on CHD risk factors were available for 1411 men and 1505 women who attended the 4th and 5th examination visits of the Framingham Offspring Study conducted between 1987 and 1995, and who had lipid values available off lipid-altering medication. Nearly all subjects were Caucasians. Data on smoking, blood pressure, height, weight, and diabetes were obtained on these subjects as previously described (Kannel et al., *Am. J. Epidemiol.* 110: 281-290 (1979); Dawber et al., *Am. J. Public Health* 41: 279-286 (1951)). CHD included the presence of myocardial infarction, angina pectoris, coronary insufficiency and coronary death. All suspected CHD events were reviewed by a panel of three physicians to ascertain the presence of CHD. Subjects taking a lipid-lowering medication (n=100) were included for the analyses of CHD prevalence at exam 5, but excluded in all other analyses.

[0034] Plasma Lipid, Lipoprotein, Apolipoprotein and CETP Measurements

[0035] Twelve-hour fasting venous blood samples were collected in tubes containing 0.1% EDTA. Plasma was separated from blood cells by centrifugation and immediately used for the measurement of lipids. Plasma total cholesterol (TC), HDL-C and triglyceride levels were measured as previously described (Cupples et al., *Circulation* 85: 111-118 (1992)). HDL-C was measured after precipitation of ApoB-containing lipoproteins with dextran-magnesium sulfate (Warnick et al., *Clin. Chem.* 28: 1379-88 (1982)). Low density lipoprotein-cholesterol (LDL-C) concentrations were estimated with the equation of Friedewald et al. (*Clin. Chem.* 18: 499-502 (1972)). Coefficients of variation for total cholesterol, HDL-C, triglyceride measurements were each less than 5 percent (McNamara and Schaefer, *Clin. Chim. Acta.* 166: 1-9 (1987)). Plasma levels of apolipoprotein (apo) AI and apoB were measured by non-competitive enzyme-linked immunosorbent assay (ELISA), using affinity-purified polyclonal antibodies (Schaefer and Ordovas, Metabolism of the apolipoproteins A-I, A-II, and A-IV. In: Segrest J, Albers J, editors. Methods in Enzymology, Plasma Lipoproteins, Part B: Characterization, Cell Biology and Metabolism. Academic Press, 1986: 420-442); Ordovas et al., *J. Lipid Res.* 28: 1216 (1987)).

[0036] Plasma lipoprotein concentrations and subclasses distributions were determined by proton nuclear magnetic resonance (NMR) spectroscopy as previously described (Otvos et al., *Clin. Chem.* 38: 1632-1638 (1992); Otvos, J. D., Measurement of lipoprotein subclass profile by nuclear magnetic resonance. In: Rifai N, Warnick G R, Dominiczak M H, editors. Handbook of lipoprotein testing. Washington: AACC Press, 1997: 497-508). Each profile displays the concentrations of six very low density lipoproteins (VLDL), one intermediate density lipoproteins (IDL), three LDL, and five HDL subclasses and the weighted-average particle sizes of VLDL, LDL and HDL. The 10 lipoprotein subclass categories used were the following: large VLDL and remnants (80-220 nm), intermediate VLDL (35-80 nm), small VLDL (27-35 nm), large LDL (21.3-27.0 nm), intermediate LDL (19.8-21.2), small LDL (18.3-19.7 nm), large HDL (8.8-13.0 nm), intermediate HDL (7.8-8.8 nm), and small HDL (7.3-7.7 nm). Levels of VLDL subclasses are expressed in units of triglyceride (mmol/L), and those of LDL and HDL subclasses in units of cholesterol (mmol/L). LDL and HDL subclass distributions determined by gradient gel electrophoresis and NMR have been shown to be closely correlated (Otvos et al., *Clin. Chem.* 38: 1632-1638 (1992)). However, it should be noted that given the characteristics of this methodology, there could be some overlap between the IDL fraction and the small VLDL, as well as with the large LDL subfraction. Nevertheless, this should not have a major effect over the associations examined given the low concentrations of IDL found in fasting plasma of normal subjects.

[0037] CETP activity was determined using a CETP Activity Kit by Roar Biomedical, Inc. (New York, N.Y.). This kit includes a donor (synthetic phospholipid and cholesteryl ester particles) and acceptor particles (VLDL). The fluorescent neutral lipid is present in a self-quenched state when contained within the core of the donor. The CETP mediated transfer is determined by the increase in fluorescence intensity as the fluorescent neutral lipid is removed from the self quenched donor to the acceptor. Briefly, for each sample assayed, 10 ul of plasma was diluted (1:10) in 90 ul of sample buffer (10 mM tris, 150 mM NaCl, 2 mM EDTA, pH 7.4). In a fluorescent compatible microtiter plate (Dynex Laboratories), 20 ul of the plasma dilution was combined with 4 ul of donor and 4 ul of acceptor in a total

volume of 200 ul, and incubated for 3 hours at 37° C. The assay was read in a fluorescent spectrometer at excitation wavelength of 465 nm and emission wavelength of 535 nm. A standard curve was used, according to manufacturer guidelines, to derive the relationship between fluorescence intensity and mass transfer. Plasma controls were run in each plate to account for plate to plate variation. For standardization, the unquenched fluorescence intensity of the fluorescent cholesteryl ester contained within the donor particle core was determined by dispersing 5 ul of donor (fluorescent CE concentration 146 ug/ml—reported by manufacturer) in 2 ml of 100% isopropanol. Serial dilutions of the dispersion were made to generate a standard curve of fluorescence intensity (ex. 465 nm/em. 535 nm) vs. mass of fluorescent CE. The fluorescence intensity transferred in the assay of plasma samples was applied to the standard curve to determine mass transfer. The intra- and interassay coefficients of variation were less than 3%.

[0038] DNA Analysis

[0039] Genomic DNA was isolated from peripheral blood leucocytes by standard methods (Miller et al., *Nucleic Acids Res.* 16: 1215 (1989)). CETP genotype was performed as described by Fumeron et al. (*J. Clin. Invest.* 96: 1664-1671 (1995)). A fragment of 535 base pairs in intron 1 of CETP gene was amplified by polymerase chain reaction (PCR) in a DNA Thermal Cycler (PTC-100, MJ Research, Inc., Watertown, Mass.), using oligonucleotide primers (Forward: 5'-CACTAGCCCAGAGAGAGGAGTGCC-3' SEQ ID NO: 1 and Reverse: 5'-CTGAGCCCAGCCGCACACTAAC-3' SEQ ID NO: 2). Each amplification was performed using 100 ng of genomic DNA in a volume of 50 μL containing 40 pmol of each oligonucleotide, 0.2 mM dNTPs, 1.5 mM $MgCl_2$, 10 mM Tris, pH 8.4 and 0.25 U of Taq polymerase. DNA templates were denatured at 95° C. for 3 min and then each PCR reaction was subjected to 30 cycles with a temperature cycle consisting of 95° C. for 30 sec, 60° C. for 30 sec, and 72° C. for 45 sec, and finally an extension at 72° C. for 5 min. The PCR products were subjected to restriction enzyme analysis by digestion with 4 units of the restriction endonuclease TaqI for 16 μL of PCR sample at 65° C. for 2 h in the buffer recommended by the manufacturer (Gibco-BRL) and the fragments separated by electrophoresis on an 1.5% agarose gel. After electrophoresis, the gel was treated with ethidium bromide for 20 minutes and DNA fragments were visualized by UV illumination. The resulting fragments were 174 bp and 361 bp for the B1 allele, and 535 bp for the uncut B2 allele. ApoE genotype was carried out as previously described (Hixson and Vernier, *J. Lipid Res.* 31: 545-548 (1990)).

[0040] Statistical Analyses

[0041] To compare men and women who participated in the study, chi-square tests for categorical measures and two-sample t tests for continuous measures were employed. The allele frequency of the B2 allele and APOE alleles was estimated with the chromosome counting method and use of a chi-square test to compare the frequency in men and women. To evaluate the relationship between the CETP genotypes and lipid levels, analysis of covariance (ANCOVA) techniques which accounted for the familial relationships among the members of the study (mostly siblings and cousins) were used. Two approaches were used to accomplish these analyses. First, a repeated measures approach was employed, which assumed an exchangeable correlation structure among all members of a family, (PROC MIXED, SAS). Since this approach does not accurately represent the true correlation structure within these pedigrees, a measured genotype approach (Boerwinkle and Utermann, *Am. J. Hum. Genet.* 42: 104-112 (1988)) as implemented in SOLAR, a variance component analysis computer package for quantitative traits measured in pedigrees of arbitrary size (Almasy and Blangero, *Am. J. Hum. Genet.* 62: 1198-1211 (1998)), was also employed. The latter approach fully accounts for the different types of relationships within a pedigree in performing an analysis of variance on the defined genotypes. In these analyses, several different models were used to adjust for potential confounders. First, essentially crude results were obtained, which accounted only for the family structure; second, adjustments were made for age, body mass index (BMI), smoking, alcohol consumption, beta-blockers, and (in women) menopausal status and hormonal replacement therapy. In the final analysis, ApoE genotypes were added to the model with E2/E2 and E2/E3 in one group, E3/E4 and E4/E4 in a second group, and E3/E3 as the reference group. Subjects with E2/E4 genotypes, of which there were very few, were excluded.

[0042] A sensitivity analysis was carried out to estimate the validity and precision of the regression coefficients for the CETP genotypic variables when additional independent terms were included into the model. Because similar results were obtained for both sexes, data from men and women were analyzed together to improve statistical power. Regression coefficients and 95% confidence intervals for B1B2 and B2B2 genotypes as compared with B1B1 were calculated by fitting several linear regression models with dummy variables for categorical and interaction terms as follows: model 1: CETP genotype (B1B1, B1B2 and B2B2). Model 2: model 1+gender. Model 3: model 2 +BMI. Model 4: model 3+tobacco smoking (non smoker and smoker). Model 5: model 4+alcohol consumption (consumption and no consumption). Model 6: model 5+apoE genotypes (E2, E3 and E4). In all cases, the first category was taken as reference. Regression diagnostics were employed to check the assumptions and to assess the accuracy of computations.

[0043] Finally, using a chi-square analysis, the odds of prevalent CHD at exam 5 for those with the B1B2 or B2B2 genotypes relative to those with the B1B1 genotype were estimated. CHD includes myocardial infarction, angina pectoris, and coronary insufficiency. To adjust the estimated odds ratio for covariates, logistic regression was employed. Generalized estimating equations with a logit link was also applied to account for the correlation among the observations, and obtained essentially the same results. Hence, the results are reported assuming independent observations.

[0044] Relevant statistical analyses are presented below.

