Genetic variation and the lipid response to dietary intervention: a systematic review[1–3]

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ABSTRACT

There is wide interindividual variation in the lipid and lipoprotein responses to dietary change, and the existence of consistent hypo- and hyperresponders supports the hypothesis that responsiveness is related to genetic variation. Many studies have investigated the possibility that the heterogeneity in responsiveness to changes in dietary fat, cholesterol, and fiber intake is explained by variation in genes whose products affect lipoprotein metabolism, eg, apolipoproteins, enzymes, and receptors. A systematic review of the literature was carried out to investigate the effect of genetic variation on the lipid response to dietary intervention. A search strategy for the MEDLINE database retrieved 2540 articles from 1966 to February 2002. This strategy was adapted and performed on the EMBASE database, which retrieved 2473 articles from 1980 to week 9, 2002. Reference lists from relevant journal articles were also checked. This is the first systematic review of the literature, and it summarizes results available from 74 relevant articles. There is evidence to suggest that variation in the genes for apolipoprotein (apo) A-I, apo A-IV, apo B, and apo E contributes to the heterogeneity in the lipid response to dietary intervention. However, the effects of genetic variation are not consistently seen and are sometimes conflicting. Future studies need to have much larger sample sizes based on power calculations and carefully controlled dietary interventions and should investigate the effects of polymorphisms in multiple genes instead of the effects of polymorphisms in single genes. *Am J Clin Nutr* 2003;77:1098–111.

KEY WORDS Polymorphism, genotype, diet, lipids, lipoproteins, cardiovascular disease

INTRODUCTION

Cardiovascular disease has a multifactorial etiology with many established risk factors. The nonmodifiable risk factors include older age, male sex, and a family history of premature cardiovascular disease, whereas the modifiable risk factors include cigarette smoking, obesity, hypertension, physical inactivity, diabetes mellitus, elevated total cholesterol and LDL-cholesterol concentrations, and reduced HDL-cholesterol concentrations (1).

Serum cholesterol concentrations are profoundly influenced by the composition of dietary fat, with saturated fatty acids (SFAs) being the major determinant of serum cholesterol (2). Equations have been developed to predict the responses of total, LDL, and HDL cholesterol to dietary change (2–5), but there is wide interindividual variation in these lipid and lipoprotein responses (6–8). The existence of consistent hypo- and hyperresponders (9, 10) supports the hypothesis that responsiveness is related to genetic variation.

Many studies have investigated this possibility and have largely focused on genes whose products affect lipoprotein metabolism, eg, apolipoproteins, enzymes, and receptors. Although there have been several reviews of such studies (11–20), none were performed in a systematic manner, which may have led to articles being omitted and introduced bias toward positive findings. For example, one review included a summary table of 28 studies that examined interactions between the apolipoprotein (apo) E genotype and diet with changes in dietary fat or cholesterol (17); however, the present systematic review identified 16 additional relevant studies that could have been included.

It is possible that conclusions from nonsystematic reviews may not be accurate because they do not take into account all of the available evidence, and there is no basis for the selection of the studies that are included in the review. This is the first systematic review of the literature. The evidence available from 74 articles describing studies that have investigated the effect of genetic variation on the lipid response to dietary interventions were examined.

METHODS

A literature search strategy was developed to identify studies that had measured the lipid and lipoprotein responses to dietary interventions in different genotype groups. The literature strategy for the MEDLINE (National Library of Medicine, Bethesda, MD) database, which was searched from 1996 to week 4 of February

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TABLE 1
Literature strategy for MEDLINE: from 1966 to week 4 of February 2002 and the number of articles retrieved

Search history	No. of articles retrieved
1) (cholesterol$ or lipoprotein$ or ldl$ or hdl$ or vldl$ or triglyceride$ or triglycerol$ or triacylglyceride$ or triacylglycerol$ or apo$).mp. [*mp = title, abstract, cas registry/ec number word, mesh subject heading*]	253045
2) (polymorphism$ or allele$ or genotype$ or phenotype$ or isoform$ or mutation$ or gene or genes or genetic$).mp.	916912
3) (diet$ or food$ or nutri$ or supplement$ or vitamin$ or meal$ or fat or fats or fatty or egg$).mp.	712539
4) *1* and *2* and *3*	5221
5) limit *4* to human	2908
6) limit *5* to (all infant <birth to 23 months> or all child <0 to 18 years>)	368
7) *5* not *6*	2540

2002, and the number of articles retrieved are shown in **Table 1**. The strategy was adapted and performed on the EMBASE database (Elsevier Science BV, Amsterdam) from 1980 to week 9 of 2002, and reference lists from relevant articles were checked. Articles were excluded if the intervention involved restriction of energy intake or overfeeding, if the intervention was combined with drug or exercise therapy, if the subjects were children or had diabetes, or if the articles did not clearly assess whether responses to diet were significantly different between genotype groups. This search generated 74 relevant articles on dietary intervention studies and 17 reviews on gene-diet interactions.

The original studies retrieved, according to the polymorphism studied, are summarized in **Tables 2–7**. The details given for each study include the first author, the number and sex of the subjects, the number of subjects in each genotype group, the type of dietary intervention, and the results, ie, whether there was a significantly greater response of plasma total cholesterol, LDL cholesterol, HDL cholesterol, VLDL cholesterol, or triacylglycerol in one genotype group than in another. The responses were generally in the expected direction, ie, a reduction in lipid and lipoprotein concentrations after a reduction in dietary cholesterol and SFA intakes. In most cases, the direction of the response was the same for each genotype group. In these cases, the genotype that showed the largest response to the dietary intervention is shown.

RESULTS

Apolipoprotein A-I, C-III, and A-IV gene cluster

Of 13 reports, 5 found that the presence of the apo A-I–75 (*G/A*) *A* allele instead of the common *G* allele resulted in greater LDL-cholesterol responses to changes in dietary fat (Table 2). In addition, significant interactions between the *G/A* genotype and diet were found for changes in total and LDL cholesterol when subjects changed from a low-fat diet to a diet high in monounsaturated fatty acids (MUFAs) (24). When the effect of this polymorphism with the apo C-III *Sst*I polymorphism was studied, it was found that total and LDL-cholesterol concentrations decreased most in subjects with the *G/G-S1/S2* polymorphism and increased most in subjects with the *G/A-S1/S1* polymorphism (24). No significant interactions between diet and other polymorphisms in the apo A-I gene were shown.

Variation at the apo C-III *Sst*I site influenced dietary responsiveness such that after the subjects changed from a low-fat diet to a high-MUFA diet, LDL-cholesterol concentrations increased in *S1/S1* subjects but decreased in *S1/S2* subjects (24, 32). Variation at the apo C-III *Sac*I or C1100T polymorphic sites has not been associated with the magnitude of the lipid response.

The evidence that exists for an interaction between diet and the apo A-IV glutamine-histidine mutation at position 360 (Gln360His) suggests that *Gln/Gln* subjects show significantly greater total and LDL-cholesterol responses and that *Gln/His* subjects show greater HDL-cholesterol responses to changes in dietary fat, cholesterol, or both. Although Wallace et al (37) found no significant differences in LDL-cholesterol responses between genotypes, dense LDL cholesterol decreased more in subjects carrying the *His* allele when polyunsaturated fatty acids (PUFAs) replaced SFAs in the diet. In the same study, there was a significant difference in HDL-cholesterol responses between genotype groups such that concentrations decreased in *Gln/Gln* subjects and increased in *Gln/His* subjects.

The presence of serine instead of threonine at position 347 in the apo A-IV gene was associated with increased total and LDL-cholesterol responsiveness when subjects switched from a high-SFA diet to a National Cholesterol Education Program Step I diet (23). When the same subjects changed from the National Cholesterol Education Program Step I diet to a high-MUFA diet, subjects with the *Thr/Thr* genotype had a 1% decrease in total cholesterol concentrations, whereas subjects with the *Ser* allele had a 5% increase in total cholesterol concentrations (23). When the Thr347Ser and the apo A-I–75 (*G/A*) genotypes were combined, carriers of the *A* and *Ser* alleles showed greater LDL-cholesterol responses to changes in dietary fat (23). However, Carmena-Ramon et al (36) investigated both the Gln360His and Thr347Ser polymorphisms and found no gene-diet or haplotype-diet interactions.

Apolipoprotein B

The evidence for an interaction between the *Xba*I polymorphism and diet is inconsistent (Table 3). In 2 studies, *X−X−* subjects showed greater LDL-cholesterol responses (42, 46), whereas Tikkanen et al (40) found that subjects carrying the *X+* allele had greater total, LDL-, and HDL-cholesterol responses. However in Xu et al's (92) analysis of these data, the *Xba*I polymorphism only explained a significant proportion of variance of the change in HDL cholesterol. Pajukanta et al (43) found no significant effect on LDL-cholesterol responsiveness, although *X−X−* subjects showed the greatest HDL_2- and VLDL-cholesterol responses. Finally, Lopez-Miranda et al (45) studied the effect of the *Xba*I polymorphism in subjects with the common apo *E3/3* genotype and found that *X−X−* subjects showed the greatest triacylglycerol response. Rantala et al (46) conducted a meta-analysis of all published dietary trials, including their own trial (46). In their analysis of 8 studies, *X−X+* subjects had greater LDL responses than did *X+X+* subjects and no significant differences in the responses of total or HDL cholesterol or triacylglycerol were found between genotypes.

Two of 7 interventions found that the *Eco*RI *R−* allele was associated with significantly greater total and LDL-cholesterol responses to changes in dietary fat and cholesterol (44, 46). Rantala et al's (46) meta-analysis of 7 studies found that *R−R−* subjects had significantly greater total and LDL-cholesterol responses than did the *R+R+* subjects.

