Genetic influences on blood lipids and cardiovascular disease risk: tools for primary prevention[1–4]

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ABSTRACT

Genetic polymorphism in human populations is part of the evolutionary process that results from the interaction between the environment and the human genome. Recent changes in diet have upset this equilibrium, potentially influencing the risk of most common morbidities such as cardiovascular diseases, obesity, diabetes, and cancer. Reduction of these conditions is a major public health concern, and such a reduction could be achieved by improving our ability to detect disease predisposition early in life and by providing more personalized behavioral recommendations for successful primary prevention. In terms of cardiovascular diseases, polymorphisms at multiple genes have been associated with differential effects in terms of lipid metabolism; however, the connection with cardiovascular disease has been more elusive, and considerable heterogeneity exists among studies regarding the predictive value of genetic markers. This may be because of experimental limitations, the intrinsic complexity of the phenotypes, and the aforementioned interactions with environmental factors. The integration of genetic and environmental complexity into current and future research will drive the field toward the implementation of clinical tools aimed at providing dietary advice optimized for the individual's genome. This may imply that dietary changes are implemented early in life to gain maximum benefit. However, it is important to highlight that most reported studies have focused on adult populations and to extrapolate these findings to children and adolescents may not be justified until proper studies have been carried out in these populations and until the ethical and legal issues associated with this new field are adequately addressed. *Am J Clin Nutr* 2009;89(suppl):1509S–17S.

INTRODUCTION

The major public health concerns in the developed world (ie, cardiovascular disease, cancer, diabetes, and obesity) have both genetic and environmental causes. The interface between public health and genetics consists of working toward an understanding of how genes and the environment act together to cause these diseases and how the environment (eg, diet) might be modified in a more personalized fashion to help prevent or delay the onset of disease. As such, cardiovascular disease (CVD), the leading cause of mortality in most industrialized countries, is a multifactorial disease that is associated with nonmodifiable risk factors, such as age, sex, and genetic background, and with modifiable risk factors, including dyslipidemia, obesity, hypertension, and insulin resistance, all of them components of the metabolic syndrome, as well as other more novel risk factors related to inflammation (ie, C-reactive protein) (1) Although considerable strides have been made toward controlling all these risk factors, the area in which we have gained more knowledge has been in relation to dyslipidemia.

Lipoproteins are macromolecular complexes of lipids and proteins that originate mainly from the liver and intestine and are involved in the transport and redistribution of lipids in the body. Lipid and lipoprotein metabolism can be viewed as a complex biological pathway containing multiple steps. Lipid homeostasis is achieved by the coordinated action of a large number of nuclear factors, binding proteins, apolipoproteins, enzymes, and receptors involving hundreds of genes. Lipid metabolism is also closely linked with energy metabolism and is subjected to many hormonal controls that are essential for adjustment to environmental and internal conditions.

In view of the accumulated evidence linking lipoprotein metabolism with the development of atherosclerosis, the major emphasis for CVD prevention and therapy has been placed on lowering serum cholesterol concentration, with the clinical standards being defined by the National Cholesterol Education Program–Adult Treatment Panel convened by the National Heart, Lung, and Blood Institute (2, 3). Since the publication of the National Cholesterol Education Program–Adult Treatment Panel III guidelines, several large-scale clinical trials of cholesterol lowering have been conducted, the findings of which have the potential to further refine current clinical practice standards (4, 5). Although most of the beneficial evidence from lowering serum LDL-cholesterol values in reducing CVD morbidity and mortality comes from pharmacologic interventions, the National

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Cholesterol Education Program has emphasized that therapeutic lifestyle change should be the primary treatment for lowering cholesterol values, with drug therapies reserved for cases in which lifestyle modification is ineffective. The modifications advocated include dietary changes, increased physical activity, and weight management. The recommended dietary changes include restriction of the amount of saturated fat to <7% of calories and of cholesterol to <200 mg/d and an increase in viscous fiber (10–24 g/d) and plant stanols/sterols (2 g/d) to enhance LDL lowering (3). However, it is not known how many individuals can achieve the recommended concentrations of serum lipids by using this approach because of our current inability to predict individual plasma lipid response to dietary changes (6).