STATISTICAL ANALYSIS OF THE CETP *TAQIB* POLYMORPHISM PROJECT

Ordovas Project on CETP: Homozygote 11 vs 12,22 1
Including Subjects on Cholesterol Lowering Drugs

SEX=Men

TABLE OF CHDPREV4 BY CHDEPR4

CHDPREV4(Prevalent CHD at Exam 4)

CHDEPR4(Prevalent Early CHD at Exam 4)

Frequency / Percent / Row Pct / Col Pct	0	1	Total
0	1383 91.53 100.00 96.65	0 0.00 0.00 0.00	1383 91.53
1	48 3.18 37.50 3.35	80 5.29 62.50 100.00	128 8.47
Total	1431 94.71	80 5.29	1511 100.00

Ordovas Project on CETP: Homozygote 11 vs 12,22 2
Including Subjects on Cholesterol Lowering Drugs

SEX=Men

TABLE OF CHDPREV5 BY CHDEPR5

CHDPREV5(Prevalent CHD at Exam 5)

CHDEPR5(Prevalent Early CHD at Exam 5)

Frequency / Percent / Row Pct / Col Pct	0	1	Total
0	1348 89.21 100.00 94.66	0 0.00 0.00 0.00	1348 89.21
1	76 5.03 46.63 5.34	87 5.76 53.37 100.00	163 10.79
Total	1424 94.24	87 5.76	1511 100.00

Ordovas Project on CETP: Homozygote 11 vs 12,22 3
Including Subjects on Cholesterol Lowering Drugs

SEX=Men

TABLE OF CETP2 BY CHDPREV4

CETP2 CHDPREV4(Prevalent CHD at Exam 4)

Frequency / Percent / Row Pct / Col Pct	0	1	Total
0	412	45	457
	27.27	2.98	30.24
	90.15	9.85	
	29.79	35.16	
1	971	83	1054
	64.26	5.49	69.76
	92.13	7.87	
	70.21	64.84	
Total	1383	128	1511
	91.53	8.47	100.00

STATISTICS FOR TABLE OF CETP2 BY CHDPREV4

Statistic	DF	Value	Prob
Chi-Square	1	1.599	0.206
Likelihood Ratio Chi-Square	1	1.559	0.212
Continuity Adj. Chi-Square	1	1.355	0.244
Mantel-Haenszel Chi-Square	1	1.598	0.206
Fisher's Exact Test (Left)			0.123
(Right)			0.913
(2-Tail)			0.227
Phi Coefficient		-0.033	
Contingency Coefficient		0.033	
Cramer's V		-0.033	

Sample Size = 1511

Ordovas Project on CETP: Homozygote 11 vs 12,22 4
Including Subjects on Cholesterol Lowering Drugs

SEX=Men

TABLE OF CETP2 BY CHDPREV5

CETP2 CHDPREV5(Prevalent CHD at Exam 5)

Frequency / Percent / Row Pct / Col Pct	0	1	Total
0	396	61	457
	26.21	4.04	30.24
	86.65	13.35	
	29.38	37.42	
1	952	102	1054
	63.00	6.75	69.76
	90.32	9.68	
	70.62	62.58	
Total	1348	163	1511
	89.21	10.79	100.00

STATISTICS FOR TABLE OF CETP2 BY CHDPREV5

Statistic	DF	Value	Prob
Chi-Square	1	4.463	0.035
Likelihood Ratio Chi-Square	1	4.312	0.038
Continuity Adj. Chi-Square	1	4.089	0.043
Mantel-Haenszel Chi-Square	1	4.460	0.035
Fisher's Exact Test (Left)			0.023
(Right)			0.985
(2-Tail)			0.038
Phi Coefficient		-0.054	
Contingency Coefficient		0.054	
Cramer's V		-0.054	

Sample Size = 1511

Ordovas Project on CETP: Homozygote 11 vs 12,22 5
Including Subjects on Cholesterol Lowering Drugs

SEX=Men

TABLE OF CETP2 BY CHDEPR4

CETP2 CHDEPR4(Prevalent Early CHD at Exam 4)

Frequency / Percent / Row Pct / Col Pct	0	1	Total
0	431	26	457
	28.52	1.72	30.24
	94.31	5.69	
	30.12	32.50	
1	1000	54	1054
	66.18	3.57	69.76
	94.88	5.12	
	69.88	67.50	
Total	1431	80	1511
	94.71	5.29	100.00

STATISTICS FOR TABLE OF CETP2 BY CHDEPR4

Statistic	DF	Value	Prob
Chi-Square	1	0.204	0.652
Likelihood Ratio Chi-Square	1	0.201	0.654
Continuity Adj. Chi-Square	1	0.106	0.744
Mantel-Haenszel Chi-Square	1	0.203	0.652
Fisher's Exact Test (Left)			0.367
(Right)			0.721
(2-Tail)			0.708
Phi Coefficient		-0.012	
Contingency Coefficient		0.012	
Cramer's V		-0.012	

Sample Size = 1511

Ordovas Project on CETP: Homozygote 11 vs 12,22 6
Including Subjects on Cholesterol Lowering Drugs

SEX=Men

TABLE OF CETP2 BY CHDEPR5

CETP2 CHDEPR5(Prevalent Early CHD at Exam 5)

Frequency / Percent / Row Pct / Col Pct	0	1	Total
0	427	30	457
	28.26	1.99	30.24
	93.44	6.56	
	29.99	34.48	
1	997	57	1054
	65.98	3.77	69.76
	94.59	5.41	
	70.01	65.52	
Total	1424	87	1511
	94.24	5.76	100.00

STATISTICS FOR TABLE OF CETP2 BY CHDEPR5

Statistic	DF	Value	Prob
Chi-Square	1	0.786	0.375
Likelihood Ratio Chi-Square	1	0.768	0.381
Continuity Adj. Chi-Square	1	0.587	0.444
Mantel-Haenszel Chi-Square	1	0.785	0.376
Fisher's Exact Test (Left)			0.220
(Right)			0.843
(2-Tail)			0.400
Phi Coefficient		-0.023	
Contingency Coefficient		0.023	
Cramer's V		-0.023	

Sample Size = 1511

Ordovas Project on CETP: Homozygote 11 vs 12,22 7
Including Subjects on Cholesterol Lowering Drugs

SEX=Men

TABLE OF CETP2 BY CHDINC5

CETP2 CHDINC5(Incidenct CHD between Exams 4 and 5)

Frequency / Percent / Row Pct / Col Pct	0	1	Total
0	396	16	412
	28.63	1.16	29.79
	96.12	3.88	
	29.38	45.71	
1	952	19	971
	68.84	1.37	70.21
	98.04	1.96	
	70.62	54.29	
Total	1348	35	1383
	97.47	2.53	100.00

Frequency Missing = 128

STATISTICS FOR TABLE OF CETP2 BY CHDINC5

Statistic	DF	Value	Prob
Chi-Square	1	4.353	0.037
Likelihood Ratio Chi-Square	1	4.039	0.044
Continuity Adj. Chi-Square	1	3.607	0.058
Mantel-Haenszel Chi-Square	1	4.350	0.037
Fisher's Exact Test (Left)			0.032
(Right)			0.986
(2-Tail)			0.059
Phi Coefficient		-0.056	
Contingency Coefficient		0.056	
Cramer's V		-0.056	

Effective Sample Size = 1383
Frequency Missing = 128

Ordovas Project on CETP: Homozygote 11 vs 12,22 8
Including Subjects on Cholesterol Lowering Drugs

SEX=Women

TABLE OF CHDPREV4 BY CHDEPR4
CHDPREV4(Prevalent CHD at Exam 4)
CHDEPR4(Prevalent Early CHD at Exam 4)

Frequency / Percent / Row Pct / Col Pct	0	1	Total
0	1537	0	1537
	96.85	0.00	96.85
	100.00	0.00	
	99.87	0.00	
1	2	48	50
	0.13	3.02	3.15
	4.00	96.00	
	0.13	100.00	
Total	1539	48	1587
	96.98	3.02	100.00

Ordovas Project on CETP: Homozygote 11 vs 12,22 9
Including Subjects on Cholesterol Lowering Drugs

SEX=Women

TABLE OF CHDPREV5 BY CHDEPR5
CHDPREV5(Prevalent CHD at Exam 5)
CHDEPR5(Prevalent Early CHD at Exam 5)

Frequency / Percent / Row Pct / Col Pct	0	1	Total
0	1525	0	1525
	96.09	0.00	96.09
	100.00	0.00	
	99.80	0.00	
1	3	59	62
	0.19	3.72	3.91
	4.84	95.16	
	0.20	100.00	
Total	1528	59	1587
	96.28	3.72	100.00

Ordovas Project on CETP: Homozygote 11 vs 12,22 10
Including Subjects on Cholesterol Lowering Drugs

SEX=Women

TABLE OF CETP2 BY CHDPREV4

CETP2 CHDPREV4(Prevalent CHD at Exam 4)

Frequency / Percent / Row Pct / Col Pct	0	1	Total
0	490	14	504
	30.88	0.88	31.76
	97.22	2.78	
	31.88	28.00	
1	1047	36	1083
	65.97	2.27	68.24
	96.68	3.32	
	68.12	72.00	
Total	1537	50	1587
	96.85	3.15	100.00

STATISTICS FOR TABLE OF CETP2 BY CHDPREV4

Statistic	DF	Value	Prob
Chi-Square	1	0.336	0.562
Likelihood Ratio Chi-Square	1	0.344	0.558
Continuity Adj. Chi-Square	1	0.181	0.670
Mantel-Haenszel Chi-Square	1	0.336	0.562
Fisher's Exact Test (Left)			0.766
(Right)			0.341
(2-Tail)			0.645
Phi Coefficient		0.015	
Contingency Coefficient		0.015	
Cramer's V		0.015	

Sample Size = 1587

Ordovas Project on CETP: Homozygote 11 vs 12,22 11
Including Subjects on Cholesterol Lowering Drugs

SEX=Women

TABLE OF CETP2 BY CHDPREV5

CETP2 CHDPREV5(Prevalent CHD at Exam 5)

Frequency / Percent / Row Pct / Col Pct	0	1	Total
0	489	15	504
	30.81	0.95	31.76
	97.02	2.98	
	32.07	24.19	
1	1036	47	1083
	65.28	2.96	68.24
	95.66	4.34	
	67.93	75.81	
Total	1525	62	1587
	96.09	3.91	100.00

STATISTICS FOR TABLE OF CETP2 BY CHDPREV5

Statistic	DF	Value	Prob
Chi-Square	1	1.704	0.192
Likelihood Ratio Chi-Square	1	1.786	0.181
Continuity Adj. Chi-Square	1	1.360	0.244
Mantel-Haenszel Chi-Square	1	1.702	0.192
Fisher's Exact Test (Left)			0.929
(Right)			0.120
(2-Tail)			0.212
Phi Coefficient		0.033	
Contingency Coefficient		0.033	
Cramer's V		0.033	

Sample Size = 1587

Ordovas Project on CETP: Homozygote 11 vs 12,22 12
Including Subjects on Cholesterol Lowering Drugs

SEX=Women

TABLE OF CETP2 BY CHDEPR4

CETP2 CHDEPR4(Prevalent Early CHD at Exam 4)

Frequency / Percent / Row Pct / Col Pct	0	1	Total
0	492	12	504
	31.00	0.76	31.76
	97.62	2.38	
	31.97	25.00	
1	1047	36	1083
	65.97	2.27	68.24
	96.68	3.32	
	68.03	75.00	
Total	1539	48	1587
	96.98	3.02	100.00

STATISTICS FOR TABLE OF CETP2 BY CHDEPR4

Statistic	DF	Value	Prob
Chi-Square	1	1.043	0.307
Likelihood Ratio Chi-Square	1	1.088	0.297
Continuity Adj. Chi-Square	1	0.746	0.388
Mantel-Haenszel Chi-Square	1	1.042	0.307
Fisher's Exact Test (Left)			0.882
(Right)			0.195
(2-Tail)			0.348
Phi Coefficient		0.026	
Contingency Coefficient		0.026	
Cramer's V		0.026	

Sample Size = 1587

Ordovas Project on CETP: Homozygote 11 vs 12,22 13
Including Subjects on Cholesterol Lowering Drugs

SEX=Women

TABLE OF CETP2 BY CHDEPR5

CETP2 CHDEPR5(Prevalent Early CHD at Exam 5)