TABLE 2
Apolipoprotein A-I, C-III, and A-IV gene cluster[1]

Polymorphism and study	Subjects	Genotype groups	Intervention	Response[2]				
				Chol	LDL	HDL	VLDL	TG
Apo A-I–75 (*G/A*)								
Lopez-Miranda et al (21)	50 M	36 *G/G*, 14 *G/A*	NCEP-I vs high-fat, high-MUFA diet	NS	*G/A*	NS	—	NS
Lopez-Miranda et al (22)	42 M and F		High-SFA vs high-PUFA diet	—[3]	*G/A*	NS	—	—
Clifton et al (12)	96 M and F	68 *G/G*, 28 *G/A*	Low-fat, low-chol vs high-fat, high-chol diet	—	NS	—	—	—
Jansen et al (23)	41 M	23 *G/G*, 18 *G/A*	High-SFA vs NCEP-I diet	—	*G/A*	—	—	—
Jansen et al (23)	41 M	23 *G/G*, 18 *G/A*	NCEP-I vs high-MUFA diet	—	*G/A*	—	—	—
Lopez-Miranda et al (24)	89 M	58 *G/G*, 31 *G/A*	NCEP-I vs high-fat, high-MUFA diet	S	S	NS	—	NS
Meng et al (25)	42 M	27 *G/G*, 15 *G/A* and *A/A*	Low-fat, low-chol diet	NS	NS	NS	—	NS
Meng et al (25)	44 F	31 *G/G*, 13 *G/A* and *A/A*	Low-fat, low-chol diet	NS	NS	NS	—	NS
Carmena-Ramon et al (26)	69 M and F, FH	51 *G/G*, 18 *G/A*	NCEP-I diet	NS	NS	NS	NS	NS
Mata et al (27)	26 M	21 *G/G*, 5 *G/A*	High-SFA vs high-PUFA diet	NS	NS	NS	—	NS
Mata et al (27)	26 M	21 *G/G*, 5 *G/A*	High-SFA vs high-MUFA diet	NS	NS	NS	—	NS
Mata et al (27)	24 F	16 *G/G*, 8 *G/A*	High-SFA vs high-PUFA diet	*G/A*	*G/A*	NS	—	NS
Mata et al (27)	24 F	16 *G/G*, 8 *G/A*	High-SFA vs high-MUFA diet	NS	NS	NS	—	NS
Promoter *Msp*I								
Gylling et al (28)	29 M	21 *M+M+*, 8 *M+M−* and *M−M−*	Low-chol vs high-chol diet	—	NS	—	—	—
+83 (*Msp*I±)								
Carmena-Ramon et al (26)	69 M and F, FH	64 +/+, 5 −/+	NCEP-I diet	NS	NS	NS	NS	NS
Apo C-III								
C1100T								
Humphries et al (29)	55 M and F	38 *C/C*, 17 *C/T* and *T/T*	High-SFA vs high-PUFA diet	NS	NS	NS	NS	NS
Wallace et al (30)	55 M and F, HC	29 *C/C*, 26 *C/T* and *T/T*	High-SFA vs high-PUFA diet	NS	—	—	—	—
*Sac*I								
Hegele et al (31)	67 M and F	53 *1/1*, 14 *1/2*	Wheat- or oat-bran supplementation	NS	NS	NS	—	NS
*Sst*I								
Lopez-Miranda et al (32)	50 M	40 *S1/S1*, 10 *S1/S2*	NCEP-I vs high-fat, high-MUFA diet	—	S	—	—	—
Gylling et al (28)	29 M	24 *S1/S1,* 5 *S1/S2* and *S2/S2*	Low-chol vs high-chol diet	—	NS	—	—	—
Lopez-Miranda et al (24)	90 M	67 *S1/S1*, 23 *S1/S2*	NCEP-I vs high-fat, high-MUFA diet	S	S	NS	—	NS
Apo A-IV								
Gln360His								
Mata et al (33)	93 M	76 *Gln/Gln*, 17 *Gln/His*	High-fat, high-chol vs low-fat, low-chol diet	*Gln/Gln*	*Gln/Gln*	NS	—	NS
Mata et al (33)	60 F	48 *Gln/Gln*, 12 *Gln/His*	High-fat, high-chol vs low-fat, low-chol diet	NS	NS	NS	—	NS
McCombs et al (34)	23 M and F	12 *Gln/Gln*, 11 *Gln/His*	Low-chol vs high-chol diet	*Gln/Gln*	*Gln/Gln*	NS	—	NS
Jansen et al (35)	41 M	33 *Gln/Gln*, 8 *Gln/His*	High-SFA vs NCEP-I diet	NS	NS	*Gln/His*	—	NS
Jansen et al (35)	41 M	33 *Gln/Gln*, 8 *Gln/His*	NCEP-I vs high-MUFA diet	NS	NS	*Gln/His*	—	NS
Jansen et al (35)	41 M	33 *Gln/Gln*, 8 *Gln/His*	High-SFA vs high-MUFA diet	NS	NS	NS	—	NS
Schaefer et al (8)	71 M	63 *Gln/Gln*, 8 *Gln/His*	High-fat, high-chol vs NCEP-2 diet	NS	NS	NS	—	NS
Schaefer et al (8)	47 F	42 *Gln/Gln*, 5 *Gln/His*	High-fat, high-chol vs NCEP-2 diet	NS	NS	NS	—	NS
Carmena-Ramon et al (36)	67 M and F, FH	51 *Gln/Gln*, 16 *Gln/His*	NCEP-I diet	NS	NS	NS	NS	NS
Wallace et al (37)	44 M and F, HC	38 *Gln/Gln*, 6 *Gln/His*	High-SFA vs high-PUFA diet	—	NS	S	—	NS
Weggemans et al (38)	50 M and F	33 *Gln/Gln*, 17 *Gln/His* and *His/His*	High-SFA, low-chol vs high-SFA, high-chol diet	NS	NS	NS	—	—
Weinberg et al (39)	26 M and F	14 *Gln/Gln*, 12 *Gln/His*	High-chol, high-SFA diet	—	NS	NS	—	—
Weinberg et al (39)	24 M and F	13 *Gln/Gln*, 11 *Gln/His*	High-chol, high-PUFA diet	—	NS	NS	—	—
Gln360His								
Weinberg et al (39)	22 M and F	12 *Gln/Gln*, 10 *Gln/His*	High-chol, low-fat diet	—	NS	NS	—	—

(Continued)

TABLE 2 (*Continued*)

Polymorphism and study	Subjects	Genotype groups	Intervention	Response[2] Chol	LDL	HDL	VLDL	TG
Thr347Ser								
Jansen et al (23)	41 M	25 *Thr/Thr*, 16 *Ser* (*Thr/Ser* and *Ser/Ser*)	High-SFA vs NCEP-I diet	*Ser*	*Ser*	NS	—	NS
Jansen et al (23)	41 M	25 *Thr/Thr*, 16 *Ser* (*Thr/Ser* and *Ser/Ser*)	NCEP-I vs high-MUFA diet	S	NS	NS	—	NS
Carmena-Ramon et al (36)	63 M and F, FH	44 *Thr/Thr*, 18 *Thr/Ser*, 1 *Ser/Ser*	NCEP-I diet	NS	NS	NS	NS	NS
Wallace et al (37)	44 M and F, HC	29 *Thr/Thr*, 15 *Ser* (*Thr/Ser* and *Ser/Ser*)	High-SFA vs high-PUFA diet	—	NS	—	—	—

[1] Chol, cholesterol; NCEP-I diet, National Cholesterol Education Program Step I diet; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid; PUFA, polyunsaturated fatty acid; TG, triacylglycerol; NS and S, nonsignificant and significant ($P < 0.05$) differences, respectively, between genotype groups; FH, familial hypercholesterolemic; HC, hypercholesterolemic.

[2] In most cases the direction of the response was the same for each genotype group; in these cases, the genotype showing the largest response is given.

[3] Indicates that the responses or *P* values were not clearly reported.

Only one study found an interaction between the *Msp*I polymorphism and response to diet. Rantala et al (46) found that *M+M+* subjects had significantly greater total cholesterol responses than did *M+M−* subjects to a diet high in fat and cholesterol. In addition, in their meta-analysis of 5 trials, Rantala et al found that *M+M+* subjects responded with significantly greater changes in plasma LDL-cholesterol and triacylglycerol concentrations than did *M+M−* subjects, but there were no significant effects on total or HDL-cholesterol responses.

Ten intervention studies found no significant effects of the apo B signal peptide insertion/deletion (*I/D*) polymorphism on dietary responsiveness; however, 2 studies reported a significantly greater responsiveness in subjects homozygous for the *I* allele. Lee et al (93) studied 43 men and women to compare the effects of insoluble and soluble fiber on plasma lipids. Their statistical model identified gene-diet interactions. However, they did not look specifically at differences between genotype groups; therefore, the study is not included in the tables. It was found that *D/D* subjects had similar decreases in HDL cholesterol after consumption of the insoluble- and soluble-fiber diets. However, *I/I* subjects had larger HDL-cholesterol decreases with the soluble-fiber diet, whereas *I/D* subjects had larger HDL-cholesterol decreases with the insoluble-fiber diet. The gene-diet interaction was significant ($P = 0.021$).

In response to Pajukanta et al's (43) low-fat, low-cholesterol diet, *I/I* subjects showed the greatest decrease in HDL_2. In addition, *I/I* and *I/D* subjects showed increased VLDL-cholesterol and decreased LDL-cholesterol concentrations, whereas *D/D* subjects showed decreased VLDL- cholesterol and increased LDL-cholesterol concentrations. The *I/D* polymorphism showed no significant effect on the responsiveness of total, LDL, or HDL cholesterol or triacylglycerol in a meta-analysis of 7 studies (46).

The Bsp 1261I polymorphism was not associated with the LDL response in Rantala et al's study (46). However, their analysis of the data from 2 Finnish studies showed that *B−B−* subjects responded to a diet high in fat and cholesterol, with significantly greater increases in plasma total and LDL cholesterol and significantly smaller changes in triacylglycerol than observed in the *B−B+* subjects. Finally, men homozygous for the *His* allele at codon 1896 may be more responsive than men with the less common *Arg* allele (50).

Apolipoprotein E

Variation in the apo E gene results in the 3 common alleles (ϵ2, ϵ3, and ϵ4), which can produce 3 homozygous (*E2/2*, *E3/3*, and *E4/4*) and 3 heterozygous (*E2/3*, *E2/4*, and *E3/4*) genotypes. The ϵ2, ϵ3, and ϵ4 alleles have frequencies of ≈0.08, 0.77, and 0.15, respectively, in white populations (94). The 4 studies that showed a statistically significant interaction between the variation in the apo E gene and dietary cholesterol indicate that the presence of the ϵ4 allele results in significantly greater responses in total, LDL, or HDL cholesterol; subjects with the ϵ2 allele showed the smallest response (Table 4).

Of the 46 interventions that involved altering the dietary fat content of the diet, significantly different total and LDL-cholesterol responses between genotype groups were reported in 8 and 11 studies, respectively, with carriers of the ϵ4 allele tending to show the greatest responses. Although Tikkanen et al (64) found that subjects with the E4/4 phenotype showed the greatest total and LDL-cholesterol responses to dietary change, Xu et al (92) analyzed the same data and concluded that the apo E polymorphism did not explain a significant proportion of the variation of the response. Lopez-Miranda et al (71) conducted a meta-analysis of 9 studies involving 612 subjects and found that the presence of the ϵ4 allele was associated with a significantly greater LDL response to dietary intervention.