In addition to cholesterol lowering, other pharmacologic approaches to CVD risk reduction have been investigated. These include the lowering of serum triglycerides and the raising of HDL-cholesterol concentrations. The most commonly used drugs to lower triglyceride concentrations are the fibrates. These drugs also raise HDL cholesterol and improve small dense LDL cholesterol and so would be expected to have large beneficial effects. Their use in the management of lipoprotein disorders has a history dating back to the mid-1960s. However, their prominence has lessened over the years because of unimpressive results in major clinical trials, safety concerns (7), and the emergence of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins). Moreover, the general trial results with these agents have been confusing, with varying cardiovascular benefits (8–10).

The epidemiologic, experimental, and other circumstantial evidence implicating low HDL-cholesterol concentrations as a major CVD risk has focused considerable attention on this lipoprotein fraction as a potential therapeutic target to further reduce CVD risk beyond what can be achieved with the use of statins. However, doubts about the clinical benefit achievable with treatments enhancing plasma HDL-cholesterol concentrations have been raised by the premature termination of a large phase III trial with torcetrapib, the most potent and most developed HDL-cholesterol-raising compound, because of excess mortality in patients receiving the drug (11). The causes of torcetrapib failure are presently unknown and may be related to the drug mode of action, to off-target toxic effects of the drug, or to a mixture of these. Torcetrapib failure does not mean that the concept of targeting HDL in CVD prevention is definitely ruled out. Other HDL-cholesterol-raising therapies, which act through disparate molecular mechanisms, are in various stages of preclinical and clinical development.

The considerable interindividual variation observed in monitoring these therapies in terms of lipid response, cardiovascular event response, and adverse events is bringing considerable attention to the concept of more targeted therapies based on genetic information. Pharmacogenomics (pharmacogenetics) involves the search and identification of genetic variants that influence response to drug therapy. Over the past decade, some progress has been made in our understanding of the variability associated with statin therapy (12). However, the ethical challenges in conducting the necessary research, including concerns about vulnerability and issues of consent, especially in children (13), the scientific validity of the studies, and the larger policy question of priority setting are important limitations that need to be resolved before its clinical application.

Despite the efficacy of drug therapy to normalize plasma cholesterol concentrations and the demonstrated benefits on CVD events and mortality, it is important to emphasize that diet and behavioral modification should be the first line of defense against CVD, especially in children. Regarding the connection between diet and plasma cholesterol concentrations, during the first half of the 20th century several studies showed that serum cholesterol could be modified by the composition of dietary fat (14, 15), and studies by Keys et al (16) and Hegsted et al (17) provided the first quantitative estimates of the relative effects of the various classes of dietary fatty acids and the amount of cholesterol on serum cholesterol changes. Other predictive algorithms have been developed during the ensuing years, including predictions of response for LDL and HDL cholesterol (18–20). These relations between dietary changes and serum lipid changes are well founded and predictable for groups; however, a striking variability in the response of serum cholesterol to diet between subjects was reported as early as 1933 (21), and this variability has been the subject of multiple reports (19, 22–26). Studies in experimental animal models and in humans have shown that this variability in response to dietary manipulation has a significant genetic component (27–32). Such genetic variability could have a significant effect on the success of public health policies and individual therapeutic interventions. Moreover, it could be partially responsible for the apparent lack of definite endpoint benefits shown by many dietary studies aimed at decreasing CVD (33–36).

As indicated above, the success of CVD risk–reducing strategies has been traditionally measured on the basis of their effect on plasma lipids and, more specifically, on lipoprotein concentrations. Heritability estimates for blood lipids are high, including ≈40–60% for HDL cholesterol, ≈40–50% for LDL cholesterol, and ≈35–48% for triglycerides (37), and genetic variability at candidate genes involved in lipoprotein metabolism has been clearly associated with abnormal lipid metabolism and plasma lipoprotein profiles that may contribute to the pathogenesis of atherosclerosis; however, most of the studies focus primarily on white adult populations. Likewise, there is already copious literature about how variants at candidate genes involved in lipid metabolism may affect dietary response and potentially cardiovascular risk, but again, most of the information concentrates on adults with less information available on children and adolescents, who are at stages of life that may be optimal for effective, targeted primary prevention. This review synthesizes some of the information available on children with the major emphasis being placed on *APOE*, the gene for which more knowledge has been gathered.