Frequency / Percent / Row Pct / Col Pct	0	1	Total
0	491	13	504
	30.94	0.82	31.76
	97.42	2.58	
	32.13	22.03	
1	1037	46	1083
	65.34	2.90	68.24
	95.75	4.25	
	67.87	77.97	
Total	1528	59	1587
	96.28	3.72	100.00

STATISTICS FOR TABLE OF CETP2 BY CHDEPR5

Statistic	DF	Value	Prob
Chi-Square	1	2.674	0.102
Likelihood Ratio Chi-Square	1	2.850	0.091
Continuity Adj. Chi-Square	1	2.228	0.136
Mantel-Haenszel Chi-Square	1	2.672	0.102
Fisher's Exact Test (Left)			0.966
(Right)			0.065
(2-Tail)			0.117
Phi Coefficient		0.041	
Contingency Coefficient		0.041	
Cramer's V		0.041	

Sample Size = 1587

Ordovas Project on CETP: Homozygote 11 vs 12,22 14
Including Subjects on Cholesterol Lowering Drugs

SEX=Women

TABLE OF CETP2 BY CHDINC5

CETP2 CHDINC5(Incidenct CHD between Exams 4 and 5)

Frequency / Percent / Row Pct / Col Pct	0	1	Total
0	489	1	490
	31.82	0.07	31.88
	99.80	0.20	
	32.07	8.33	
1	1036	11	1047
	67.40	0.72	68.12
	98.95	1.05	
	67.93	91.67	
Total	1525	12	1537
	99.22	0.78	100.00

Frequency Missing = 50

STATISTICS FOR TABLE OF CETP2 BY CHDINC5

Statistic	DF	Value	Prob
Chi-Square	1	3.088	0.079
Likelihood Ratio Chi-Square	1	3.872	0.049
Continuity Adj. Chi-Square	1	2.092	0.148
Mantel-Haenszel Chi-Square	1	3.086	0.079
Fisher's Exact Test (Left)			0.990
(Right)			0.065
(2-Tail)			0.118
Phi Coefficient		0.045	
Contingency Coefficient		0.045	
Cramer's V		0.045	

Effective Sample Size = 1537
Frequency Missing = 50
WARNING: 25% of the cells have expected counts less than 5. Chi-Square may not be a valid test.

Ordovas Project on CETP: Homozygote 11 vs 12,22 15
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions

---------- SEX=Men ----------

Analysis of Variance Procedure
Class Level Information

Class	Levels	Values
CETP2	2	0 1

Number of observations in by group = 163

Ordovas Project on CETP: Homozygote 11 vs 12,22 16
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions

---------- SEX=Men ----------

Analysis of Variance Procedure

Dependent Variable: AGECHD

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	1	430.3800452	430.3800452	4.64	0.0328
Error	161	14948.0164057	92.8448224		
Corrected Total	162	15378.3964509			

R-Square	C.V.	Root MSE	AGECHD Mean
0.027986	17.90373	9.635602	53.81895

Source	DF	Anova SS	Mean Square	F Value	Pr > F
CETP2	1	430.3800452	430.3800452	4.64	0.0328

Ordovas Project on CETP: Homozygote 11 vs 12,22 17
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions

---------- SEX=Men ----------

Analysis of Variance Procedure

Level of CETP2	N	AGECHD Mean	AGECHD SD
0	61	55.9201535	10.2396486
1	102	52.5623532	9.2581205

Ordovas Project on CETP: Homozygote 11 vs 12,22 18
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions

---------- SEX=Men ----------

Analysis of Variance Procedure
Scheffe's test for variable: AGECHD

NOTE: This test controls the type I experimentwise error rate but generally has a higher type II error rate than REGWF for all pairwise comparisons

Alpha= 0.05 df= 161 MSE= 92.84482
Critical Value of F= 3.89987
Minimum Significant Difference= 3.0799
WARNING: Cell sizes are not equal.
Harmonic Mean of cell sizes= 76.34356

Means with the same letter are not significantly different.

Scheffe Grouping	Mean	N	CETP2
A	55.920	61	0
B	52.562	102	1

Ordovas Project on CETP: Homozygote 11 vs 12,22 19
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions

---------- SEX=Women ----------

Analysis of Variance Procedure
Class Level Information

Class	Levels	Values
CETP2	2	0 1

Number of observations in by group = 62

Ordovas Project on CETP: Homozygote 11 vs 12,22 20
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions

---------- SEX=Women ----------

Analysis of Variance Procedure

Dependent Variable: AGECHD

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F

Model	1	10.17976397	10.17976397	0.18	0.6724
Error	60	3383.49765662	56.39162761		
Corrected Total	61	3393.67742059			

R-Square	C.V.	Root MSE	AGECHD Mean
0.003000	14.16591	7.509436	53.01060

Source	DF	Anova SS	Mean Square	F Value	Pr > F
CETP2	1	10.17976397	10.17976397	0.18	0.6724

Ordovas Project on CETP: Homozygote 11 vs 12,22 21
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions

---------- SEX=Women ----------
Analysis of Variance Procedure

Level of CETP2	N	AGECHD Mean	AGECHD SD
0	15	53.7278576	8.98003295
1	47	52.7816855	7.00081326

Ordovas Project on CETP: Homozygote 11 vs 12,22 22
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions

---------- SEX=Women ----------
Analysis of Variance Procedure
Scheffe's test for variable: AGECHD
NOTE: This test controls the type I experimentwise error rate but generally has a higher type II error rate than REGWF for all pairwise comparisons

Alpha= 0.05 df= 60 MSE= 56.39163
Critical Value of F= 4.00119
Minimum Significant Difference= 4.4545
WARNING: Cell sizes are not equal.
Harmonic Mean of cell sizes= 22.74194

Means with the same letter are not significantly different.

Scheffe Grouping	Mean	N	CETP2
A	53.728	15	0
A			
A	52.782	47	1

Ordovas Project on CETP: Homozygote 11 vs 12,22 23
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta Bl,SBP,DM,CHOL,HDL

The LOGISTIC Procedure

Data Set: WORK.CETPDAT
Response Variable: CHDPREV4 Prevalent CHD at Exam 4
Response Levels: 2
Number of Observations: 1511
Link Function: Logit

Response Profile

Ordered Value	CHDPREV4	Count
1	1	128
2	0	1383

Model Fitting Information and Testing Global Null Hypothesis BETA=0

Criterion	Intercept Only	Intercept and Covariates	Chi-Square for Covariates
AIC	878.772	879.213	.
SC	884.093	889.854	.
-2 LOG L	876.772	875.213	1.559 with 1 DF (p=0.2118)
Score	.	.	1.599 with 1 DF (p=0.2061)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-2.2144	0.1570	198.9254	0.0001	.	.
CETP2	1	-0.2451	0.1942	1.5926	0.2069	-0.062095	0.783

Association of Predicted Probabilities and Observed Responses

Concordant	= 24.7%	Somers' D	= 0.054
Discordant	= 19.3%	Gamma	= 0.122
Tied	= 56.0%	Tau-a	= 0.008
(177024 pairs)		c	= 0.527

Ordovas Project on CETP: Homozygote 11 vs 12,22 24
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta Bl,SBP,DM,CHOL,HDL

The LOGISTIC Procedure

Conditional Odds Ratios and 95% Confidence Intervals

Variable	Unit	Odds Ratio	Wald Confidence Limits Lower	Upper
CETP2	1.0000	0.783	0.535	1.145

Ordovas Project on CETP: Homozygote 11 vs 12,22 25
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta Bl,SBP,DM,CHOL,HDL

The LOGISTIC Procedure

Data Set: WORK.CETPDAT
Response Variable: CHDPREV5 Prevalent CHD at Exam 5
Response Levels: 2
Number of Observations: 1511

Link Function: Logit

Response Profile

Ordered Value	CHDPREV5	Count
1	1	163
2	0	1348

Model Fitting Information and Testing Global Null Hypothesis BETA=0

Criterion	Intercept Only	Intercept and Covariates	Chi-Square for Covariates
AIC	1035.677	1033.365	.
SC	1040.997	1044.006	.
-2 LOG L	1033.677	1029.365	4.312 with 1 DF (p=0.0378)
Score	.	.	4.463 with 1 DF (p=0.0346)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-1.8705	0.1375	184.9452	0.0001	.	.
CETP2	1	-0.3631	0.1725	4.4270	0.0354	-0.091968	0.696

Association of Predicted Probabilities and Observed Responses

Concordant	= 26.4%	Somers' D	= 0.080
Discordant	= 18.4%	Gamma	= 0.180
Tied	= 55.2%	Tau-a	= 0.015
(219724 pairs)		c	= 0.540

Ordovas Project on CETP: Homozygote 11 vs 12,22 26
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta Bl,SBP,DM,CHOL,HDL

The LOGISTIC Procedure

Conditional Odds Ratios and 95% Confidence Intervals

Variable	Unit	Odds Ratio	Wald Confidence Limits Lower	Upper
CETP2	1.0000	0.696	0.496	0.975

Ordovas Project on CETP: Homozygote 11 vs 12,22 27
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta Bl,SBP,DM,CHOL,HDL

The PHREG Procedure

Data Set: WORK.CETPDAT
Dependent Variable: CHD5_SUR
Censoring Variable: CHDINC5 Incidenct CHD between Exams 4 and 5
Censoring Value(s): 0
Ties Handling: BRESLOW

Summary of the Number of
Event and Censored Values

Total	Event	Censored	Percent Censored
1354	35	1319	97.42

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L	501.747	497.893	3.854 with 1 DF (p=0.0496)
Score	.	.	4.157 with 1 DF (p=0.0415)
Wald	.	.	4.001 with 1 DF (p=0.0455)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square
CETP2	1	-0.678739	0.33931	4.00133	0.0455

Ordovas Project on CETP: Homozygote 11 vs 12,22 28
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta Bl,SBP,DM,CHOL,HDL

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Conditional Risk Ratio and
95% Confidence Limits

Variable	Risk Ratio	Lower	Upper
CETP2	0.507	0.261	0.986

Ordovas Project on CETP: Homozygote 11 vs 12,22 29
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta Bl,SBP,DM,CHOL,HDL

The LOGISTIC Procedure

Data Set: WORK.CETPDAT
Response Variable: CHDPREV4 Prevalent CHD at Exam 4
Response Levels: 2
Number of Observations: 1464
Link Function: Logit

Response Profile

Ordered Value	CHDPREV4	Count
1	1	125
2	0	1339

WARNING: 47 observation(s) were deleted due to missing values for the response or explanatory variables.