Four studies found significantly different HDL-cholesterol responses between genotype groups: one study found that carriers of the ϵ4 allele had the smallest HDL-cholesterol response (71), whereas the other 3 studies found that carriers of the ϵ4 allele had the largest response (28, 54, 55, 58, 62).

Subjects with the ϵ4 allele appear to be the most responsive to changes in dietary fat and cholesterol; however, they may not be the most responsive to changes in other aspects of the diet. For example, subjects carrying the ϵ2 allele had the greatest total and LDL-cholesterol responses to wheat- or oat-bran supplementation (86).

Enzymes: lipoprotein lipase, hepatic lipase, and cholesterol 7α-hydroxylase

Three polymorphisms in the lipoprotein lipase gene have been shown to influence the response to diet (Table 5). First, the H− allele of *Hind*III is associated with greater total cholesterol and triacylglycerol responsiveness (29). Second, subjects with the S447X mutation showed significantly greater decreases in LDL-cholesterol concentrations than did subjects with the common *S/S* genotype when PUFAs replaced SFAs in the diet. Third, subjects heterozygous for the N291S polymorphism (*N/S*) showed a greater mean change in triacylglycerol concentrations than did *N/N* subjects. The *Pvu*II and T-93G polymorphisms have not shown a significant influence on dietary responsiveness.

TABLE 3
Apolipoprotein B gene[1]

Polymorphism and study	Subjects	Genotype groups	Intervention	Response[2]				
				Chol	LDL	HDL	VLDL	TG
C2488T (*Xba*I)								
Tikkanen et al (40)	103 M and F, HC	39 *X−X−*, 64 *X+* (*X−X+*, *X+X+*)	High-fat, high-chol, low-P:S vs low-fat, low-chol, high-P:S diet	*X+*	*X+*	*X+*	—[3]	NS
Friedlander et al (41)	37 M and F	20 *X−X−*, 17 *X+* (*X−X−*, *X−X+*)	Low-SFA, low-chol vs high-SFA, high-chol diet	NS	NS	NS	—	NS
Friedlander et al (42)	63 M	22 *X−X−*, 35 *X−X+*, 6 *X+X+*	Low-SFA, high-MUFA and low-SFA, high-PUFA diets	NS	*X−X−*	NS	—	NS
Pajukanta et al (43)	87 M and F	34 *X−X−*, 40 *X-X+*, 13 *X+X+*	Low-fat, low-chol diet	—	NS	*X−X−*	*X−X−*	—
Clifton et al (12) and Clifton and Abbey (14)	51 M and F, HC and NC	—	Low-chol vs high-chol diet	—	NS	NS	—	—
Gylling et al (28)	29 M	9 *X−X−*, 14 *X−X+*, 6 *X+X+*	Low-chol vs high-chol diet	—	NS	—	—	—
Friedlander et al (44)	210 M and F	88 *X−X−*, 107 *X−X+*, 15 *X+X+*	High-SFA, high-chol vs low-SFA, low-chol diet	NS	NS	NS	—	NS
Lopez-Miranda et al (45)	72 M	21 *X−X−*, 51 *X+* (*X−X+*, *X+X+*)	High-SFA vs NCEP-I diet	NS	NS	NS	—	NS
Lopez-Miranda et al (45)	72 M	21 *X−X−*, 51 *X+* (*X−X+*, *X+X+*)	High-SFA vs high-MUFA diet	NS	NS	NS	—	*X−X−*
Rantala et al (46)	44 M and F	19 *X−X−*, 16 *X−X+*, 9 *X+X+*	Low-fat, low-chol diet	—	NS	—	—	—
Rantala et al (46)	44 M and F	19 *X−X−*, 16 *X−X+*, 9 *X+X+*	High-fat, high-chol diet	—	*X−X−*	—	—	—
G4154L (*Eco*RI)								
Hegele et al (31)	67 M and F	41 *R+R+*, 21 *R+R−*, 5 *R−R−*	Wheat- or oat-bran supplementation	NS	NS	NS	—	NS
Abbey et al (47)	49 M and F	23 *R+R+*, 26 *R−* (*R+R−*, *R−R−*)	Low-fat, low-chol vs high-fat, high-chol diet	NS	NS	NS	—	NS
Friedlander et al (42)	60 M	48 *R+R+*, 11 *R+R−*, 1 *R−R−*	Low-SFA, high-MUFA and low-SFA, high-PUFA diets	NS	NS	NS	—	NS
Gylling et al (28)	29 M	20 *R+R+*, 9 *R−* (*R+R−*, *R−R−*)	Low-chol vs high-chol diet	—	NS	—	—	—
Friedlander et al (44)	206 M and F	131 *R+R+*, 75 *R−* (*R+R−*, *R−R−*)	High-SFA, high-chol vs low-SFA, low-chol diet	*R−*	*R−*	NS	—	NS
Rantala et al (46)	44 M and F	27 *R+R+*, 13 *R+R−*, 4 *R−R−*	Low-fat, low-chol diet	—	NS	—	—	—
Rantala et al (46)	44 M and F	27 *R+R+*, 13 *R+R−*, 4 *R−R−*	High-fat, high-chol diet	NS	*R−R−*	—	—	—
A3611G (*Msp*1)								
Hegele et al (31)	67 M and F	39 *M+M+*, 23 *M+M−*, 5 *M−M−*	Wheat- or oat-bran supplementation	NS	NS	NS	—	NS
Friedlander et al (42)	62 M	54 *M+M+*, 8 *M+M−*	Low-SFA, high-MUFA and low-SFA, high-PUFA diets	NS	NS	NS	—	NS
Gylling et al (28)	29 M	23 *M+M+*, 6 *M+M−* and *M−M−*	Low-chol vs high-chol diet	—	NS	—	—	—
Friedlander et al (44)	205 M and F	184 *M+M+*, 21 M+M−	High-SFA, high-chol vs low-SFA, low-chol diet	NS	NS	NS	—	NS
Rantala et al (46)	44 M and F	39 *M+M+*, 5 *M+M−*	Low-fat, low-chol diet	—	NS	—	—	—
Rantala et al (46)	44 M and F	39 *M+M+*, 5 *M+M−*	High-fat, high-chol diet	*M+M+*	NS	—	—	—
Signal peptide *I/D*								
Boerwinkle et al (48)	71 M	32 *I/I*, 32 *I/D*, 7 *D/D*	Low-chol vs high-chol diet	NS	NS	NS	—	NS
Hegele et al (31)	67 M and F	20 *I/I*, 35 *I/D*, 12 *D/D*	Wheat- or oat-bran supplementation	NS	NS	NS	—	NS
Friedlander et al (42)	62 M	41 *I/I*, 17 *I/D*, 4 *D/D*	Low-SFA, high-MUFA and low-SFA, high-PUFA diets	NS	NS	NS	—	NS
Eusufzai et al (49)	46 M	23 *I/I*, 23 *I/D* and *D/D*	High-fat, high-SFA vs low-fat, low-SFA diet	*I/I*	*I/I*	*I/I*	—	—
Eusufzai et al (49)	57 F	—	High-fat, high-SFA vs low-fat, low-SFA diet	NS	NS	NS	—	—
Humphries et al (29)	55 M and F	35 *I/I*, 20 *I/D* and *D/D*	High-SFA vs high-PUFA diet	NS	—	—	—	—
Pajukanta et al (43)	87 M and F	42 *I/I*, 38 *I/D*, 7 *D/D*	Low-fat, low-chol diet	—	S	*I/I*	S	—

(Continued)

TABLE 3 (*Continued*)

Polymorphism and study	Subjects	Genotype groups	Intervention	Response[2] Chol	LDL	HDL	VLDL	TG
Friedlander et al (44)	188 M and F	104 *I/I*, 80 *I/D*, 4 *D/D*	High-SFA, high-chol vs low-SFA, low-chol diet	NS	NS	NS	—	NS
Rantala et al (46)	44 M and F	23 *I/I*, 20 *I/D*, 1 *D/D*	Low-fat, low-chol diet	—	NS	—	—	—
Rantala et al (46)	44 M and F	23 *I/I*, 20 *I/D*, 1 *D/D*	High-fat, high-chol diet	—	NS	—	—	—
Wallace et al (30)	55 M and F, HC	32 *I/I*, 23 *I/D* and *D/D*	High-SFA vs high-PUFA diet	NS	—	—	—	—
Wallace et al (37)	46 M and F, HC	20 *I/I*, 26 *I/D* and *D/D*	High-SFA vs high-PUFA diet	—	NS	—	—	—
1261I (*Bsp*)								
Rantala et al (46)	44 M and F	22 *B+B+*, 21 *B+B−*, 1 *B−B−*	Low-fat, low-chol diet	—	NS	—	—	—
Rantala et al (46)	44 M and F	22 *B+B+*, 21 *B+B−*, 1 *B−B−*	High-fat, high-chol diet	—	NS	—	—	—
1887 *Asn/Ser*								
Ilmonen et al (50)	48 M	45 *Asn/Asn*, 3 *Asn/Ser*	Low-fat, low-chol, high-P:S diet	NS	NS	—	—	—
Ilmonen et al (50)	54 F	52 *Asn/Asn*, 2 *Asn/Ser*	Low-fat, low-chol, high-P:S diet	NS	NS	—	—	—
1896 *His/Arg*								
Ilmonen et al (50)	47 M	37 *His/His*, 10 *His/Arg*	Low-fat, low-chol, high-P:S diet	*His/His*	NS	—	—	—
Ilmonen et al (50)	54 F	44 *His/His*, 10 *His/Arg*	Low-fat, low-chol, high-P:S diet	NS	NS	—	—	—

[1] Chol, cholesterol; TG, triacylglycerol; P:S, ratio of polyunsaturated to saturated fatty acids; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; NCEP-I diet, National Cholesterol Education Program Step I diet; NS and S, nonsignificant and significant ($P < 0.05$) differences, respectively, between genotype groups; HC, hypercholesterolemic; NC, normocholesterolemic.

[2] In most cases the direction of the response was the same for each genotype group; in these cases, the genotype showing the largest response is given.

[3] Indicates that the responses or *P* values were not clearly reported.