APOLIPOPROTEIN E

Apolipoprotein E (apo E) in serum is associated with chylomicrons, VLDL cholesterol, and HDL cholesterol and serves as a ligand for the LDL receptor and the LDL receptor–related protein (38–41). When apo E deficiency is present, there is marked accumulation of cholesterol-enriched lipoproteins of a density <1.006 g/mL containing apo B-48 and apo A-IV, as well as apo B-100 (42). Moreover, in this disorder there is delayed clearance of both apo B-100 and apo B-48 within triacylglycerol-rich lipoprotein. Genetic variation at the *APOE* locus results from 3 common alleles in the population, E4, E3,

and E2, with frequencies in white populations of ≈15%, 77%, and 8%, respectively (41). Population studies, mostly in adult cohorts, have shown that plasma cholesterol, LDL-cholesterol, and apo B concentrations are highest in subjects carrying the *APOE4* isoform, intermediate in those with the *APOE3* isoform, and lowest in those with the *APOE2* isoform (43, 44). It has been suggested that *APOE* allelic variation may account for ≤7% of the variation in total and LDL-cholesterol concentrations in the general population (45). This relation between LDL-cholesterol concentrations and *APOE* genetic variation is not independent of environmental and ethnic factors, and less is known about how these effects track from birth into adulthood.

The association of the *APOE4* isoform with elevated serum cholesterol concentrations is greater in populations consuming diets rich in saturated fat and cholesterol than in other populations. These data indicate that the higher LDL-cholesterol concentrations observed in subjects carrying the *APOE4* isoform are manifested primarily in the presence of an atherogenic diet characteristic of certain societies and that the response to dietary saturated fat and cholesterol may differ among individuals with different *APOE* phenotypes. Many studies have been conducted to prove this hypothesis (31). Some investigators reported greater plasma lipid responses in subjects carrying the *APOE4* allele, whereas others failed to find significant associations between *APOE* genotype and plasma lipid response (31, 46). Important differences exist among these studies that could account for some of the discrepancies observed. Studies differed in subject sex, age, and baseline lipid concentrations, and all of these variables are known to play an important role in the variability of dietary response.

The *APOE* gene also has been implicated as one of the genetic factors mediating variability in postprandial lipemia response. The *APOE2* isoform is considered to decrease remnant clearance because of impaired affinity for the receptors. Conversely, the *APOE4* isoform should induce a faster clearance. However, studies that have compared postprandial triglyceride responses across different *APOE* genotypes have produced conflicting results, especially regarding the effects associated with the *APOE4* allele (47–53). Postprandial response was examined at 4 and 8 h by Boerwinkle et al (54) in a sample of individuals taking part in the Atherosclerosis Risk in Communities Study, following a single high-fat meal containing vitamin A (used as a marker for intestinal lipoprotein synthesis). Postprandial plasma retinyl palmitate response was significantly different among *APOE* genotypes, with delayed clearance in subjects carrying the *APOE2* allele, compared with E3/3 and E3/4 subjects; however, measurements of other lipid variables, such as triglyceride concentration and triglyceride-rich lipoprotein were not sensitive enough to detect these effects. Another study by Nikkilä et al (50), carried out in CVD cases and controls, showed that in CVD patients with the *APOE2/3* phenotype, triglyceride concentrations were highest and still increasing after 7 h, reflecting delayed chylomicron remnant clearance. The same effect also was observed in normotriglyceridemic patients with non-insulin-dependent diabetes (55) and in nondiabetic normolipemic subjects (56), although, in this report, the delayed chylomicron remnant was observed only in E2/2 individuals. The findings associated with the *APOE4* allele have been more discordant. In an earlier report, heterozygosity for this allele was associated with lower lipemic response in relation to other phenotype groups (49); however, in another study the E4 allele was associated with prolonged postprandial responses of lipids and apolipoproteins in triacylglycerol-rich lipoprotein (57).

Several mechanisms have been proposed to explain these apo E– related differences in individual response to dietary therapy. Some studies have shown that intestinal cholesterol absorption is related to *APOE* phenotype, with *APOE4* carriers absorbing more cholesterol than non-*APOE4* carriers. Other mechanisms, such as different distribution of apo E on the lipoprotein fractions, LDL apo B production, bile acid and cholesterol synthesis, and postprandial lipoprotein clearance, may also be involved.