Model Fitting Information and Testing Global Null Hypothesis BETA=0

Criterion	Intercept Only	Intercept and Covariates	Chi-Square for Covariates
AIC	856.163	758.235	.
SC	861.452	800.546	.
-2 LOG L	854.163	742.235	111.928 with 7 DF (p=0.0001)
Score	.	.	116.955 with 7 DF (p=0.0001)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-6.3417	1.1118	32.5370	0.0001	.	.
AGE4	1	0.0978	0.0121	65.5363	0.0001	0.540964	1.103
SBP4	1	-0.0136	0.00574	5.6141	0.0178	-0.134100	0.986
DIAB4	1	1.0835	0.2786	15.1272	0.0001	0.148637	2.955
BMI4	1	0.0168	0.0267	0.3981	0.5281	0.035720	1.017
CIGS4	1	0.0168	0.00766	4.7846	0.0287	0.115745	1.017
ALC4	1	-0.0456	0.0233	3.8216	0.0506	-0.133527	0.955
CETP2	1	-0.2877	0.2099	1.8781	0.1705	-0.072834	0.750

Ordovas Project on CETP: Homozygote 11 vs 12,22 30
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta Bl,SBP,DM,CHOL,HDL

The LOGISTIC Procedure

Association of Predicted Probabilities and Observed Responses

Concordant = 77.3%	Somers' D = 0.553
Discordant = 22.0%	Gamma = 0.557
Tied = 0.6%	Tau-a = 0.086
(167375 pairs)	c = 0.777

Conditional Odds Ratios and 95% Confidence Intervals

Variable	Unit	Odds Ratio	Wald Confidence Limits Lower	Upper
AGE4	1.0000	1.103	1.077	1.129
SBP4	1.0000	0.986	0.975	0.998
DIAB4	1.0000	2.955	1.712	5.102
BMI4	1.0000	1.017	0.965	1.072
CIGS4	1.0000	1.017	1.002	1.032
ALC4	1.0000	0.955	0.913	1.000
CETP2	1.0000	0.750	0.497	1.132

Ordovas Project on CETP: Homozygote 11 vs 12,22 31
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta Bl,SBP,DM,CHOL,HDL

The LOGISTIC Procedure

Data Set: WORK.CETPDAT
Response Variable: CHDPREV5 Prevalent CHD at Exam 5
Response Levels: 2
Number of Observations: 1351
Link Function: Logit

Response Profile

Ordered Value	CHDPREV5	Count
1	1	123
2	0	1228

WARNING: 160 observation(s) were deleted due to missing values for the response or explanatory variables.

Model Fitting Information and Testing Global Null Hypothesis BETA=0

Criterion	Intercept Only	Intercept and Covariates	Chi-Square for Covariates
AIC	825.964	740.200	.
SC	831.172	781.869	.
-2 LOG L	823.964	724.200	99.764 with 7 DF (p=0.0001)
Score	.	.	102.237 with 7 DF (p=0.0001)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-5.1726	1.1504	20.2172	0.0001	.	.
AGE5	1	0.0943	0.0120	61.5435	0.0001	0.511266	1.099
SBP5	1	-0.0242	0.00645	14.0377	0.0002	-0.222999	0.976
DIAB5	1	0.9891	0.2702	13.4021	0.0003	0.151637	2.689
BMI5	1	0.0224	0.0252	0.7914	0.3737	0.050869	1.023
CIGS5	1	0.00942	0.00910	1.0708	0.3008	0.056384	1.009
ALC5	1	-0.0271	0.0234	1.3450	0.2462	-0.069543	0.973
CETP2	1	-0.3564	0.2106	2.8652	0.0905	-0.090382	0.700

Ordovas Project on CETP: Homozygote 11 vs 12,22 32
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta Bl,SBP,DM,CHOL,HDL

The LOGISTIC Procedure

Association of Predicted Probabilities and Observed Responses

Concordant	= 75.3%	Somers' D	= 0.514
Discordant	= 24.0%	Gamma	= 0.517
Tied	= 0.7%	Tau-a	= 0.085
(151044 pairs)		c	= 0.757

Conditional Odds Ratios and 95% Confidence Intervals

Variable	Unit	Odds Ratio	Wald Confidence Limits Lower	Upper
AGE5	1.0000	1.099	1.073	1.125
SBP5	1.0000	0.976	0.964	0.989

DIAB5	1.0000	2.689	1.583	4.566
BMI5	1.0000	1.023	0.973	1.075
CIGS5	1.0000	1.009	0.992	1.028
ALC5	1.0000	0.973	0.930	1.019
CETP2	1.0000	0.700	0.463	1.058

Ordovas Project on CETP: Homozygote 11 vs 12,22 33
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta Bl,SBP,DM,CHOL,HDL

The PHREG Procedure

Data Set: WORK.CETPDAT
Dependent Variable: CHD5_SUR
Censoring Variable: CHDINC5 Incidenct CHD between Exams 4 and 5
Censoring Value(s): 0
Ties Handling: BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
1339	34	1305	97.46

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L	486.901	448.847	38.054 with 7 DF (p=0.0001)
Score	.	.	43.748 with 7 DF (p=0.0001)
Wald	.	.	39.750 with 7 DF (p=0.0001)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square
AGE4	1	0.081833	0.02093	15.28544	0.0001
SBP4	1	0.006343	0.00939	0.45650	0.4993
DIAB4	1	0.966197	0.45534	4.50255	0.0338
BMI4	1	0.039852	0.04166	0.91488	0.3388
CIGS4	1	0.026188	0.01173	4.98402	0.0256
ALC4	1	-0.031550	0.03810	0.68584	0.4076
CETP2	1	-0.695759	0.34968	3.95886	0.0466

Ordovas Project on CETP: Homozygote 11 vs 12,22 34
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta Bl,SBP,DM,CHOL,HDL

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Conditional Risk Ratio and 95% Confidence Limits

Variable	Risk Ratio	Lower	Upper	Label

AGE4	1.085	1.042	1.131	AGE
SBP4	1.006	0.988	1.025	SYSTOLIC BP - PHYSICIAN - 1ST READING
DIAB4	2.628	1.077	6.415	
BMI4	1.041	0.959	1.129	BODY MASS INDEX
CIGS4	1.027	1.003	1.050	CIGARETTES/PER DAY
ALC4	0.969	0.899	1.044	TOTAL ALCOHOL CONSUMPTION
CETP2	0.499	0.251	0.990	

Ordovas Project on CETP: Homozygote 11 vs 12,22 35
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta Bl,SBP,DM,CHOL,HDL

The LOGISTIC Procedure

Data Set: WORK.CETPDAT
Response Variable: CHDPREV4 Prevalent CHD at Exam 4
Response Levels: 2
Number of Observations: 1463
Link Function: Logit

Response Profile

Ordered Value	CHDPREV4	Count
1	1	124
2	0	1339

WARNING: 48 observation(s) were deleted due to missing values for the response or explanatory variables.

Model Fitting Information and Testing Global Null Hypothesis BETA=0

Criterion	Intercept Only	Intercept and Covariates	Chi-Square for Covariates
AIC	851.235	703.057	.
SC	856.523	750.651	.
-2 LOG L	849.235	685.057	164.178 with 8 DF (p=0.0001)
Score	.	.	190.697 with 8 DF (p=0.0001)

Ordovas Project on CETP: Homozygote 11 vs 12,22 36
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta Bl,SBP,DM,CHOL,HDL

The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-5.1729	1.1748	19.3878	0.0001	.	.
AGE4	1	0.0909	0.0126	51.6308	0.0001	0.503052	1.095
SBP4	1	-0.0166	0.00585	8.0201	0.0046	-0.163355	0.984
DIAB4	1	0.9286	0.2902	10.2402	0.0014	0.127428	2.531
BMI4	1	-0.0117	0.0285	0.1681	0.6818	-0.024783	0.988
CIGS4	1	0.0187	0.00795	5.5182	0.0188	0.129042	1.019
ALC4	1	-0.0490	0.0239	4.2137	0.0401	-0.143356	0.952
BETA4	1	1.6223	0.2208	53.9749	0.0001	0.306074	5.065
CETP2	1	-0.3145	0.2175	2.0907	0.1482	-0.079644	0.730

Association of Predicted Probabilities and Observed Responses

Concordant	= 81.5%	Somers' D	= 0.636
Discordant	= 17.9%	Gamma	= 0.640
Tied	= 0.6%	Tau-a	= 0.099
(166036 pairs)		c	= 0.818

Conditional Odds Ratios and 95% Confidence Intervals

Variable	Unit	Odds Ratio	Wald Confidence Limits Lower	Upper
AGE4	1.0000	1.095	1.068	1.123
SBP4	1.0000	0.984	0.972	0.995
DIAB4	1.0000	2.531	1.433	4.470
BMI4	1.0000	0.988	0.935	1.045
CIGS4	1.0000	1.019	1.003	1.035
ALC4	1.0000	0.952	0.909	0.998
BETA4	1.0000	5.065	3.285	7.808
CETP2	1.0000	0.730	0.477	1.118

Ordovas Project on CETP: Homozygote 11 vs 12,22 37
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta Bl,SBP,DM,CHOL,HDL

The LOGISTIC Procedure

Data Set: WORK.CETPDAT
Response Variable: CHDPREV5 Prevalent CHD at Exam 5
Response Levels: 2
Number of Observations: 1351
Link Function: Logit

Response Profile

Ordered Value	CHDPREV5	Count
1	1	123
2	0	1228

WARNING: 160 observation(s) were deleted due to missing values for the response or explanatory variables.

Model Fitting Information and Testing Global Null Hypothesis BETA=0

Criterion	Intercept Only	Intercept and Covariates	Chi-Square for Covariates
AIC	825.964	665.235	.
SC	831.172	712.112	.
-2 LOG L	823.964	647.235	176.729 with 8 DF (p=0.0001)
Score	.	.	228.676 with 8 DF (p=0.0001)

Ordovas Project on CETP: Homozygote 11 vs 12,22 38
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta Bl,SBP,DM,CHOL,HDL

The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-4.5024	1.2468	13.0409	0.0003	.	.
AGE5	1	0.0826	0.0128	41.3147	0.0001	0.447614	1.086
SBP5	1	-0.0239	0.00680	12.4002	0.0004	-0.221021	0.976
DIAB5	1	0.8424	0.2903	8.4183	0.0037	0.129146	2.322
BMI5	1	0.00615	0.0274	0.0504	0.8223	0.013946	1.006
CIGS5	1	0.0115	0.00961	1.4230	0.2329	0.068604	1.012
ALC5	1	-0.0308	0.0252	1.4936	0.2217	-0.079142	0.970
BETA5	1	1.8093	0.2054	77.6146	0.0001	0.352275	6.106
CETP2	1	-0.3360	0.2240	2.2490	0.1337	-0.085196	0.715

Association of Predicted Probabilities and Observed Responses

Concordant = 81.6%	Somers' D = 0.639
Discordant = 17.7%	Gamma = 0.644
Tied = 0.6%	Tau-a = 0.106
(151044 pairs)	c = 0.820

Conditional Odds Ratios and 95% Confidence Intervals

Variable	Unit	Odds Ratio	Wald Confidence Limits Lower	Upper
AGE5	1.0000	1.086	1.059	1.114
SBP5	1.0000	0.976	0.963	0.989
DIAB5	1.0000	2.322	1.314	4.102
BMI5	1.0000	1.006	0.954	1.062
CIGS5	1.0000	1.012	0.993	1.031
ALC5	1.0000	0.970	0.923	1.019
BETA5	1.0000	6.106	4.083	9.133
CETP2	1.0000	0.715	0.461	1.109

Ordovas Project on CETP: Homozygote 11 vs 12,22 39
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta B1,SBP,DM,CHOL,HDL

The PHREG Procedure

Data Set: WORK.CETPDAT
Dependent Variable: CHD5_SUR
Censoring Variable: CHDINC5 Incidenct CHD between Exams 4 and 5
Censoring Value(s): 0
Ties Handling: BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
1339	34	1305	97.46

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L	486.901	448.423	38.478 with 8 DF (p=0.0001)
Score	.	.	44.215 with 8 DF (p=0.0001)
Wald	.	.	39.531 with 8 DF (p=0.0001)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square
AGE4	1	0.081405	0.02105	14.95723	0.0001
SBP4	1	0.005906	0.00935	0.39929	0.5275
DIAB4	1	0.938380	0.45630	4.22925	0.0397
BMI4	1	0.037158	0.04226	0.77328	0.3792
CIGS4	1	0.026381	0.01174	5.04675	0.0247
ALC4	1	-0.032145	0.03801	0.71526	0.3977
BETA4	1	0.290585	0.43466	0.44693	0.5038
CETP2	1	-0.701449	0.34961	4.02563	0.0448

Ordovas Project on CETP: Homozygote 11 vs 12,22 40
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta Bl,SBP,DM,CHOL,HDL

The PHREG Procedure
Analysis of Maximum Likelihood Estimates

Conditional Risk Ratio and
95% Confidence Limits

Variable	Risk Ratio	Lower	Upper	Label
AGE4	1.085	1.041	1.130	AGE
SBP4	1.006	0.988	1.025	SYSTOLIC BP - PHYSICIAN - 1ST READING
DIAB4	2.556	1.045	6.251	
BMI4	1.038	0.955	1.127	BODY MASS INDEX
CIGS4	1.027	1.003	1.051	CIGARETTES/PER DAY
ALC4	0.968	0.899	1.043	TOTAL ALCOHOL CONSUMPTION
BETA4	1.337	0.570	3.135	BETA BLOCKERS
CETP2	0.496	0.250	0.984	

Ordovas Project on CETP: Homozygote 11 vs 12,22 41
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta Bl,SBP,DM,CHOL,HDL

The LOGISTIC Procedure

Data Set: WORK.CETPDAT
Response Variable: CHDPREV4 Prevalent CHD at Exam 4
Response Levels: 2
Number of Observations: 1450
Link Function: Logit

Response Profile

Ordered Value	CHDPREV4	Count
1	1	123
2	0	1327

WARNING: 61 observation(s) were deleted due to missing values for the response or explanatory variables.