Variation at the hepatic lipase *Nla*III and *Msp*I sites was not associated with the response to diet (31, 87). However, in the study by Lee et al (93) that was described above, homozygotes for valine (*V/V*) at position 73 had smaller decreases in LDL cholesterol with the insoluble-fiber diet than with the soluble-fiber diet, but the LDL-cholesterol responses to the 2 diets were similar for the heterozygotes for methionine. This gene-diet interaction was significant ($P = 0.036$). Variation in the cholesterol 7α-hydroxylase gene has not been associated with dietary responsiveness (42).

LDL receptor gene

A significant interaction between diet and variation in the LDL receptor gene was shown in 2 studies (Table 6). After wheat- or oat-bran supplementation, the total and LDL-cholesterol reductions were significantly different among the *Hinc*II genotype groups, with *2/2* subjects showing the greatest reduction and *1/1* subjects showing the smallest reduction (31). Clifton et al (12) and Clifton and Abbey (14) investigated variation at a *Pvu*II site, and subjects lacking the cutting site were found to have greater HDL responses to low-fat diets.

Other genes

Subjects homozygous for the presence of the *Taq*IB cutting site (*B1/B1*) of the cholesteryl ester transfer protein gene showed greater total and LDL-cholesterol responses to changes in the type of dietary fat than did subjects who were homozygous or heterozygous for the *B2* allele in 1 of 3 studies (30) (Table 7). No evidence exists for a significant association between the I405V polymorphism and the response to changes in the amount of dietary fat and cholesterol.

A polymorphism in the intestinal fatty acid–binding protein gene at amino acid residue 54 results in either alanine (*A54*) or threonine (*T54*). One study showed that *T54/T54* subjects had greater total and LDL-cholesterol responses to a soluble-fiber diet than did the other 2 genotypes, and the heterozygotes had a significantly greater total cholesterol response to soluble fiber than did the *A54/A54* homozygotes (89).

The Leu7Pro polymorphism in the neuropeptide Y gene has been investigated in one study in relation to dietary response; however, no significant effect was shown (90).

M/N blood groups have been associated with LDL-cholesterol responses to dietary change such that significantly different responses were noted between *M/N* subjects who responded the least and the 2 homozygote groups (blood groups *M/M* and *N/N*) who responded the most (91).

Magnitude of the response

Because of the heterogeneity in the type and duration of the interventions described, the magnitude of the lipid response to dietary interventions varied widely: in one study (46) the change in LDL cholesterol in the apo B *Eco*RI *R−R−* genotype group was as large as 59% of the baseline concentration. In the studies that showed a significant difference in response between genotype groups, the results also varied widely: in some studies, the difference in response between 2 genotype groups was ≈20% of the baseline lipid concentration (12, 46). However, the magnitude of these differences cannot be estimated with any accuracy, largely because most studies had only a small number of subjects in the rare genotype group.

The proportion of variance in the lipid response attributable to a single polymorphism is not likely to be > 10% (92). Therefore, individual genes contribute only a small part to the variation in the lipid response; however, when several genes are considered, the proportion of variance explained could be larger.

DISCUSSION

Evidence for a gene-diet interaction

Evidence suggests that variation in the genes for apolipoproteins A-I, A-IV, B, and E may contribute to the heterogeneity in the lipid response to dietary intervention. Specifically, carriers of the

TABLE 4
Apolipoprotein E gene[1]

Study	Subjects	Genotype groups	Intervention	Response[2]				
				Chol	LDL	HDL	VLDL	TG
Intervention: dietary cholesterol								
Brenninkmeijer et al (51)	11 M	6 *E3* (*2/3*, *3/3*), 5 *E4* (*3/4, 4/4*)	High-chol diet	NS	NS	—[3]	—	NS
Boerwinkle et al (48)	71 M	13 *E2/3*, 48 *E3/3*, 10 *E3/4*	Low-chol vs high-chol diet	NS	NS	NS	—	NS
Glatz et al (52)	32 M and F	1 *E2/2*, 4 *E2/3*, 17 *E3/3*, 6 *E3/4*, 4 *E4/4*	Low-chol vs high-chol diet	NS	—	—	—	—
McPherson et al (53)	30 M	6 *E2/3*, 12 *E3/3*, 12 *E3/4*	Low-chol vs high-chol diet	—	NS	—	—	—
Miettinen (54), Gylling and Miettinen (55), and Gylling et al (28)	29 M	8 *E2* (*2/2, 2/3, 2/4*), 9 *E3* (*3/3*), 12 *E4* (*3/4, 4/4*)	Low-chol vs high-chol diet	*E3* and *4*	*E3* and *4*	*E4*	—	—
Lehtimaki et al (56)	36 M and F	9 *E2/3*, 11 *E3/3*, 13 *E3/4*, 3 *E4/4*	Low-chol vs high-chol diet	NS	*E4/4*	NS	—	NS
Jones et al (57)	13 M	7 *E2* (*2/2, 2/3*), 6 *E4* (*3/4, 4/4*)	Low-chol vs high-chol diet	NS	NS	NS	—	NS
Martin et al (58)	30 M	5 *E2/3*, 11 *E3/3*, 14 *E3/4*	Low-chol vs high-chol diet	—	NS	*E3/4*	—	—
Ginsberg et al (59)	20 M	15 *E4* − (*2/2, 2/3, 3/3*), 5 *E3/4*	4 diets differing in chol content	NS	NS	—	—	—
Ginsberg et al (60)	13 F	8 *E2* (*2/3, 3/3*), 5 *E4* (*3/4, 4/4*)	3 diets differing in chol content	NS	NS	NS	—	NS
McCombs et al (34)	23 M and F	4 *E2/3*, 1 *E2/4*, 14 *E3/3*, 4 *E3/4*	Low-chol vs high-chol diet	—	NS	—	—	—
Sarkkinen et al (61)	45 M and F	15 *E3/3*, 15 *E3/4*, 15 *E4/4*	Low-chol vs high-chol diet	*E4/4*	NS	NS	—	NS
Weggemans et al (62)	103 M and F	18 *E2* (*2/2, 2/3*), 62 *E3/3*, 23 *E4* (*3/4, 4/4*)	Low-chol vs high-chol diet	NS	—	NS	—	—
Intervention: dietary fat								
Fisher et al (63)	8 M	3 *E2/3*, 5 *E3/3*	Corn oil ± chol vs coconut oil ± chol	NS	NS	NS	NS	NS
Tikkanen et al (64)	110 M and F	102 *E2/3*, *3/3* and *4/3*, 8 *E4/4*	High-fat, high-chol, low-P:S vs low-fat, low-chol, high-P:S diet	*E4/4*	*E4/4*	NS	—	NS
Glatz et al (52)	22 M and F		High-PUFA vs high-SFA diet	NS	—	—	—	—
Manttari et al (65)	117 M, DL	75 *E2/2, 2/3* and *3/3*; 42 *E4* (*3/4, 4/4*)	High-fat, low-P:S vs low-fat, lower chol, high-P:S diet	*E4*	*E4*	NS	—	NS
Savolainen et al (66)	22 M	11 *E3/3*, 11 *E4* (*3/4, 4/4*)	Low-fat, low-chol vs high-fat, high-chol diet	NS	NS	NS	—	NS
Savolainen et al (66)	22 F	12 *E3/3*, 10 *E4* (*3/4, 4/4*)	Low-fat, low-chol vs high-fat, high-chol diet	NS	NS	NS	—	NS
Cobb and Risch (67)	67 M and F	13 *E2/3*, 44 *E3/3*, 8 *E3/4*, 2 *E4/4*	Low-P:S diet vs high-P:S, lower chol diet	—	NS	—	NS	—
Sundram et al (68)	38 M	11 *E2/3*, 22 *E3/3*, 5 *E3/4*	Palm oil as major fat source	NS	NS	NS	NS	NS
Vanhanen et al (69)	33 M and F, HC	16 *E3/3*, 17 *E4* (*3/4, 4/4*)	RO mayonnaise vs RO and sitostanol ester mayonnaise replacing 50 g fat	NS	NS	—	—	—
Denke and Grundy (70)	41 M, HC	1 *E2/2*, 9 *E2/3*, 19 *E3/3*, 11 *E3/4*, 1 *E4/4*	High-SFA, high-chol vs NCEP-I diet	—	NS	—	—	—
Lopez-Miranda et al (71)	83 M	13 *E2/3*, 60 *E3/3*, 10 *E3/4*	High-fat, high-chol vs low-fat, low-chol diet	NS	*E3/4 E3/3* and *2/3*		—	NS
Lopez-Miranda et al (71)	45 F	4 *E2/3*, 34 *E3/3*, 7 *E3/4*	High-fat, high-chol vs low-fat, low-chol diet	NS	NS	NS	—	NS
Miettinen and Vanhanen (72)	23 M and F, HC	15 *E3* (*2/2, 3/3*), 8 *E4* (*3/4, 4/4*)	RO mayonnaise replacing 50 g fat	*E4*	NS	—	—	—
Miettinen and Vanhanen (72)	23 M and F, HC	15 *E3* (*2/2, 3/3*), 8 *E4* (*3/4, 4/4*)	RO and plant sterols replacing 50g fat	NS	*E4*	—	—	—
Sarkkinen et al (73)	37 M and F, HC	1 *E2* (*2/3, 2/4*), 22 *E3/3*, 14 *E4* (*3/4, 4/4*)	High-fat, high-SFA diet	NS	NS	—	—	—

(Continued)

TABLE 4 (*Continued*)