Other genetic variants within the *APOE* locus have been investigated in relation to the association with lipid phenotypes and response to dietary intervention. The current evidence suggests that variability in the *APOE* promoter region is associated independently of the traditional E2, E3, and E4 alleles with plasma, lipid concentrations (58), dietary response (59–61), and CVD risk (62).

Some of the recent findings in children and adolescents regarding the association of genetic variability at the *APOE* locus and plasma lipid concentrations are shown in **Table 1** (63–84). In general, the data suggest that the influence of the *APOE* gene on plasma lipid concentrations manifests early in life, and it may track during the lifespan. Therefore, this genetic predisposition could be easily detected and the information used to implement early disease prevention with dietary and behavioral education and modification. However, several issues need to be considered before taking this apparently obvious path to disease prevention, the first one being ethical. *APOE* may be a marker for CVD risk and dietary response, but the association between *APOE4* and Alzheimer's (85) needs to be taken into consideration. Guidelines are needed before such approach can be put in place (86) because individuals being tested for one condition may not want to know their risk for another condition, especially when there is no successful therapy. The second issue is more physiologic and relates to the fact that *APOE* genetic variability may have significant prebirth effects, and some of these have been proven to be quite paradoxic. Thus, it has been shown that in a Scottish cohort of perinatal deaths (87), the *APOE2* allele was overrepresented as compared with healthy newborns, which suggests that this allele may be detrimental to pregnancy outcome. In contrast, the prevalence of *APOE4* was higher in healthy liveborn infants compared with stillbirths and with adults. In addition, an intriguing cross-talk between the maternal and fetal alleles may affect lipoprotein metabolism in the mother through placental mechanisms (88). These investigators took advantage of the fact that placental proteins are encoded from the fetal genome and examined the associations between lipids of 525 pregnant women and the presence, in their newborns, of the *APOE* genetic polymorphism. After adjustment for maternal polymorphisms, newborn *APOE2* (compared with *APOE3/E3*) was associated, again paradoxically, with higher maternal LDL cholesterol. This significant association was independent of the *APOE* alleles carried by the mothers and of lipid concentrations in newborns. Such findings support the active role of *APOE* in the metabolism of maternal lipoproteins and suggest that fetal genes may modulate the risk of problems related to maternal dyslipidemia (preeclampsia, pancreatitis, and future cardiovascular disease). Therefore, contrary to the negative implications of *APOE4* later in life, it appears that the *APOE2* allele may

TABLE 1
Genetic associations between the *APOE* locus and lipid-related traits in children[1]