Model Fitting Information and Testing Global Null Hypothesis BETA=0

Criterion	Intercept Only	Intercept and Covariates	Chi-Square for Covariates
AIC	844.173	677.537	.
SC	849.452	740.888	.
-2 LOG L	842.173	653.537	188.637 with 11 DF (p=0.0001)
Score	.	.	224.918 with 11 DF (p=0.0001)

Ordovas Project on CETP: Homozygote 11 vs 12,22 42
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta Bl,SBP,DM,CHOL,HDL

The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-3.4651	1.4331	5.8459	0.0156	.	.
AGE4	1	0.0915	0.0130	49.5441	0.0001	0.506841	1.096
SBP4	1	-0.0153	0.00598	6.5880	0.0103	-0.151027	0.985
DIAB4	1	0.9569	0.2974	10.3492	0.0013	0.131218	2.604
CHOL4	1	-0.00382	0.00282	1.8352	0.1755	-0.078158	0.996
HDL4	1	-0.0176	0.0113	2.4395	0.1183	-0.109884	0.983
BMI4	1	-0.0311	0.0308	1.0219	0.3121	-0.065567	0.969
CIGS4	1	0.0158	0.00849	3.4792	0.0621	0.108872	1.016
ALC4	1	-0.0447	0.0257	3.0135	0.0826	-0.131235	0.956
BETA4	1	1.4030	0.2306	37.0180	0.0001	0.265128	4.067
CHOLRX4	1	1.6806	0.3243	26.8618	0.0001	0.193198	5.369
CETP2	1	-0.2529	0.2252	1.2616	0.2614	-0.064054	0.777

Association of Predicted Probabilities and Observed Responses

Concordant = 83.3%	Somers' D = 0.672
Discordant = 16.2%	Gamma = 0.675
Tied = 0.5%	Tau-a = 0.104
(163221 pairs)	c = 0.836

Ordovas Project on CETP: Homozygote 11 vs 12,22 43
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta Bl,SBP,DM,CHOL,HDL

The LOGISTIC Procedure

Conditional Odds Ratios and 95% Confidence Intervals

Variable	Unit	Odds Ratio	Wald Confidence Limits Lower	Upper
AGE4	1.0000	1.096	1.068	1.124
SBP4	1.0000	0.985	0.973	0.996
DIAB4	1.0000	2.604	1.453	4.664

CHOL4	1.0000	0.996	0.991	1.002
HDL4	1.0000	0.983	0.961	1.004
BMI4	1.0000	0.969	0.913	1.030
CIGS4	1.0000	1.016	0.999	1.033
ALC4	1.0000	0.956	0.909	1.006
BETA4	1.0000	4.067	2.588	6.391
CHOLRX4	1.0000	5.369	2.844	10.137
CETP2	1.0000	0.777	0.499	1.207

Ordovas Project on CETP: Homozygote 11 vs 12,22 44
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta Bl,SBP,DM,CHOL,HDL

The LOGISTIC Procedure

Data Set: WORK.CETPDAT
Response Variable: CHDPREV5 Prevalent CHD at Exam 5
Response Levels: 2
Number of Observations: 1347
Link Function: Logit

Response Profile

Ordered Value	CHDPREV5	Count
1	1	123
2	0	1224

WARNING: 164 observation(s) were deleted due to missing values for the response or explanatory variables.

Model Fitting Information and Testing Global Null Hypothesis BETA=0

Criterion	Intercept Only	Intercept and Covariates	Chi-Square for Covariates
AIC	825.199	633.368	.
SC	830.405	695.836	.
-2 LOG L	823.199	609.368	213.830 with 11 DF (p=0.0001)
Score	.	.	277.546 with 11 DF (p=0.0001)

Ordovas Project on CETP: Homozygote 11 vs 12,22 45
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta Bl,SBP,DM,CHOL,HDL

The LOGISTIC Procedure
Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-3.6714	1.5357	5.7156	0.0168	.	.
AGE5	1	0.0815	0.0135	36.4634	0.0001	0.442234	1.085
SBP5	1	-0.0213	0.00699	9.2492	0.0024	-0.196270	0.979
DIAB5	1	0.7978	0.3030	6.9340	0.0085	0.121981	2.221
CHOL5	1	-0.00149	0.00322	0.2144	0.6433	-0.029003	0.999
HDL5	1	-0.0136	0.0116	1.3647	0.2427	-0.084439	0.987
BMI5	1	-0.0116	0.0292	0.1567	0.6923	-0.026229	0.988
CIGS5	1	0.0118	0.0100	1.3954	0.2375	0.071029	1.012
ALC5	1	-0.0307	0.0266	1.3349	0.2479	-0.078658	0.970
BETA5	1	1.6592	0.2107	61.9822	0.0001	0.323464	5.255
CHOLRX5	1	1.6224	0.2615	38.4823	0.0001	0.249055	5.065
CETP2	1	-0.3075	0.2334	1.7346	0.1878	-0.077975	0.735

Association of Predicted Probabilities and Observed Responses

Concordant = 84.8%	Somers' D = 0.701
Discordant = 14.7%	Gamma = 0.705
Tied = 0.6%	Tau-a = 0.116
(150552 pairs)	c = 0.850

Ordovas Project on CETP: Homozygote 11 vs 12,22 46
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta Bl,SBP,DM,CHOL,HDL

The LOGISTIC Procedure

Conditional Odds Ratios and 95% Confidence Intervals

Variable	Unit	Odds Ratio	Wald Confidence Limits Lower	Upper
AGE5	1.0000	1.085	1.057	1.114
SBP5	1.0000	0.979	0.966	0.992
DIAB5	1.0000	2.221	1.226	4.021
CHOL5	1.0000	0.999	0.992	1.005
HDL5	1.0000	0.987	0.964	1.009
BMI5	1.0000	0.988	0.933	1.047
CIGS5	1.0000	1.012	0.992	1.032
ALC5	1.0000	0.970	0.921	1.022
BETA5	1.0000	5.255	3.477	7.943
CHOLRX5	1.0000	5.065	3.034	8.457
CETP2	1.0000	0.735	0.465	1.162

Ordovas Project on CETP: Homozygote 11 vs 12,22 47
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta Bl,SBP,DM,CHOL,HDL

The PHREG Procedure

Data Set: WORK.CETPDAT
Dependent Variable: CHD5_SUR
Censoring Variable: CHDINC5 Incidenct CHD between Exams 4 and 5
Censoring Value(s): 0
Ties Handling: BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
1327	34	1293	97.44

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L	486.279	440.285	45.994 with 11 DF (p=0.0001)
Score	.	.	52.571 with 11 DF (p=0.0001)
Wald	.	.	44.527 with 11 DF (p=0.0001)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square
AGE4	1	0.081377	0.02169	14.07661	0.0002
SBP4	1	0.007582	0.00946	0.64233	0.4229
DIAB4	1	0.940167	0.45958	4.18493	0.0408
CHOL4	1	0.006048	0.00453	1.78352	0.1817
HDL4	1	-0.029403	0.02002	2.15632	0.1420
BMI4	1	0.020283	0.04488	0.20427	0.6513
CIGS4	1	0.025019	0.01199	4.35358	0.0369
ALC4	1	-0.035452	0.03991	0.78892	0.3744
BETA4	1	0.081277	0.44726	0.03302	0.8558
CHOLRX4	1	1.059225	0.56200	3.55220	0.0595
CETP2	1	-0.619461	0.35391	3.06369	0.0801

Ordovas Project on CETP: Homozygote 11 vs 12,22 48
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Men: Adjusted for Age,BMI,Cigs/Day,Alc,Beta Bl,SBP,DM,CHOL,HDL

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Conditional Risk Ratio and 95% Confidence Limits

Variable	Risk Ratio	Lower	Upper	Label
AGE4	1.085	1.040	1.132	AGE
SBP4	1.008	0.989	1.026	SYSTOLIC BP - PHYSICIAN - 1ST READING
DIAB4	2.560	1.040	6.302	
CHOL4	1.006	0.997	1.015	TOTAL CHOLESTEROL
HDL4	0.971	0.934	1.010	HDL
BMI4	1.020	0.935	1.114	BODY MASS INDEX
CIGS4	1.025	1.002	1.050	CIGARETTES/PER DAY
ALC4	0.965	0.893	1.044	TOTAL ALCOHOL CONSUMPTION
BETA4	1.085	0.451	2.606	BETA BLOCKERS
CHOLRX4	2.884	0.959	8.678	
CETP2	0.538	0.269	1.077	

Ordovas Project on CETP: Homozygote 11 vs 12,22 49
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Women: Adjusted for Age,BMI,Cigs/Day,Alcl,Beta Bl,SBP,DM,CHOL,HDL,Meno,HRT

The LOGISTIC Procedure

Data Set: WORK.CETPDAT
Response Variable: CHDPREV4 Prevalent CHD at Exam 4
Response Levels: 2
Number of Observations: 1587
Link Function: Logit

Response Profile

Ordered Value	CHDPREV4	Count
1	1	50
2	0	1537

Model Fitting Information and Testing Global Null Hypothesis BETA=0

Criterion	Intercept Only	Intercept and Covariates	Chi-Square for Covariates
AIC	446.166	447.822	.
SC	451.535	458.561	.
-2 LOG L	444.166	443.822	0.344 with 1 DF (p=0.5576)
Score	.	.	0.336 with 1 DF (p=0.5619)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-3.5553	0.2711	172.0512	0.0001	.	.
CETP2	1	0.1852	0.3197	0.3355	0.5624	0.047545	1.203

Association of Predicted Probabilities and Observed Responses

Concordant	= 23.0%	Somers' D	= 0.039
Discordant	= 19.1%	Gamma	= 0.092
Tied	= 58.0%	Tau-a	= 0.002
(76850 pairs)		c	= 0.519

Ordovas Project on CETP: Homozygote 11 vs 12,22 50
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Women: Adjusted for Age,BMI,Cigs/Day,Alcl,Beta Bl,SBP,DM,CHOL,HDL,Meno,HRT