Study	Subjects	Genotype groups	Intervention	Response[2]				
				Chol	LDL	HDL	VLDL	TG
Sarkkinen et al (73)	41 M and F, HC	1 *E2* (*2/3, 2/4*), 20 *E3/3*, 20 *E4* (*3/4, 4/4*)	AHA-type diet	NS	NS	—	—	—
Sarkkinen et al (73)	40 M and F, HC	3 *E2* (2/3, 2/4), 27 *E3/3*, 10 *E4* (*3/4, 4/4*)	Monoene-enriched diet	NS	*E3/3*	—	—	—
Sarkkinen et al (73)	40 M and F, HC	5 *E2* (*2/3, 2/4*), 19 *E3/3*, 16 *E4* (*3/4, 4/4*)	Reduced-fat diet	NS	NS	—	—	—
Cox et al (74)	40 M and F	31 *E3* (*2/3, 3/3*), 9 *E4* (*2/4, 3/4, 4/4*)	High-SFA vs high-PUFA diet	NS	—	—	—	—
Dreon et al (75)	103 M	10 *E2/3*, 65 *E3/3*, 28 *E4* (*3/4, 4/4*)	High-fat vs low-fat diet	*E4*	NS	NS	—	NS
Friedlander et al (42)	57 M	4 *E2/3*, 1 *E2/4*, 49 *E3/3*, 3 *E3/4*	Low-SFA, high-MUFA and low-SFA, high-PUFA diets	*E3/4*	*E3/4*	NS	—	NS
Schaefer et al (76)	15 M	10 *E3/3*, 5 *E3/4*	High-fat, high-chol vs NCEP-II diet	—	*E3/4*	—	—	—
Schaefer et al (76)	11 F	8 *E3/3*, 3 *E3/4*	High-fat, high-chol vs NCEP-II diet	—	*E3/3*	—	—	—
Zambon et al (77)	122 M and F, HL	27 *E2/3*, 48 *E3/3*, 47 *E3/4*	High-fat, high-MUFA vs low-fat, high-MUFA, low-chol diet	NS	NS	NS	NS	NS
Bergeron and Havel (78)	15 M	8 *E3/3*, 7 *E3/4*	High-fat, high-PUFA diet	—	—	—	—	*E3/4*
Jansen et al (23)	41 M	6 *E2/3*, 1 *E2/4*, 33 *E3/3*, 1 *E3/4*	High-SFA vs NCEP-I diet	—	NS	—	—	—
Jansen et al (23)	41 M	6 *E2/3*, 1 *E2/4*, 33 *E3/3*, 1 *E3/4*	NCEP-I vs high-MUFA diet	—	NS	—	—	—
Lefevre et al (79)	103 M and F	11 *E2* (*2/2, 2/3, 2/4*), 57 *E3/3*, 35 *E4* (*3/4, 4/4*)	AHA-1 diet	NS	NS	NS	—	NS
Lefevre et al (79)	103 M and F	11 *E2* (*2/2, 2/3, 2/4*), 57 *E3/3*, 35 *E4* (*3/4, 4/4*)	Low-SFA diet	NS	NS	NS	—	NS
Lopez-Miranda et al (24)	89 M	7 *E2/3*, 77 *E3/3*, 5 *E3/4*	NCEP-I vs high-fat, high-MUFA diet	—	*E3/4*	—	—	—
Schaefer et al (8)	58 M	49 *E3/3*, 9 *E3/4*	High-fat, high-chol vs NCEP-II diet	NS	*E3/4*	NS	—	NS
Schaefer et al (8)	38 F	25 *E3/3*, 13 *E3/4*	High-fat, high-chol vs NCEP-II diet	NS	NS	NS	—	NS
Mata et al (27)	48 M and F	3 *E2/3*, 1 *E2/4*, 33 *E3/3*, 11 *E3/4*	High-SFA vs high-PUFA diet	NS	NS	NS	—	NS
Mata et al (27)	48 M and F	3 *E2/3*, 1 *E2/4*, 33 *E3/3*, 11 *E3/4*	High-SFA vs high-MUFA diet	NS	NS	NS	—	NS
Sarkkinen et al (61)	45 M and F, HC	15 *E3/3*, 15 *E3/4*, 15 *E4/4*	High-fat vs modified NCEP diet	*E4/4*	NS	NS	—	NS
Sarkkinen et al (61)	45 M and F, HC	15 *E3/3*, 15 *E3/4*, 15 *E4/4*	High-fat vs modified NCEP and chol diet	*E4/4*	NS	NS	—	NS
Tso et al (80)	18 F	3 *E2/3*, 12 *E3/3*, 3 *E3/4*	8:0 and 10:0, and 12:0 SFA diets	NS	NS	NS	—	NS
Tso et al (80)	18 F	4 *E2/3*, 1 *E2/4*, 10 *E3/3*, 3 *E3/4*	14:0, 16:0 and 18:0 SFA diets	NS	NS	NS	—	NS
Carmena-Ramon et al (81)	66 M and F, FH	7 *E2/3*, 53 *E3/3*, 6 *E4* (*3/4, 4/4*)	NCEP-I diet	NS	NS	NS	NS	NS
Friedlander et al (44)	186 M and F	25 *E2/3*, 132 *E3/3*, 29 *E3/4*	High-SFA, high-chol vs low-SFA, low-chol diet	NS	NS	NS	—	NS
Hallikainen et al (82)	22 M and F, HC	14 *E3/3*, 8 *E3/4*	5 different doses of plant stanol ester	—	NS	—	—	—
Hallikainen et al (83)	34 M and F, HC	22 *E3/3*, 12 *E3/4*	Stanol ester and sterol ester margarines	— —	*E3/4*	—	—	—
Minihane et al (84)	50 M, DL	8 *E2/3*, 22 *E3/3*, 20 *E4* (*3/4, 4/4*)	6 g fish oil/d	S	NS	NS	—	NS
Wallace et al (30)	53 M and F, HC	5 *E2/3*, 30 *E3/3*, 18 *E3/4*	High-SFA vs high-PUFA diet	NS	—	—	—	—
Weggemans et al (62)	210 M and F	31 *E2* (*2/2, 2/3*), 130 *E3/3*, 49 *E4* (*3/4, 4/4*)	SFA vs *cis* unSFA or carbohydrates	NS	NS	NS	—	—
Weggemans et al (62)	82 M and F	13 *E2* (*2/2, 2/3*), 46 *E3/3*, 23 *E4* (*3/4, 4/4*)	Trans fat vs *cis* unSFA	NS	NS	NS	—	—

(*Continued*)

TABLE 4 (*Continued*)

Polymorphism and study	Subjects	Genotype groups	Intervention	Response[2]				
				Chol	LDL	HDL	VLDL	TG
Intervention: other than fat and cholesterol								
Gaddi et al (85)	20 M and F, FH	7 *E2/3,* 9 *E3/3*, 4 *E3/4*,	Animal-protein vs soy-protein diet	*E3/3* and *3/4*	—	—	—	—
Jenkins et al (86)	67 M and F	13 *E2* (*2/2, 2/3*), 38 *E3/3*, 16 *E4* (*3/4, 4/4*)	Wheat- or oat-bran supplementation	*E2*	*E2*	NS	—	NS
Weggemans et al (62)	117 M and F	18 *E2* (*2/2, 2/3*), 70 *E3/3*, 29 *E4* (*3/4, 4/4*)	Coffee diterpenes cafestol and kahweol	NS	NS	*E4*	—	—

[1] Chol, cholesterol; TG, triacylglycerol; P:S, ratio of polyunsaturated to saturated fatty acids; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; RO, rapeseed oil; NCEP-I and NCEP-II diets, National Cholesterol Education Program Step I and Step II diets; AHA, American Heart Association; MUFA, monounsaturated fatty acid; NS and S, nonsignificant and significant ($P < 0.05$) differences, respectively, between genotype groups; HC, hypercholesterolemic; DL, dyslipidemic; HL, hyperlipidemic; FH, familial hypercholesterolemic.

[2] In most cases the direction of the response was the same for each genotype group; in these cases, the genotype showing the largest response is given.

[3] Indicates that the responses or *P* values were not clearly reported.

rare *A* allele of the apo A-I–75 *G/A* polymorphism, the common *Gln* allele of the apo A-IV Gln360His polymorphism, the rare *R*− allele of the apo B *Eco*RI polymorphism, the common *I* allele of the apo B signal peptide *I/D* polymorphism, the apo B XbaI *X*− allele, and the apo ϵ4 allele tend to show the greatest total and LDL-cholesterol responses to dietary change.

Many studies were unable to show significantly different responses between these genotype groups, and the genotypes showing the greatest response are not necessarily consistent between studies. For example, Tikkanen et al (40) found that subjects carrying the apo B XbaI *X*+ allele had greater decreases in total, LDL, and HDL cholesterol than did *X*−*X*− subjects in response to a diet low in fat and cholesterol, which contrasts with the results of other studies (42, 43, 46). Similarly, the results in Table 4 are not consistent, with *E3/3* subjects showing a greater LDL response than carriers of the ϵ4 allele after a MUFA-rich diet (73). Also, HDL-cholesterol responses have been shown to be greatest in persons carrying the ϵ4 allele (54, 58) and also in *E3/3* and *E2/3* subjects (71) after changing the content of dietary fat, cholesterol, or both.

There was insufficient evidence to assess whether lipid responsiveness is affected by variation in the genes for apo C-III, lipoprotein lipase, hepatic lipase, cholesterol 7α-hydroxylase, the LDL receptor, the cholesteryl ester transfer protein, or the intestinal fatty acid–binding protein. Although each of these gene products is essential in lipid metabolism, only a handful of studies have investigated variation in these genes, and most of these studies were unable to show significant gene-diet interactions.

Publication bias

Publication bias is a problem with any systematic review because "studies with results that are significant, interesting, from large well-funded studies, or of higher quality are more likely to be submitted, published, or published more rapidly than work without such characteristics" (95). Therefore, it is possible that other relevant dietary intervention studies with genotype information exist but were not included in this review because they have not been published. It is possible that the literature strategy for this systematic review missed studies because the genotype analyses were not mentioned in their title, abstract, or subject headings; a hand search of relevant journals may have identified more studies.

In the search for explanations for the heterogeneity in lipid responses, reviewers may tend to highlight studies showing significant effects of genetic variation while ignoring a large proportion of studies that found no such results. Studies showing nonsignificant or conflicting results cannot be ignored, especially because they outnumber the studies showing significant effects, notwithstanding the unpublished studies that could have nonsignificant and uninteresting results. Therefore, one has to ask the question "If genetic variability plays a role in the heterogeneity of lipid and lipoprotein responses to dietary change, why have so many studies been unable to demonstrate this with statistical significance?"

Possible reasons for conflicting results

There are many possible reasons why studies have been unable to show statistically significant gene-diet interactions. First, it is highly probable that lipid responses to dietary change are under polygenic control, with each gene contributing a relatively small effect. However, most studies have attempted to find only single-gene effects. For example, Gylling et al (28) found that the apo B *Eco*RI polymorphism had no effect on the LDL-cholesterol response to cholesterol feeding in all subjects, but in carriers of the apo ϵ4 allele, those carrying the *R*+ allele showed significantly greater LDL-cholesterol responses than did the *R*−*R*− subjects. In the future, genotyping at multiple loci will be required to identify the best therapy for improving lipid and lipoprotein profiles.