No. of subjects (reference)	Population	Ages	Design	Comments
247 (63)	White girls (Project HeartBeat!)	8–14 y at baseline	Mixed longitudinal	At baseline, mean TC values were E2/3 < E3/3 < E3/4 ($P < 0.001$). The *APOE* effect on TC and LDL cholesterol and their change during adolescence is strong and may be modified by factors affecting growth, maturation, and reproductive function.
1520 (64)	Bogalusa Heart Study	5–14 y at baseline	16-y follow-up	The E2 allele lowered the adulthood LDL-cholesterol concentration to a greater extent than the childhood concentration ($P < 0.05$). The *APOE* locus not only influences the concentrations and tracking of certain lipoproteins from childhood to adulthood but also modulates the association between lifestyle-related factors (ie, waist-hip) and lipoproteins.
203 (65)	Hungarian and Romani children	≈4.3 y of age	Cross-sectional	*APOE* allele frequencies differed between Hungarian and Romani children as did the association with TC (E2 < E3 < E4 in Hungarians, not significant; and E3 << E4 ≈ E2, $P < 0.5$ in Romanis).
515 (66)	Columbia University Biomarkers Study	Mean age: 9.7 y	Cross-sectional	The *APOE2* allele was associated with an antiatherogenic lipid pattern in children.
60 (67)	Columbia University Biomarkers Study	Mean age: 14.0 y	Standardized fat load	*APOE* genotype was not associated with the postprandial triglycerides or retinyl palmitate responses.
36 (68)	Special Turku Coronary Risk Factor Intervention Project	13-mo-old children	Intervention	*APOE4* children may absorb cholesterol and plant sterols more effectively than the children with *APOE* 3/3 phenotype without compensatory reduction in endogenous synthesis of cholesterol.
63 (69)	Familial hypercholesterolemia	8–17 y	Randomized, double-blind, placebo-controlled clinical trial with simvastatin	The contribution of APOE polymorphism and the dosage of simvastatin to LDL-cholesterol responsiveness is influenced by the nature of the *LDLR* gene mutation.
1062 (70)	Special Turku Coronary Risk Factor Intervention Project	7-mo at baseline	Mixed longitudinal/ intervention	*APOE* strongly influenced tracking of non-HDL cholesterol and apo B values in early childhood, whereas dietary intervention had no effect on tracking of any of the lipids.
1255 (71)	White schoolchildren	6–7 y old	Cross-sectional	The influence of *APOE* on TC, LDL cholesterol, and apo B concentrations is more evident in girls than in boys. This difference in effect is not due to sex hormones.
933 (72)	White schoolchildren	6–8 y old	Cross-sectional	Interaction between *APOE* genotype and birth weight could be an important determinant of TC, LDL-cholesterol, and apo B concentrations and could influence atherosclerosis development later in life.
81 (73)	Special Turku Coronary Risk Factor Intervention Project	6 y old	Randomized prospective trial	Plant stanol esters reduce serum cholesterol concentration in healthy children irrespective of their sex or *APOE4* phenotype.
450 (74)	Familial hypercholesterolemia	—	Cross-sectional	*APOE4* allele was associated with lower HDL-cholesterol concentrations in an affected sib-pair analysis, which strongly suggests that *APOE4* influences HDL-cholesterol concentrations in children with familial hypercholesterolemia. Moreover, the strong association suggests that *APOE4* carries an additional disadvantage for children with familial hypercholesterolemia.
81 (75)	Obese children	Mean age: 9.4 y	Case-control	*APOE* seems to influence some lipid profile abnormalities associated with obesity in childhood. However, clustering of risk factors and insulin resistance seem not to be dependent on APOE polymorphism.
257 (76)	Birth cohort	6.7–8.1 y old	Cross-sectional	*APOE* and *CETP* loci have an additive and interactive influence on plasma lipid and lipoprotein concentrations in children.
348 (77)	Vietnamese children living in urban and rural areas	7–9 y old	Cross-sectional	Plasma lipid profiles of *APOE4* carriers may be a risk factor for atherogenesis in Vietnamese children having Westernized eating habits.
420 (78)	Mexicans living in Mexico City	12–16 y old	Cross-sectional	Unlike previous studies in the adult Mexican population, these results in children show that lipid and lipoprotein concentrations are under the influence of APOE polymorphism.
1274 (79)	Healthy children from 4 Spanish regions	6–8 y old	Cross-sectional	The *APOE* gene may be a genetic determinant for ischemic heart disease in relatively isolated populations.

(Continued)

TABLE 1 (*Continued*)

No. of subjects (reference)	Population	Ages	Design	Comments
926 (80)	Healthy children from 4 Spanish regions	6–8 y old	Cross-sectional	The association between apo E and lipophilic antioxidant concentrations is dependent mainly on the effect of the polymorphism on lipoprotein concentrations.
691 (81)	Colombian children	5–15 y old	Cross-sectional	The *APOE4* allele was associated with higher concentrations of TC, LDL cholesterol, and apo B-100.
414 (82)	Brazilian children	5–15 y old	Cross-sectional	In this highly admixed population sample, an *APOE2* antiatherogenic lipid pattern is already detected in children.
1736 (83)	Cardiovascular Risk in Young Finns Study	3–18 y at baseline	Longitudinal	The LDL-lowering effect of the *APOE2* allele was greater in adulthood than in childhood. APOE polymorphism is associated with lipid concentrations at different ages and affects the longitudinal change in LDL cholesterol from childhood to adulthood.
1221 (84)	Cardiovascular Risk in Young Finns Study	3–18 y at baseline	Longitudinal	*APOE* polymorphism affects the concentration of circulating high-sensitivity C-reactive protein already in children and young adults. Male *APOE4* carriers have consistently lower high-sensitivity C-reactive protein concentrations. In females, *APOE4* carriers had lower high-sensitivity C-reactive protein concentrations in childhood but not in adulthood.

[1] TC, total cholesterol.

be a marker of prenatal risk for the fetus and the mother. This hypothesis has been further supported by Corbo et al (89), who observed that in preindustrial populations, the highest fertility was associated with the *APOE4* allele and by Wright et al (90) who showed that the *APOE4* isoform may have advantages over those with the E2 or E3 isoforms with respect to early life neuronal/brain development. These findings suggest that some positive selection for increased performance early in life may compromise the ability to cope with the aging process (91). In addition, there is little information about gene-diet interactions in children from controlled intervention studies. However, a recent report has proposed intrauterine gene-diet interactions predisposing for early- and adult-life phenotypes (92).