The LOGISTIC Procedure

Conditional Odds Ratios and 95% Confidence Intervals

Variable	Unit	Odds Ratio	Wald Confidence Limits Lower	Upper
CETP2	1.0000	1.203	0.643	2.252

Ordovas Project on CETP: Homozygote 11 vs 12,22 51
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Women: Adjusted for Age,BMI,Cigs/Day,Alcl,Beta Bl,SBP,DM,CHOL,HDL,Meno,HRT

The LOGISTIC Procedure

Data Set: WORK.CETPDAT
Response Variable: CHDPREV5 Prevalent CHD at Exam 5
Response Levels: 2
Number of Observations: 1587
Link Function: Logit

Response Profile

Ordered Value	CHDPREV5	Count
1	1	62
2	0	1525

Model Fitting Information and Testing Global Null Hypothesis BETA=0

Criterion	Intercept Only	Intercept and Covariates	Chi-Square for Covariates
AIC	525.611	525.825	.
SC	530.981	536.564	.
-2 LOG L	523.611	521.825	1.786 with 1 DF (p=0.1814)
Score	.	.	1.704 with 1 DF (p=0.1918)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-3.4843	0.2621	176.6867	0.0001	.	.
CETP2	1	0.3913	0.3016	1.6838	0.1944	0.100474	1.479

Association of Predicted Probabilities and Observed Responses

Concordant	= 24.3%	Somers' D	= 0.079
Discordant	= 16.4%	Gamma	= 0.193
Tied	= 59.3%	Tau-a	= 0.006
(94550 pairs)		c	= 0.539

Ordovas Project on CETP: Homozygote 11 vs 12,22 52
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Women: Adjusted for Age,BMI,Cigs/Day,Alcl,Beta Bl,SBP,DM,CHOL,HDL,Meno,HRT

The LOGISTIC Procedure

Conditional Odds Ratios and 95% Confidence Intervals

Variable	Unit	Odds Ratio	Wald Confidence Limits Lower	Upper
CETP2	1.0000	1.479	0.819	2.671

Ordovas Project on CETP: Homozygote 11 vs 12,22 53
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Women: Adjusted for Age,BMI,Cigs/Day,Alcl,Beta Bl,SBP,DM,CHOL,HDL,Meno,HRT

The PHREG Procedure

Data Set: WORK.CETPDAT
Dependent Variable: CHD5_SUR
Censoring Variable: CHDINC5 Incidenct CHD between Exams 4 and 5
Censoring Value(s): 0
Ties Handling: BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
1498	12	1486	99.20

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L	174.916	171.004	3.912 with 1 DF (p=0.0479)
Score	.	.	3.115 with 1 DF (p=0.0776)
Wald	.	.	2.495 with 1 DF (p=0.1142)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square
CETP2	1	1.649863	1.04447	2.49521	0.1142

Ordovas Project on CETP: Homozygote 11 vs 12,22 54
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Women: Adjusted for Age,BMI,Cigs/Day,Alcl,Beta Bl,SBP,DM,CHOL,HDL,Meno,HRT

The PHREG Procedure
Analysis of Maximum Likelihood Estimates

Conditional Risk Ratio and 95% Confidence Limits

Variable	Risk Ratio	Lower	Upper
CETP2	5.206	0.672	40.325

Ordovas Project on CETP: Homozygote 11 vs 12,22 55
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Women: Adjusted for Age,BMI,Cigs/Day,Alcl,Beta Bl,SBP,DM,CHOL,HDL,Meno,HRT

The LOGISTIC Procedure

Data Set: WORK.CETPDAT
Response Variable: CHDPREV4 Prevalent CHD at Exam 4
Response Levels: 2
Number of Observations: 1525
Link Function: Logit

Response Profile

Ordered Value	CHDPREV4	Count
1	1	49
2	0	1476

WARNING: 62 observation(s) were deleted due to missing values for the response or explanatory variables.
WARNING: There is possibly a quasicomplete separation in the sample points. The maximum likelihood estimate may not exist.
WARNING: The LOGISTIC procedure continues in spite of the above warning. Results shown are based on the last maximum likelihood iteration. Validity of the model fit is questionable.

Model Fitting Information and Testing Global Null Hypothesis BETA=0

Criterion	Intercept Only	Intercept and Covariates	Chi-Square for Covariates
AIC	435.326	373.009	.
SC	440.655	426.307	.
-2 LOG L	433.326	353.009	80.316 with 9 DF (p=0.0001)
Score	.	.	74.800 with 9 DF (p=0.0001)

Ordovas Project on CETP: Homozygote 11 vs 12,22 56
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Women: Adjusted for Age,BMI,Cigs/Day,Alcl,Beta Bl,SBP,DM,CHOL,HDL,Meno,HRT

The LOGISTIC Procedure

WARNING: The validity of the model fit is questionable.

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-9.7860	1.4718	44.2107	0.0001	.	.
AGE4	1	0.1060	0.0244	18.9075	0.0001	0.569861	1.112
SBP4	1	-0.00184	0.00828	0.0492	0.8245	-0.020002	0.998
DIAB4	1	1.0272	0.4705	4.7674	0.0290	0.106550	2.793
BMI4	1	0.0127	0.0272	0.2190	0.6398	0.037041	1.013
CIGS4	1	0.00788	0.0159	0.2467	0.6194	0.043005	1.008
ALC4	1	-0.2955	0.1167	6.4072	0.0114	-0.429955	0.744
MENO4	1	0.6538	0.5402	1.4649	0.2261	0.179082	1.923
ESTRO4	1	-12.5862	284.1	0.0020	0.9647	-1.861841	0.000
CETP2	1	0.1519	0.3344	0.2063	0.6497	0.039055	1.164

Association of Predicted Probabilities and Observed Responses

Concordant	= 83.9%	Somers' D	= 0.688
Discordant	= 15.1%	Gamma	= 0.695
Tied	= 1.1%	Tau-a	= 0.043
(72324 pairs)		c	= 0.844

Conditional Odds Ratios and 95% Confidence Interval

Variable	Unit	Odds Ratio	Wald Confidence Limits Lower	Upper
AGE4	1.0000	1.112	1.060	1.166
SBP4	1.0000	0.998	0.982	1.015
DIAB4	1.0000	2.793	1.111	7.024
BMI4	1.0000	1.013	0.960	1.068
CIGS4	1.0000	1.008	0.977	1.040
ALC4	1.0000	0.744	0.592	0.935
MENO4	1.0000	1.923	0.667	5.544
ESTRO4	1.0000	0.000	0.000	999.000
CETP2	1.0000	1.164	0.604	2.242

Ordovas Project on CETP: Homozygote 11 vs 12,22 57
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Women: Adjusted for Age,BMI,Cigs/Day,Alcl,Beta Bl,SBP,DM,CHOL,HDL,Meno,HRT

The LOGISTIC Procedure

Data Set: WORK.CETPDAT
Response Variable: CHDPREV5 Prevalent CHD at Exam 5
Response Levels: 2
Number of Observations: 1454
Link Function: Logit

Response Profile

Ordered Value	CHDPREV5	Count

1	1	55
2	0	1399

WARNING: 133 observation(s) were deleted due to missing values for the response or explanatory variables.

Model Fitting Information and Testing Global Null Hypothesis BETA=0

Criterion	Intercept Only	Intercept and Covariates	Chi-Square for Covariates
AIC	470.114	433.551	.
SC	475.396	486.372	.
-2 LOG L	468.114	413.551	54.563 with 9 DF (p=0.0001)
Score	.	.	63.651 with 9 DF (p=0.0001)

Ordovas Project on CETP: Homozygote 11 vs 12,22 58
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Women: Adjusted for Age,BMI,Cigs/Day,Alcl,Beta Bl,SBP,DM,CHOL,HDL,Meno,HRT

The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-9.0312	1.4204	40.4268	0.0001	.	.
AGE5	1	0.0883	0.0227	15.0831	0.0001	0.474249	1.092
SBP5	1	0.00190	0.00764	0.0618	0.8036	0.020900	1.002
DIAB5	1	1.3036	0.3935	10.9774	0.0009	0.153905	3.682
BMI5	1	0.0123	0.0256	0.2292	0.6321	0.036607	1.012
CIGS5	1	0.00210	0.0158	0.0178	0.8940	0.010493	1.002
ALC5	1	-0.1338	0.0816	2.6876	0.1011	-0.193413	0.875
MENO5	1	-0.1924	0.5561	0.1197	0.7293	-0.050216	0.825
ESTRO5	1	-0.2663	0.4570	0.3395	0.5601	-0.055847	0.766
CETP2	1	0.3661	0.3328	1.2102	0.2713	0.093888	1.442

Association of Predicted Probabilities and Observed Responses

Concordant = 77.0%	Somers' D = 0.554
Discordant = 21.6%	Gamma = 0.562
Tied = 1.3%	Tau-a = 0.040
(76945 pairs)	c = 0.777

Conditional Odds Ratios and 95% Confidence Intervals

Variable	Unit	Odds Ratio	Wald Confidence Limits Lower	Upper
AGE5	1.0000	1.092	1.045	1.142
SBP5	1.0000	1.002	0.987	1.017
DIAB5	1.0000	3.682	1.703	7.962
BMI5	1.0000	1.012	0.963	1.064
CIGS5	1.0000	1.002	0.972	1.034
ALC5	1.0000	0.875	0.745	1.027
MENO5	1.0000	0.825	0.277	2.454
ESTRO5	1.0000	0.766	0.313	1.876
CETP2	1.0000	1.442	0.751	2.768

Ordovas Project on CETP: Homozygote 11 vs 12,22 59
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Women: Adjusted for Age,BMI,Cigs/Day,Alcl,Beta Bl,SBP,DM,CHOL,HDL,Meno,HRT

The PHREG Procedure

Data Set: WORK.CETPDAT
Dependent Variable: CHD5_SUR
Censoring Variable: CHDINC5 Incidenct CHD between Exams 4 and 5
Censoring Value(s): 0
Ties Handling: BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
1476	12	1464	99.19

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L	174.571	161.556	13.015 with 9 DF (p=0.1619)
Score	.	.	15.931 with 9 DF (p=0.0683)
Wald	.	.	13.026 with 9 DF (p=0.1614)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square
AGE4	1	0.009761	0.04195	0.05413	0.8160
SBP4	1	0.023936	0.01626	2.16711	0.1410
DIAB4	1	1.479159	0.85687	2.97988	0.0843
BMI4	1	-0.000823	0.05618	0.0002147	0.9883
CIGS4	1	0.002398	0.02849	0.00708	0.9329
ALC4	1	0.087004	0.08020	1.17678	0.2780
MENO4	1	-0.126104	0.79523	0.02515	0.8740
ESTRO4	1	0.933869	0.80734	1.33801	0.2474
CETP2	1	1.682293	1.04712	2.58115	0.1081

Ordovas Project on CETP: Homozygote 11 vs 12,22 60
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Women: Adjusted for Age,BMI,Cigs/Day,Alcl,Beta Bl,SBP,DM,CHOL,HDL,Meno,HRT

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Conditional Risk Ratio and 95% Confidence Limits

Variable	Risk Ratio	Lower	Upper	Label
AGE4	1.010	0.930	1.096	AGE
SBP4	1.024	0.992	1.057	SYSTOLIC BP - PHYSICIAN - 1ST READING
DIAB4	4.389	0.819	23.537	
BMI4	0.999	0.895	1.115	BODY MASS INDEX

CIGS4	1.002	0.948	1.060	CIGARETTES/PER DAY
ALC4	1.091	0.932	1.277	TOTAL ALCOHOL CONSUMPTION
MENO4	0.882	0.185	4.189	PERIODS STOPPED 1YR OR MORE (FEMALE)
ESTRO4	2.544	0.523	12.382	ORAL ESTROGEN
CETP2	5.378	0.691	41.871	

Ordovas Project on CETP: Homozygote 11 vs 12,22 61
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Women: Adjusted for Age,BMI,Cigs/Day,Alcl,Beta Bl,SBP,DM,CHOL,HDL,Meno,HRT

The LOGISTIC Procedure

Data Set: WORK.CETPDAT
Response Variable: CHDPREV4 Prevalent CHD at Exam 4
Response Levels: 2
Number of Observations: 1525
Link Function: Logit

Response Profile

Ordered Value	CHDPREV4	Count
1	1	49
2	0	1476

WARNING: 62 observation(s) were deleted due to missing values for the response or explanatory variables.
WARNING: There is possibly a quasicomplete separation in the sample points. The maximum likelihood estimate may not exist.
WARNING: The LOGISTIC procedure continues in spite of the above warning. Results shown are based on the last maximum likelihood iteration. Validity of the model fit is questionable.