Most of the studies summarized in this review lacked sufficient statistical power to detect any but a very strong effect because the sample sizes were too small, particularly for genotypes with low frequencies of the rare allele. However, many of the studies were retrospective and were not designed to examine gene-diet interactions, but data were reexamined after the availability of new information from genotype analyses. Therefore, it is perhaps not surprising that significant effects were not found in many studies because the numbers of individuals in each genotype group were so small. In many studies there were too few subjects homozygous for the rare allele to allow an analysis that would take into account differences in the response between heterozygotes and homozygotes. For apo E, where there are 6 possible genotypes, differences in the grouping of these could also lead to differences in results between studies. This illustrates that meta-analyses are important because they can detect effects with greater power and greater precision because of their inflated sample size (46, 71). In addition, in studies with small sample sizes, genotype misclassification of one individual may significantly affect the interpretation and validity of the results.

Conflicting results may also occur because of the different dietary protocols that were followed. The studies reviewed varied

TABLE 5
Genes coding for enzymes[1]

Polymorphism and study	Subjects	Genotype groups	Intervention	Response[2]				
				Chol	LDL	HDL	VLDL	TG
Lipoprotein lipase								
*Hind*III								
Humphries et al (29)	55 M and F	45 *H+H+*, 10 *H−* (*H+H−*, *H−H−*)	High-SFA vs high-PUFA diet	*H−*	—[3]	—	—	*H−*
Chamberlain et al (87)	83 M and F, HC	48 *H+H+*, 24 *H+H−*, 11 *H−H−*	Low-SFA, low-chol diet	NS	NS	NS	—	NS
Wallace et al (30)	55 M and F, HC	23 *H+H+*, 32 *H−* (*H+H−*, *H−H−*)	High-SFA vs high-PUFA diet	NS	—	—	—	—
*Pvu*II								
Chamberlain et al (87)	83 M and F, HC	23 *1/1*, 42 *1/2*, 18 *2/2*	Low-SFA, low-chol diet	NS	NS	NS	—	NS
S447*X*								
Friedlander et al (44)	191 M and F	146 *S/S*, 45 *S/X*	High-SFA, high-chol vs low-SFA, low-chol diet	NS	NS	NS	—	NS
Wallace et al (30)	55 M and F, HC	47 *S/S*, 8 *S/X* and *X/X*	High-SFA vs high-PUFA diet	NS	—	—	—	—
Wallace et al (37)	46 M and F, HC	39 *S/S*, 7 *S/X*	High-SFA vs high-PUFA diet	—	*S/X*	NS	—	NS
T-93G								
Friedlander et al (44)	194 M and F	185 *T/T*, 9 *T/G*	High-SFA, high-chol vs low-SFA, low-chol diet	NS	NS	NS	—	NS
N291S								
Friedlander et al (44)	194 M and F	190 *N/N*, 4 *N/S*	High-SFA, high-chol vs low-SFA, low-chol diet	NS	NS	NS	—	N/S
Hepatic lipase								
V73M (*Nla*III)								
Hegele et al (31)	67 M and F	61 *V/V*, 6 *V/M*	Wheat- or oat-bran supplementation	NS	NS	NS	—	NS
*Msp*I								
Chamberlain et al (87)	83 M and F, HC	24 *1/1*, 39 *1/2*, 20 2/2	Low-SFA, low-chol diet	NS	NS	NS	—	NS
Cholesterol 7α-hydroxylase								
Intron 2								
Friedlander et al (42)	55 M	15 *12−12−*, 26 *12−12+*, 14 *12+12+*	Low-SFA, high-MUFA and low-SFA, high-PUFA diets	NS	NS	NS	—	NS
Intron 4								
Friedlander et al (42)	45 M	10 *14−14−*, 30 *14−14+*, 5 *14+14+*	Low-SFA, high-MUFA and low-SFA, high-PUFA diets	NS	NS	NS	—	NS

[1] Chol, cholesterol; TG, triacylglycerol; SFA, saturated fatty acid; PUFA, polyunsaturated fatty acid; MUFA, monounsaturated fatty acid; NS, nonsignificant difference between genotype groups; HC, hypercholesterolemic.
[2] In most cases the direction of the response was the same for each genotype group; in these cases, the genotype showing the largest response is given.
[3] Indicates that the responses or *P* values were not clearly reported.

widely in the composition and length of the baseline and experimental diets. The dietary factors responsible for the changes seen in each genotype group are not clear because many studies modified several dietary factors, and so the dietary content in future studies should be tightly controlled and compliance must be strictly measured, ie, not only for cholesterol and the amount and type of fatty acids but also for other influential dietary components such as fiber and plant sterols. In addition, these studies investigated fasting lipid and lipoprotein concentrations; however, the effect of genetic variation may be more evident in the postprandial state than in the less-common fasting state.

Differences in the age, sex, body mass index, menopausal status, dietary backgrounds, and baseline lipid values of the participants could also have contributed to the discrepancies between the results. For instance, subjects with the ϵ4 allele tend to have higher baseline total and LDL-cholesterol concentrations, and so greater responses in these subjects could reflect the regression to the mean phenomenon. However in Mantarri et al's (65) study, baseline cholesterol concentrations were not significantly different between carriers and noncarriers of the ϵ4 allele, showing that the greater total and LDL-cholesterol responses in the ϵ4 group were not due to regression to the mean. It is also possible that weight change could account for differences in lipid and lipoprotein changes.

In addition, a significant effect may not reflect a causal relation but the allele may be in linkage disequilibrium with another one that does. For example, the base change that results in the *Xba*I site in the gene for apo B does not alter the amino acid, and so it may be in linkage disequilibrium with another functional mutation.

Conclusion

Evidence suggests that genetic variation may contribute to the heterogeneity in lipid responsiveness. At present, the evidence is

TABLE 6
LDL receptor gene[1]

Polymorphism and study	Subjects	Genotype groups	Intervention	Response[2] Chol	LDL	HDL	VLDL	TG
*Hinc*II								
Hegele et al (31)	67 M and F	15 *1/1*, 37 *1/2*, 15 *2/2*	Wheat- or oat-bran supplementation	*2/2*	*2/2*	NS	—[3]	NS
Friedlander et al (42)	62 M	10 *1/1*, 30 *1/2*, 22 *2/2*	Low-SFA, high-MUFA and low-SFA, high-PUFA diets	NS	NS	NS	—	NS
*Stu*I								
Friedlander et al (42)	62 M	57 *S+S+*, 5 *S+S−*	Low-SFA, high-MUFA and low-SFA, high-PUFA diets	NS	NS	NS	—	NS
*Pvu*II								
Gylling et al (28)	29 M	17 *P−P−*, 12 *P−P+*	Low-chol vs high-chol diet	—	NS	—	—	—
*Pvu*II								
Clifton et al (12)								
Clifton and Abbey (14)	23 M, HC	15 *AA* (+/+), 8 *B* (+/− and −/−)	High-fat vs low-fat diet	—	—	*B*	—	—
Clifton et al (12)								
Clifton and Abbey (14)	23 M, HC	15 *AA* (+/+), 8 *B* (+/− and −/−)	High-fat vs low-fat vegetarian diet	—	NS	*B*	—	—
Clifton et al (12)								
Clifton and Abbey (14)	23 M, HC		Low-chol vs high-chol diet	—	NS	NS	—	—
*Ava*II								
Friedlander et al (42)	62 M	22 *A−A−*, 31 *A−A+*, 9 *A+A+*	Low-SFA, high-MUFA and low-SFA, high-PUFA diets	NS	NS	NS	—	NS

[1] Chol, cholesterol; TG, triacylglycerol; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; NS, nonsignificant difference between genotype groups; HC, hypercholesterolemic.
[2] In most cases the direction of the response was the same for each genotype group; in these cases, the genotype showing the largest response is given.
[3] Indicates that the responses or *P* values were not clearly reported.

TABLE 7
Other genes[1]

Polymorphism and study	Subjects	Genotype groups	Intervention	Response[2] Chol	LDL	HDL	VLDL	TG
Cholesteryl ester transfer protein gene								
TaqIB								
Wallace et al (30)	55 M and F, HC	17 *B1/B1*, 38 *B1/B2* and *B2/B2*	High-SFA vs high-PUFA diet	*B1/B1*	*B1/B1*	NS	—[3]	NS
Wallace et al (37)	46 M and F, HC	14 *B1/B1*, 32 *B1/B2* and *B2/B2*	High-SFA vs high-PUFA diet	—	NS	—	—	—
Carmena-Ramon et al (88)	77 M and F, FH	22 *B1/B1*, 44 *B1/B2*, 11 *B2/B2*	NCEP-I diet	—	NS	NS	—	NS
I405V								
Friedlander et al (44)	194 M and F	72 *I/I*, 88 V/I, 34 V/V	High-SFA, high-chol vs low-SFA, low-chol diet	NS	NS	NS	—	NS
Intestinal fatty acid–binding protein gene (FABP2)								
Codon 54 *Ala/Thr*								
Hegele et al (89)	43 M and F	21 *A54/A54*, 20 *T54/A54*, 2 *T54/T54*	High-insoluble-fiber diet vs high-soluble-fiber diet	*T54/T54*	*T54/T54*	NS	—	NS
Neuropeptide Y gene								
Leu7Pro								
Schwab et al (90)	68 M and F	58 *Leu7Leu*, 10 *Leu7Pro*	High-fat vs reduced-fat diet	NS	NS	NS	—	NS
M/N blood group								
Birley et al (91)	127 M and F	38 *M/M*, 67 *M/N*, 22 *N/N*	Low-fat diet and wheat bran supplement	—	*N/N* and *M/M*	—	—	—

[1] Chol, cholesterol; TG, triacylglycerol; SFA, saturated fatty acid; PUFA, polyunsaturated fatty acid; NCEP-I diet, National Cholesterol Education Program Step I diet; NS, nonsignificant difference between genotype groups; HC, hypercholesterolemic; FH, familial hypercholesterolemic.
[2] In most cases the direction of the response was the same for each genotype group; in these cases, the genotype showing the largest response is given.
[3] Indicates that the responses or *P* values were not clearly reported.

limited but suggestive and justifies the need for future studies with much larger sample sizes based on power calculations, with carefully controlled dietary interventions, and that investigate the effects of polymorphisms in multiple genes rather than in single genes. Investigating gene-diet interactions will increase our knowledge of the mechanisms involved in lipid metabolism and improve our understanding of the role of diet in reducing cardiovascular disease risk.