Model Fitting Information and Testing Global Null Hypothesis BETA=0

Criterion	Intercept Only	Intercept and Covariates	Chi-Square for Covariates
AIC	435.326	352.682	.
SC	440.655	411.309	.
-2 LOG L	433.326	330.682	102.644 with 10 DF (p=0.0001)
Score	.	.	121.967 with 10 DF (p=0.0001)

Ordovas Project on CETP: Homozygote 11 vs 12,22 62
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Women: Adjusted for Age,BMI,Cigs/Day,Alcl,Beta Bl,SBP,DM,CHOL,HDL,Meno,HRT

The LOGISTIC Procedure
WARNING: The validity of the model fit is questionable.

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-9.3526	1.5502	36.3996	0.0001	.	.
AGE4	1	0.1093	0.0257	18.1307	0.0001	0.587960	1.116
SBP4	1	-0.00759	0.00863	0.7739	0.3790	-0.082689	0.992
DIAB4	1	0.7967	0.5014	2.5250	0.1121	0.082636	2.218
BMI4	1	0.0120	0.0280	0.1833	0.6686	0.034847	1.012
CIGS4	1	0.0148	0.0164	0.8143	0.3668	0.080968	1.015

ALC4	1	-0.2828	0.1178	5.7627	0.0164	-0.411464	0.754
BETA4	1	1.7220	0.3438	25.0931	0.0001	0.253748	5.596
MENO4	1	0.4592	0.5496	0.6981	0.4034	0.125781	1.583
ESTRO4	1	-13.2266	369.7	0.0013	0.9715	-1.956577	0.000
CETP2	1	0.0481	0.3448	0.0195	0.8890	0.012374	1.049

Association of Predicted Probabilities and Observed Responses

Concordant = 86.8%	Somers' D = 0.744
Discordant = 12.4%	Gamma = 0.750
Tied = 0.9%	Tau-a = 0.046
(72324 pairs)	c = 0.872

Conditional Odds Ratios and 95% Confidence Intervals

Variable	Unit	Odds Ratio	Wald Confidence Limits Lower	Upper
AGE4	1.0000	1.116	1.061	1.173
SBP4	1.0000	0.992	0.976	1.009
DIAB4	1.0000	2.218	0.830	5.926
BMI4	1.0000	1.012	0.958	1.069
CIGS4	1.0000	1.015	0.983	1.048
ALC4	1.0000	0.754	0.598	0.949
BETA4	1.0000	5.596	2.853	10.976
MENO4	1.0000	1.583	0.539	4.648
ESTRO4	1.0000	0.000	0.000	999.000
CETP2	1.0000	1.049	0.534	2.063

Ordovas Project on CETP: Homozygote 11 vs 12,22 63
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Women: Adjusted for Age,BMI,Cigs/Day,Alcl,Beta Bl,SBP,DM,CHOL,HDL,Meno,HRT

The LOGISTIC Procedure

Data Set: WORK.CETPDAT
Response Variable: CHDPREV5 Prevalent CHD at Exam 5
Response Levels: 2
Number of Observations: 1452
Link Function: Logit

Response Profile

Ordered Value	CHDPREV5	Count
1	1	55
2	0	1397

WARNING: 135 observation(s) were deleted due to missing values for the response or explanatory variables.

Model Fitting Information and Testing Global Null Hypothesis BETA=0

Criterion	Intercept Only	Intercept and Covariates	Chi-Square for Covariates
AIC	469.960	401.313	.
SC	475.241	459.401	.
-2 LOG L	467.960	379.313	88.647 with 10 DF (p=0.0001)
Score	.	.	120.653 with 10 DF (p=0.0001)

Ordovas Project on CETP: Homozygote 11 vs 12,22 64
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Women: Adjusted for Age,BMI,Cigs/Day,Alcl,Beta Bl,SBP,DM,CHOL,HDL,Meno,HRT

The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-9.3092	1.5283	37.1057	0.0001	.	.
AGE5	1	0.0925	0.0241	14.6662	0.0001	0.495934	1.097
SBP5	1	5.007E-6	0.00780	0.0000	0.9995	0.000054976	1.000
DIAB5	1	0.9920	0.4094	5.8707	0.0154	0.117198	2.697
BMI5	1	0.0105	0.0260	0.1617	0.6876	0.031242	1.011
CIGS5	1	0.0143	0.0158	0.8181	0.3657	0.071083	1.014
ALC5	1	-0.1542	0.0856	3.2447	0.0717	-0.222572	0.857
BETA5	1	1.8215	0.2844	41.0299	0.0001	0.302890	6.181
MENO5	1	-0.2394	0.5838	0.1681	0.6818	-0.062485	0.787
ESTRO5	1	-0.3477	0.4689	0.5499	0.4584	-0.072969	0.706
CETP2	1	0.3270	0.3402	0.9242	0.3364	0.083856	1.387

Association of Predicted Probabilities and Observed Responses

Concordant	= 83.4%	Somers' D	= 0.677
Discordant	= 15.7%	Gamma	= 0.684
Tied	= 1.0%	Tau-a	= 0.049
(76835 pairs)		c	= 0.839

Conditional Odds Ratios and 95% Confidence Intervals

Variable	Unit	Odds Ratio	Wald Confidence Limits Lower	Upper
AGE5	1.0000	1.097	1.046	1.150
SBP5	1.0000	1.000	0.985	1.015
DIAB5	1.0000	2.697	1.209	6.016
BMI5	1.0000	1.011	0.960	1.063
CIGS5	1.0000	1.014	0.983	1.046
ALC5	1.0000	0.857	0.725	1.014
BETA5	1.0000	6.181	3.540	10.792
MENO5	1.0000	0.787	0.251	2.472
ESTRO5	1.0000	0.706	0.282	1.771
CETP2	1.0000	1.387	0.712	2.701

Ordovas Project on CETP: Homozygote 11 vs 12,22 65
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Women: Adjusted for Age,BMI,Cigs/Day,Alcl,Beta Bl,SBP,DM,CHOL,HDL,Meno,HRT

The PHREG Procedure

Data Set: WORK.CETPDAT
Dependent Variable: CHD5_SUR
Censoring Variable: CHDINC5 Incidenct CHD between Exams 4 and 5
Censoring Value(s): 0
Ties Handling: BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
1476	12	1464	99.19

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L	174.571	161.437	13.134 with 10 DF (p=0.2163)
Score	.	.	16.409 with 10 DF (p=0.0885)
Wald	.	.	13.408 with 10 DF (p=0.2017)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square
AGE4	1	0.010400	0.04201	0.06128	0.8045
SBP4	1	0.022594	0.01668	1.83560	0.1755
DIAB4	1	1.453828	0.86109	2.85057	0.0913
BMI4	1	-0.001268	0.05617	0.0005097	0.9820
CIGS4	1	0.003074	0.02872	0.01146	0.9147
ALC4	1	0.084172	0.08113	1.07640	0.2995
BETA4	1	0.297695	0.84120	0.12524	0.7234
MENO4	1	-0.153327	0.80038	0.03670	0.8481
ESTRO4	1	0.939680	0.80788	1.35290	0.2448
CETP2	1	1.671343	1.04735	2.54654	0.1105

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Conditional Risk Ratio and 95% Confidence Limits

Variable	Risk Ratio	Lower	Upper	Label
AGE4	1.010	0.931	1.097	AGE
SBP4	1.023	0.990	1.057	SYSTOLIC BP - PHYSICIAN - 1ST READING
DIAB4	4.279	0.791	23.139	
BMI4	0.999	0.895	1.115	BODY MASS INDEX
CIGS4	1.003	0.948	1.061	CIGARETTES/PER DAY
ALC4	1.088	0.928	1.275	TOTAL ALCOHOL CONSUMPTION
BETA4	1.347	0.259	7.004	BETA BLOCKERS
MENO4	0.858	0.179	4.118	PERIODS STOPPED 1YR OR MORE (FEMALE)
ESTRO4	2.559	0.525	12.467	ORAL ESTROGEN
CETP2	5.319	0.683	41.434	

The LOGISTIC Procedure

Data Set: WORK.CETPDAT
Response Variable: CHDPREV4 Prevalent CHD at Exam 4
Response Levels: 2
Number of Observations: 1482
Link Function: Logit

Response Profile

Ordered Value	CHDPREV4	Count
1	1	49
2	0	1433

WARNING: 105 observation(s) were deleted due to missing values for the response or explanatory variables.
WARNING: There is possibly a quasicomplete separation in the sample points. The maximum likelihood estimate may not exist.
WARNING: The LOGISTIC procedure continues in spite of the above warning. Results shown are based on the last maximum likelihood iteration. Validity of the model fit is questionable.

Model Fitting Information and Testing Global Null Hypothesis BETA=0

Criterion	Intercept Only	Intercept and Covariates	Chi-Square for Covariates
AIC	432.476	343.822	.
SC	437.777	418.038	.
-2 LOG L	430.476	315.822	114.654 with 13 DF (p=0.0001)
Score	.	.	147.058 with 13 DF (p=0.0001)

Ordovas Project on CETP: Homozygote 11 vs 12,22 68
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Women: Adjusted for Age,BMI,Cigs/Day,Alcl,Beta Bl,SBP,DM,CHOL,HDL,Meno,HRT

The LOGISTIC Procedure
WARNING: The validity of the model fit is questionable.

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-7.9373	1.8858	17.7159	0.0001	.	.
AGE4	1	0.1062	0.0264	16.2199	0.0001	0.572944	1.112
SBP4	1	-0.00903	0.00897	1.0148	0.3137	-0.098627	0.991
DIAB4	1	0.6446	0.5078	1.6114	0.2043	0.067199	1.905
CHOL4	1	-0.00014	0.00398	0.0012	0.9724	-0.003021	1.000
HDL4	1	-0.0190	0.0130	2.1350	0.1440	-0.158556	0.981
BMI4	1	0.00573	0.0303	0.0358	0.8499	0.016560	1.006
CIGS4	1	0.0106	0.0173	0.3767	0.5394	0.057412	1.011
ALC4	1	-0.2616	0.1209	4.6839	0.0304	-0.380082	0.770
BETA4	1	1.6943	0.3547	22.8184	0.0001	0.248999	5.443
CHOLRX4	1	1.4510	0.4920	8.6968	0.0032	0.128099	4.267
MENO4	1	0.4332	0.5581	0.6026	0.4376	0.118661	1.542
ESTRO4	1	-13.0598	347.3	0.0014	0.9700	-1.942244	0.000
CETP2	1	0.1732	0.3565	0.2359	0.6272	0.044519	1.189

Association of Predicted Probabilities and Observed Responses

Concordant = 87.6%		Somers' D	= 0.762
Discordant = 11.4%		Gamma	= 0.769
Tied = 1.0%		Tau-a	= 0.049
(70217 pairs)		c	= 0.881

Ordovas Project on CETP: Homozygote 11 vs 12,22 69
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Women: Adjusted for Age,BMI,Cigs/Day,Alcl,Beta Bl,SBP,DM,CHOL,HDL,Meno,HRT

The LOGISTIC Procedure
WARNING: The validity of the model fit is questionable.

Conditional Odds Ratios and 95% Confidence Intervals

Variable	Unit	Odds Ratio	Wald Confidence Limits Lower	Upper
AGE4	1.0000	1.112	1.056	1.171
SBP4	1.0000	0.991	0.974	1.009
DIAB4	1.0000	1.905	0.704	5.154
CHOL4	1.0000	1.000	0.992	1.008
HDL4	1.0000	0.981	0.957	1.007
BMI4	1.0000	1.006	0.948	1.067
CIGS4	1.0000	1.011	0.977	1.046
ALC4	1.0000	0.770	0.607	0.976
BETA4	1.0000	5.443	2.716	10.908
CHOLRX4	1.0000	4.267	1.627	11.194
MENO4	1.0000	1.542	0.517	4.605
ESTRO4	1.0000	0.000	0.000	999.000
CETP2	1.0000	1.189	0.591	2.391

Ordovas Project on CETP: Homozygote 11 vs 12,22 70
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Women: Adjusted for Age,BMI,Cigs/Day,Alcl,Beta Bl,SBP,DM,CHOL,HDL,Meno,HRT

The LOGISTIC Procedure

Data Set: WORK.CETPDAT
Response Variable: CHDPREV5 Prevalent CHD at Exam 5
Response Levels: 2
Number of Observations: 1443
Link Function: Logit

Response Profile

Ordered Value	CHDPREV5	Count
1	1	53
2	0	1390

WARNING: 144 observation(s) were deleted due to missing values for the response or explanatory variables.

Model Fitting Information and Testing Global Null Hypothesis BETA=0

Criterion	Intercept Only	Intercept and Covariates	Chi-Square for Covariates
AIC	456.273	389.152	.
SC	461.547	462.995	.
-2 LOG L	454.273	361.152	93.121 with 13 DF (p=0.0001)
Score	.	.	129.083 with 13 DF (p=0.0001)

Ordovas Project on CETP: Homozygote 11 vs 12,22 71
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Women: Adjusted for Age,BMI,Cigs/Day,Alcl,Beta Bl,SBP,DM,CHOL,HDL,Meno,HRT

The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-8.6993	1.7988	23.3893	0.0001	.	.
AGE5	1	0.0903	0.0249	13.2089	0.0003	0.484363	1.095
SBP5	1	-0.00220	0.00806	0.0746	0.7848	-0.024160	0.998
DIAB5	1	0.6675	0.4376	2.3264	0.1272	0.078554	1.949
CHOL5	1	0.00348	0.00380	0.8368	0.3603	0.072761	1.003
HDL5	1	-0.0175	0.0114	2.3368	0.1263	-0.150035	0.983
BMI5	1	0.00329	0.0278	0.0139	0.9060	0.009799	1.003
CIGS5	1	0.00964	0.0170	0.3221	0.5703	0.047635	1.010
ALC5	1	-0.1024	0.0857	1.4291	0.2319	-0.147813	0.903
BETA5	1	1.6905	0.2956	32.7113	0.0001	0.279263	5.422
CHOLRX5	1	0.8647	0.3757	5.2976	0.0214	0.114128	2.374
MENO5	1	-0.3021	0.5886	0.2635	0.6077	-0.078986	0.739
ESTRO5	1	-0.2251	0.4746	0.2250	0.6353	-0.047279	0.798
CETP2	1	0.4206	0.3573	1.3862	0.2391	0.107790	1.523

Association of Predicted Probabilities and Observed Responses

Concordant = 83.8%	Somers' D = 0.687
Discordant = 15.1%	Gamma = 0.694
Tied = 1.1%	Tau-a = 0.049
(73670 pairs)	c = 0.843

Ordovas Project on CETP: Homozygote 11 vs 12,22 72
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Women: Adjusted for Age,BMI,Cigs/Day,Alcl,Beta Bl,SBP,DM,CHOL,HDL,Meno,HRT

The LOGISTIC Procedure

Conditional Odds Ratios and 95% Confidence Intervals

Variable	Unit	Odds Ratio	Wald Confidence Limits Lower	Upper
AGE5	1.0000	1.095	1.043	1.149
SBP5	1.0000	0.998	0.982	1.014
DIAB5	1.0000	1.949	0.827	4.596
CHOL5	1.0000	1.003	0.996	1.011
HDL5	1.0000	0.983	0.961	1.005
BMI5	1.0000	1.003	0.950	1.060
CIGS5	1.0000	1.010	0.977	1.044

ALC5	1.0000	0.903	0.763	1.068
BETA5	1.0000	5.422	3.038	9.677
CHOLRX5	1.0000	2.374	1.137	4.959
MENO5	1.0000	0.739	0.233	2.343
ESTRO5	1.0000	0.798	0.315	2.024
CETP2	1.0000	1.523	0.756	3.067

Ordovas Project on CETP: Homozygote 11 vs 12,22 73
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Women: Adjusted for Age,BMI,Cigs/Day,Alcl,Beta Bl,SBP,DM,CHOL,HDL,Meno,HRT

The PHREG Procedure

Data Set: WORK.CETPDAT
Dependent Variable: CHD5_SUR
Censoring Variable: CHDINC5 Incidenct CHD between Exams 4 and 5
Censoring Value(s): 0
Ties Handling: BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
1433	12	1421	99.16

Testing Global Null Hypothesis: BETA=0

Criterion	Without Covariates	With Covariates	Model Chi-Square
-2 LOG L	173.850	153.224	20.626 with 13 DF (p=0.0807)
Score	.	.	31.540 with 13 DF (p=0.0028)
Wald	.	.	24.372 with 13 DF (p=0.0279)

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square
AGE4	1	-0.000704	0.04546	0.0002396	0.9877
SBP4	1	0.023043	0.01727	1.78117	0.1820
DIAB4	1	0.921724	0.92603	0.99073	0.3196
CHOL4	1	0.009840	0.00659	2.22751	0.1356
HDL4	1	-0.029163	0.02403	1.47261	0.2249
BMI4	1	-0.038251	0.06541	0.34202	0.5587
CIGS4	1	-0.006371	0.03052	0.04358	0.8346
ALC4	1	0.090996	0.09165	0.98586	0.3208
BETA4	1	-0.066919	0.91563	0.00534	0.9417
CHOLRX4	1	1.394601	0.85211	2.67863	0.1017
MENO4	1	-0.198818	0.79866	0.06197	0.8034
ESTRO4	1	0.735728	0.85231	0.74513	0.3880
CETP2	1	1.803263	1.05698	2.91063	0.0880

Ordovas Project on CETP: Homozygote 11 vs 12,22 74
Including Subjects on Cholesterol Lowering Drugs
Tables 2-7 Regressions
Women: Adjusted for Age,BMI,Cigs/Day,Alcl,Beta Bl,SBP,DM,CHOL,HDL,Meno,HRT

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Variable	Risk Ratio	Conditional Risk Ratio and 95% Confidence Limits Lower	Upper	Label
AGE4	0.999	0.914	1.092	AGE
SBP4	1.023	0.989	1.059	SYSTOLIC BP - PHYSICIAN - 1ST READING
DIAB4	2.514	0.409	15.436	
CHOL4	1.010	0.997	1.023	TOTAL CHOLESTEROL
HDL4	0.971	0.927	1.018	HDL
BMI4	0.962	0.847	1.094	BODY MASS INDEX
CIGS4	0.994	0.936	1.055	CIGARETTES/PER DAY
ALC4	1.095	0.915	1.311	TOTAL ALCOHOL CONSUMPTION
BETA4	0.935	0.155	5.628	BETA BLOCKERS
CHOLRX4	4.033	0.759	21.428	
MENO4	0.820	0.171	3.922	PERIODS STOPPED 1YR OR MORE (FEMALE)
ESTRO4	2.087	0.393	11.092	ORAL ESTROGEN
CETP2	6.069	0.765	48.178	

1. A method for assessing risk for the development of cardiovascular disease in an individual, comprising:

a) isolating nucleic acid from the individual;

b) analyzing the nucleic acid for the presence of the TaqIB polymorphism of the cholesteryl ester transfer protein gene;

c) determining from the analysis of step b) whether the individual:

i) is homozygous for the TaqIB polymorphism;

ii) is heterozygous for the TaqIB polymorphism; or

iii) does not possess the TaqIB polymorphism; and

d) assessing the risk for the development of cardiovascular disease in the individual on the basis of determinations made in step c).

2. The method of claim 1 wherein a determination in step c) that the individual does not possess the TaqIB polymorphism correlates with high increased risk for the development of cardiovascular disease.

3. The method of claim 1 wherein a determination in step c) that the individual is heterozygous for the TaqIB polymorphism correlates with moderate increased risk for the development of cardiovascular disease.

4. The method of claim 1 wherein a determination in step c) that the individual is homozygous for the TaqIB polymorphism correlates with no increased risk for the development of cardiovascular disease.

5. The method of claim 1 wherein the susceptibility is assessed on the basis of the determinations made in step c) in combination with additional determinations of one or more known factors of cardiovascular disease risk.

6. The method of claim 5 wherein the factor is genetic.

7. The method of claim 5 wherein the factor is environmental.

8. The method of claim 7 wherein the environmental factor is dietary.

9. The method of claim 1 wherein the individual is male.

10. The method of claim 1 wherein the individual is female.

11. The method of claim 1 wherein the nucleic acid is genomic DNA.

12. The method of claim 11 wherein the nucleic acid is analyzed for the presence of the TaqIB polymorphism by PCR amplification of a suitable section of the first intron of the cholesteryl ester transfer protein gene followed by restriction analysis of the fragment for the presence of a TaqI restriction site at a position corresponding to nucleotide 277 of the first intron, wherein the presence of the TaqI restriction site indicates the absence of the TaqIB polymorphism, and the absence of the TaqI restriction site indicates the presence of the TaqIB polymorphism.

13. The method of claim 12 wherein the suitable section of the first intron is 535 base pairs in length and is amplified using the forward primer 5'-CACTAGCCCAGAGAGAG-GAGTGCC-3' and the reverse primer 5'-CTGAGCCCAGC-CGCACACTAAC-3'.

14. The method of claim 1 wherein the cardiovascular disease is selected from the group consisting of myocardial infarction, angina pectoris, coronary insufficiency and coronary death.

15. A kit for assessing risk for the development of cardiovascular disease in an individual, comprising oligonucleotide primers for the amplification of a suitable section of the first intron of the cholesteryl ester transfer protein gene encompassing the TaqI restriction site of the B1 allele of the CETP gene, the presence of the TaqI restriction site being indicative of the absence of the TaqIB polymorphism.

16. The kit of claim 15 wherein the oligonucleotide primers are the forward primer 5'-CACTAGCCCA-GAGAGAGGAGTGCC-3' and the reverse primer 5'-CT-GAGCCCAGCCGCACACTAAC-3'.

17. The kit of claim 15 which further includes indicators for additional known factors of cardiovascular disease risk.

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