REFERENCES

1. Peyser PA. Genetic epidemiology of coronary artery disease. Epidemiol Rev 1997;19:80–90.
2. Hegsted DM, Ausman LM, Johnson JA, Dallal GE. Dietary fat and serum lipids: an evaluation of the experimental data. Am J Clin Nutr 1993;57:875–83.
3. Keys A, Anderson JT, Grande F. Prediction of serum cholesterol responses of man to changes in fats in the diet. Lancet 1957;2: 959–66.
4. Hegsted DM, McGandy RB, Myers ML, Stare FJ. Quantitative effects of dietary fat on serum cholesterol in man. Am J Clin Nutr 1965;17:281–95.
5. Cobb MM, Teitlebaum H. Determinants of plasma cholesterol responsiveness to diet. Br J Nutr 1994;71:271–82.
6. Jacobs DR, Anderson JT, Hannan P, Keys A, Blackburn H. Variability in individual serum cholesterol response to change in diet. Arteriosclerosis 1983;3:349–56.
7. McNamara DJ, Kolb R, Parker TS, et al. Heterogeneity of cholesterol homeostasis in man: Response to changes in dietary fat quality and cholesterol quantity. J Clin Invest 1987;79:1729–39.
8. Schaefer EJ, Lamon-Fava S, Ausman LM, et al. Individual variability in lipoprotein cholesterol response to National Cholesterol Education Program Step 2 diets. Am J Clin Nutr 1997;65:823–30.
9. Beynen AC, Katan MB, van Zutphen LFM. Hypo- and hyperresponders: individual differences in the response of serum cholesterol concentration to changes in diet. Adv Lipid Res 1987;22:115–71.
10. Katan MB, Beynen AC, de Vries JH, Nobels A. Existence of consistent hypo- and hyperresponders to dietary cholesterol in man. Am J Epidemiol 1986;123:221–34.
11. Ordovas JM, Lopez-Miranda J, Mata P, Perez-Jimenez F, Lichtenstein AH, Schaefer EJ. Gene-diet interaction in determining plasma lipid response to dietary intervention. Atherosclerosis 1995;118(suppl):S11–27.
12. Clifton P, Kind K, Jones C, Noakes M. Response to dietary fat and cholesterol and genetic polymorphisms. Clin Exp Pharmacol Physiol 1997;24:A21–5.
13. Tikkanen MJ. Apolipoprotein E polymorphism and plasma cholesterol response to dietary change. World Rev Nutr Diet 1997;80:15–21.
14. Clifton PM, Abbey M. Genetic control of response to dietary fat and cholesterol. World Rev Nutr Diet 1997;80:1–14.
15. Dreon DM, Krauss RM. Diet-gene interactions in human lipoprotein metabolism. J Am Coll Nutr 1997;16:313–24.
16. Ordovas JM, Schaefer EJ. Genes, variation of cholesterol and fat intake and serum lipids. Curr Opin Lipidol 1999;10:15–22.
17. Ordovas JM. The genetics of serum lipid responsiveness to dietary interventions. Proc Nutr Soc 1999;58:171–87.
18. Ordovas JM, Schaefer EJ. Genetic determinants of plasma lipid response to dietary intervention: the role of the *APOA1/C3/A4* gene cluster and the *APOE* gene. Br J Nutr 2000;83(suppl):S127–36.
19. Ye SQ, Kwiterovich PO Jr. Influence of genetic polymorphisms on responsiveness to dietary fat and cholesterol. Am J Clin Nutr 2000; 72(suppl):1275S–84S.
20. Ordovas JM. Gene-diet interaction and plasma lipid response to dietary intervention. Curr Atheroscler Rep 2001;3:200–8.
21. Lopez-Miranda J, Ordovas JM, Espino A, et al. Influence of mutation in human apolipoprotein A-1 gene promoter on plasma LDL cholesterol response to dietary fat. Lancet 1994;343:1246–9.
22. Lopez-Miranda J, Mata P, Ordovas JM, et al. The *G/A* mutation at the apo A-I gene promoter predicts plasma LDL response to a high PUFA diet. Atherosclerosis 1994;109:144 (abstr).
23. Jansen S, Lopez-Miranda J, Salas J, et al. Effect of 347-serine mutation in apoprotein A-IV on plasma LDL cholesterol response to dietary fat. Arterioscler Thromb Vasc Biol 1997;17:1532–8.
24. Lopez-Miranda J, Jansen S, Ordovas JM, et al. Influence of the *Sst*I polymorphism at the apolipoprotein C-III gene locus on the plasma low-density-lipoprotein-cholesterol response to dietary monounsaturated fat. Am J Clin Nutr 1997;66:97–103.
25. Meng QH, Pajukanta P, Valsta L, Aro A, Pietinen P, Tikkanen MJ. Influence of apolipoprotein A-1 promoter polymorphism on lipid levels and responses to dietary change in Finnish adults. J Intern Med 1997;241:373–8.
26. Carmena-Ramon RF, Ordovas JM, Ascaso JF, Real J, Priego MA, Carmena R. Influence of genetic variation at the apo A-I gene locus on lipid levels and response to diet in familial hypercholesterolemia. Atherosclerosis 1998;139:107–13.
27. Mata P, Lopez-Miranda J, Pocovi M, et al. Human apolipoprotein A-I gene promoter mutation influences plasma low density lipoprotein cholesterol response to dietary fat saturation. Atherosclerosis 1998;137:367–76.
28. Gylling H, Kontula K, Koivisto UM, Miettinen HE, Miettinen TA. Polymorphisms of the genes encoding apoproteins A-I, B, C-III, and E and LDL receptor, and cholesterol and LDL metabolism during increased cholesterol intake. Common alleles of the apoprotein E gene show the greatest regulatory impact. Arterioscler Thromb Vasc Biol 1997;17:38–44.
29. Humphries SE, Talmud PJ, Cox C, Sutherland W, Mann J. Genetic factors affecting the consistency and magnitude of changes in plasma cholesterol in response to dietary challenge. QJM 1996;89:671–80.
30. Wallace AJ, Mann JI, Sutherland WH, et al. Variants in the cholesterol ester transfer protein and lipoprotein lipase genes are predictors of plasma cholesterol response to dietary change. Atherosclerosis 2000;152:327–36.
31. Hegele RA, Zahariadis G, Jenkins AL, et al. Genetic variation associated with differences in the response of plasma apolipoprotein B levels to dietary fibre. Clin Sci 1993;85:269–75.
32. Lopez-Miranda J, Ordovas JM, Marin C, et al. The *Sst*I polymorphic site at the apolipoprotein C-III gene predicts plasma low density lipoprotein response to changes in dietary fat in young men. Circulation 1994;90:I-74 (abstr).
33. Mata P, Ordovas JM, Lopez-Miranda J, et al. ApoA-IV phenotype affects diet-induced plasma LDL cholesterol lowering. Arterioscler Thromb 1994;14:884–91.
34. McCombs RJ, Marcadis DE, Ellis J, Weinberg RB. Attenuated hypercholesterolemic response to a high-cholesterol diet in subjects heterozygous for the apolipoprotein A-IV-2 allele. N Engl J Med 1994; 331:706–10.
35. Jansen S, Lopez-Miranda J, Ordovas JM, et al. Effect of 360His mutation in apolipoprotein A-IV on plasma HDL-cholesterol response to dietary fat. J Lipid Res 1997;38:1995–2002.
36. Carmena-Ramon R, Ascaso JF, Real JT, Ordovas JM, Carmena R. Genetic variation at the apoA-IV gene locus and response to diet in familial hypercholesterolemia. Arterioscler Thromb Vasc Biol 1998;18:1266–74.
37. Wallace AJ, Humphries SE, Fisher RM, Mann JI, Chisholm A, Sutherland WH. Genetic factors associated with response of LDL subfractions to change in the nature of dietary fat. Atherosclerosis 2000; 149:387–94.
38. Weggemans RM, Zock PL, Meyboom S, Funke H, Katan MB. Apolipoprotein A4–1/2 polymorphism and response of serum lipids to dietary cholesterol in humans. J Lipid Res 2000;41:1623–8.
39. Weinberg RB, Geissinger BW, Kasala K, et al. Effect of apolipoprotein A-IV genotype and dietary fat on cholesterol absorption in humans. J Lipid Res 2000;41:2035–41.
40. Tikkanen MJ, Xu CF, Hamalainen T, et al. XbaI polymorphism of the apolipoprotein B gene influences plasma lipid response to diet intervention. Clin Genet 1990;37:327–34.
41. Friedlander Y, Kaufmann NA, Cedar H, Kark JD. XbaI polymorphism of the apolipoprotein B gene and plasma lipid and lipoprotein

response to dietary fat and cholesterol: a clinical trial. Clin Genet 1993;43:223–31.
42. Friedlander Y, Berry EM, Eisenberg S, Stein Y, Leitersdorf E. Plasma lipids and lipoproteins response to a dietary challenge: analysis of four candidate genes. Clin Genet 1995;47:1–12.
43. Pajukanta PE, Valsta LM, Aro A, Pietinen P, Helio T, Tikkanen MJ. The effects of the apolipoprotein B signal peptide (ins/del) and XbaI polymorphisms on plasma lipid responses to dietary change. Atherosclerosis 1996;122:1–10.
44. Friedlander Y, Leitersdorf E, Vecsler R, Funke H, Kark J. The contribution of candidate genes to the response of plasma lipids and lipoproteins to dietary challenge. Atherosclerosis 2000;152:239–48.
45. Lopez-Miranda J, Marin C, Castro P, et al. The effect of apolipoprotein B xbaI polymorphism on plasma lipid response to dietary fat. Eur J Clin Invest 2000;30:678–84.
46. Rantala M, Rantala TT, Savolainen MJ, Friedlander Y, Kesaniemi YA. Apolipoprotein B gene polymorphisms and serum lipids: meta-analysis of the role of genetic variation in responsiveness to diet. Am J Clin Nutr 2000;71:713–24.
47. Abbey M, Hirata F, Chen GZ, et al. Restriction fragment length polymorphism of the apolipoprotein B gene and response to dietary fat and cholesterol. Can J Cardiol 1995;11(suppl):79G–85G.
48. Boerwinkle E, Brown SA, Rohrbach K, Gotto AM, Patsch W. Role of apolipoprotein E and B gene variation in determining response of lipid, lipoprotein, and apolipoprotein levels to increased dietary cholesterol. Am J Hum Genet 1991;49:1145–54.
49. Eusufzai S, Ngai CI, Holleran SF, Ginsberg HN. Effects of apoprotein B signal peptide polymorphism on the lipid response to reduction of dietary saturated fat. Circulation 1996;94(suppl):I–97 (abstr).
50. Ilmonen M, Helio T, Butler R, et al. Two new immunogenetic polymorphisms of the apoB gene and their effect on serum lipid levels and responses to changes in dietary fat intake. Arterioscler Thromb Vasc Biol 1995;15:1287–93.
51. Brenninkmeijer BJ, Stuyt PMJ, Demacker PNM, Stalenhoef AFH, van't Laar A. ApoE polymorphism and lipoprotein concentrations during a cholesterol-rich diet. Arteriosclerosis 1987;7:516a (abstr).
52. Glatz JFC, Demacker PNM, Turner PR, Katan MB. Response of serum cholesterol in relation to apolipoprotein E phenotype. Nutr Metab Cardiovasc Dis 1991;1:13–7.
53. McPherson R, Martin L, Connelly PW, Tall A, Milne R, Marcel Y. Plasma cholesteryl ester transfer protein (CETP) response to cholesterol feeding varies according to apo E phenotype. Circulation 1991; 84(suppl)II–680 (abstr).
54. Miettinen TA. Impact of apo E phenotype on the regulation of cholesterol metabolism. Ann Med 1991;23:181–6.
55. Gylling H, Miettinen TA. Cholesterol absorption and synthesis related to low density lipoprotein metabolism during varying cholesterol intake in men with different apoE phenotypes. J Lipid Res 1992;33: 1361–71.
56. Lehtimaki T, Moilanen T, Solakivi T, Laippala P, Ehnholm C. Cholesterol-rich diet induced changes in plasma lipids in relation to apolipoprotein E phenotype in healthy students. Ann Med 1992; 24:61–6.
57. Jones PJ, Main BF, Frohlich JJ. Response of cholesterol synthesis to cholesterol feeding in men with different apolipoprotein E genotypes. Metabolism 1993;42:1065–71.
58. Martin LJ, Connelly PW, Nancoo D, et al. Cholesteryl ester transfer protein and high density lipoprotein responses to cholesterol feeding in men: relationship to apolipoprotein E genotype. J Lipid Res 1993; 34:437–46.
59. Ginsberg HN, Karmally W, Siddiqui M, et al. A dose-response study of the effects of dietary cholesterol on fasting and postprandial lipid and lipoprotein metabolism in healthy young men. Arterioscler Thromb 1994;14:576–86.
60. Ginsberg HN, Karmally W, Siddiqui M, et al. Increases in dietary cholesterol are associated with modest increases in both LDL and HDL cholesterol in healthy young women. Arterioscler Thromb Vasc Biol 1995;15:169–78.
61. Sarkkinen E, Korhonen M, Erkkila A, Ebeling T, Uusitupa M. Effect of apolipoprotein E polymorphism on serum lipid response to the separate modification of dietary fat and dietary cholesterol. Am J Clin Nutr 1998;68:1215–22.
62. Weggemans RM, Zock PL, Ordovas JM, Pedro-Botet J, Katan MB. Apoprotein E genotype and the response of serum cholesterol to dietary fat, cholesterol and cafestol. Atherosclerosis 2001;154: 547–55.
63. Fisher EA, Blum CB, Zannis VI, Breslow JL. Independent effects of dietary saturated fat and cholesterol on plasma lipids, lipoproteins, and apolipoprotein E. J Lipid Res 1983;24:1039–48.
64. Tikkanen MJ, Huttunen JK, Ehnholm C, Pietinen P. Apolipoprotein E4 homozygosity predisposes to serum cholesterol elevation during high fat diet. Arteriosclerosis 1990;10:285–8.
65. Manttari M, Koskinen P, Ehnholm C, Huttunen JK, Manninen V. Apolipoprotein E polymorphism influences the serum cholesterol response to dietary intervention. Metabolism 1991;40:217–21.
66. Savolainen MJ, Rantala M, Kervinen K, et al. Magnitude of dietary effects on plasma cholesterol concentration: role of sex and apolipoprotein E phenotype. Atherosclerosis 1991;86:145–52.
67. Cobb MM, Risch N. Low-density lipoprotein cholesterol responsiveness to diet in normolipidemic subjects. Metabolism 1993;42:7–13.
68. Sundram K, Hornstra G, von Houwelingen AC, Kester AD. Replacement of dietary fat with palm oil: effect on human serum lipids, lipoproteins and apolipoproteins. Br J Nutr 1992;68:677–92.
69. Vanhanen HT, Blomqvist S, Ehnholm C, et al. Serum cholesterol, cholesterol precursors, and plant sterols in hypercholesterolemic subjects with different apoE phenotypes during dietary sitostanol ester treatment. J Lipid Res 1993;34:1535–44.
70. Denke MA, Grundy SM. Individual response to a cholesterol-lowering diet in 50 men with moderate hypercholesterolemia. Arch Intern Med 1994;154:317–25.
71. Lopez-Miranda J, Ordovas JM, Mata P, et al. Effect of apolipoprotein E phenotype on diet-induced lowering of plasma low density lipoprotein cholesterol. J Lipid Res 1994;35:1965–75.
72. Miettinen TA, Vanhanen H. Dietary sitostanol related to absorption, synthesis and serum level of cholesterol in different apolipoprotein E phenotypes. Atherosclerosis 1994;105:217–26.
73. Sarkkinen ES, Uusitupa MI, Pietinen P, et al. Long-term effects of three fat-modified diets in hypercholesterolemic subjects. Atherosclerosis 1994;105:9–23.
74. Cox C, Mann J, Sutherland W, Ball M. Individual variation in plasma cholesterol response to dietary saturated fat. BMJ 1995;311:1260–4.
75. Dreon DM, Fernstrom HA, Miller B, Krauss RM. Apolipoprotein E isoform phenotype and LDL subclass response to a reduced-fat diet. Arterioscler Thromb Vasc Biol 1995;15:105–11.
76. Schaefer EJ, Lichtenstein AH, Lamon-Fava S, et al. Efficacy of a National Cholesterol Education Program Step 2 diet in normolipidemic and hypercholesterolemic middle-aged and elderly men and women. Arterioscler Thromb Vasc Biol 1995;15:1079–85.
77. Zambon D, Ros E, Casals E, Sanllehy C, Bertomeu A, Campero I. Effect of apolipoprotein E polymorphism on the serum lipid response to a hypolipidemic diet rich in monounsaturated fatty acids in patients with hypercholesterolemia and combined hyperlipidemia. Am J Clin Nutr 1995;61:141–8.
78. Bergeron N, Havel RJ. Prolonged postprandial responses of lipids and apolipoproteins in triglyceride-rich lipoproteins of individuals expressing an apolipoprotein epsilon 4 allele. J Clin Invest 1996;97: 65–72.
79. Lefevre M, Ginsberg HN, Kris-Etherton PM, et al. ApoE genotype does not predict lipid response to changes in dietary saturated fatty acids in a heterogeneous normolipidemic population. The DELTA Research Group. Dietary effects on lipoproteins and thrombogenic activity. Arterioscler Thromb Vasc Biol 1997;17:2914–23.

80. Tso TK, Park S, Tsai YH, Williams G, Snook JT. Effect of apolipoprotein E polymorphism on serum lipoprotein response to saturated fatty acids. Lipids 1998;33:139–48.
81. Carmena-Ramon R, Real JT, Ascaso JF, Ordovas JM, Carmena R. Effect of apolipoprotein E genotype on lipid levels and response to diet in familial hypercholesterolemia. Nutr Metab Cardiovasc Dis 2000;10:7–13.
82. Hallikainen MA, Sarkkinen ES, Uusitupa MI. Plant stanol esters affect serum cholesterol concentrations of hypercholesterolemic men and women in a dose-dependent manner. J Nutr 2000;130:767–76.
83. Hallikainen MA, Sarkkinen ES, Gylling H, Erkkila AT, Uusitupa MI. Comparison of the effects of plant sterol ester and plant stanol ester-enriched margarines in lowering serum cholesterol concentrations in hypercholesterolaemic subjects on a low-fat diet. Eur J Clin Nutr 2000;54:715–25.
84. Minihane AM, Khan S, Leigh-Firbank EC, et al. ApoE polymorphism and fish oil supplementation in subjects with an atherogenic lipoprotein phenotype. Arterioscler Thromb Vasc Biol 2000;20:1990–7.
85. Gaddi A, Ciarrocchi A, Matteucci A, et al. Dietary treatment for familial hypercholesterolemia—differential effects of dietary soy protein according to the apolipoprotein E phenotypes. Am J Clin Nutr 1991;53:1191–6.
86. Jenkins DJ, Hegele RA, Jenkins AL, et al. The apolipoprotein E gene and the serum low-density lipoprotein cholesterol response to dietary fiber. Metabolism 1993;42:585–93.
87. Chamberlain JC, Hill D, Shenkin A. Dietary treatment of hypercholesterolaemia: lack of relationship between individual response and genetic variation at the lipase loci. The Fluvastatin Genotyping Group. Ann Clin Biochem 1998;35:427–31.
88. Carmena-Ramon R, Ascaso JF, Real JT, Najera G, Ordovas JM, Carmena R. Association between the TaqIB polymorphism in the cholesteryl ester transfer protein gene locus and plasma lipoprotein levels in familial hypercholesterolemia. Metabolism 2001;50:651–6.
89. Hegele RA, Wolever TM, Story JA, Connelly PW, Jenkins DJ. Intestinal fatty acid-binding protein variation associated with variation in the response of plasma lipoproteins to dietary fibre. Eur J Clin Invest 1997;27:857–62.
90. Schwab US, Agren JJ, Valve R, et al. The impact of the leucine 7 to proline 7 polymorphism of the neuropeptide Y gene on postprandial lipemia and on the response of serum total and lipoprotein lipids to a reduced fat diet. Eur J Clin Nutr 2002;56:149–56.
91. Birley AJ, MacLennan R, Wahlqvist M, Gerns L, Pangan T, Martin NG. MN blood group affects response of serum LDL cholesterol level to a low fat diet. Clin Genet 1997;51:291–5.
92. Xu CF, Boerwinkle E, Tikkanen MJ, Huttunen JK, Humphries SE, Talmud PJ. Genetic variation at the apolipoprotein gene loci contribute to response of plasma lipids to dietary change. Genet Epidemiol 1990;7:261–75.
93. Lee E, Tu L, Abdolell M, et al. Evidence for gene-diet interaction in the response of plasma lipoproteins to dietary fibre. Nutr Metab Cardiovasc Dis 1995;5:261–8.
94. Davignon J, Gregg RE, Sing CF. Apolipoprotein E polymorphism and atherosclerosis. Arteriosclerosis 1988;8:1–21.
95. Sutton AJ, Duval SJ, Tweedie RL, Abrams KR, Jones DR. Empirical assessment of effect of publication bias on meta-analyses. BMJ 2000;320:1574–7.