OTHER GENETIC RISK PREDICTORS

As indicated earlier, cardiovascular disease is very polygenic, and there are many genes, in addition to *APOE*, involved in shaping that predisposition early in life. However, the amount of research devoted to early detection has been well below what is needed, mostly because of the uncertainties associated with predicting the risk of diseases that will manifest decades later. Nevertheless, several studies, such as the GENESIS (Growth, Exercise and Nutrition Epidemiologic Study In preSchoolers) study, have been conceived with this goal in mind. Associations between adiposity-related phenotypes and genetic variation in peroxisome proliferator–activated receptor γ (PPAR-γ; Pro12Ala and C1431T), as well as PPAR-δ (T+294C) were assessed in 2102 Greek children aged 1–6 y participating in this study (93), and the data revealed that the PPAR-γ Pro12Ala and C1431T polymorphisms were associated with increased adiposity during early childhood in a sex- and age-specific manner and independently of the PPAR-δ T+294C polymorphism.

The *PPARG* locus was also investigated in a much smaller study in the context of eating behavior (94). This is a very important issue in the context of the current increases in worldwide obesity. Young children can regulate energy precisely in the short term, which suggests an innate compensation mechanism of eating behavior. However, this precise compensation appears to be attenuated as a function of increasing adiposity, parental feeding style, and age. Polymorphisms in *PPARG* and β-adrenergic receptor (*ADRB3*) genes have been linked to increased body mass index (BMI), obesity, and, more recently, dietary nutrients and preferences. In addition, common variation in *ADRB3* interacts with *PPARG* to modulate adult body weight. Therefore, Cecil et al (94) investigated whether variants in these genes were associated with child eating behavior in 84 children aged 4–10 y and prospectively selected for variants of the *PPARG* locus (Pro12Ala, C1431T), and their findings support the notion of a genetic interaction involving *ADRB3* and *PPARG* variants that influences eating behavior in children. These differences in eating preferences may have deleterious effects on cardiovascular risk factors such as obesity, dyslipidemia, hypertension, and insulin resistance, all components of the metabolic syndrome (95).

The case for gene-sex interaction has been proposed by Dedoussis et al (96), who evaluated the association of the PPARG Pro12Ala polymorphism in blood lipid concentrations of 173 primary school children. A significant interaction between the *PPARG* gene and sex on blood lipid concentrations was detected. Pro/Pro females exhibited higher values of total cholesterol (TC) and triglycerides compared with Pro/Ala individuals. On the other hand, Pro/Pro males showed higher values of HDL cholesterol and a lower TC/HDL cholesterol ratio compared with Pro/Ala. The *PPARG* locus was also investigated in combination with the adiponectin (*ADIPOQ*) gene (97). The PPARG Pro12Ala and the ADIPOQ G276T single nucleotide polymorphisms were genotyped in 285 obese children and adolescents. Moreover, the analyses were adjusted for *APOE* genotype. No associations were found for PPARG or ADIPOQ polymorphisms with BMI, HDL cholesterol, triglycerides, or insulin resistance. Wild-type carriers of the PPARG

Pro12Ala homozygous carriers of the variant allele of *ADIPOQ* G276T and *APOE4* carriers had higher total and LDL-cholesterol concentrations. Therefore, genetic variants in candidate genes for insulin resistance were associated with cholesterol concentrations in obese children and adolescents and may offer additional information in the risk assessment of obese children.

Another potentially informative locus is the melanocortin-3 receptor in view of the central role of the melanocortin system in the long-term regulation of energy homeostasis. Santoro et al (98) screened the MC3R coding region in 184 obese girls and boys after 6 and 12 mo of a weight loss program. The C17A (Thr6Lys) and G241A (Val81Ile) were not associated with significant differences in baseline BMI; however, at follow-up, heterozygotes showed a significantly higher BMI. When these children were divided according to the amount of weight lost, a higher prevalence of heterozygotes was observed among subjects who lowered their BMI. Therefore, these results suggest a gene-diet interaction between the MC3R C17A and G241A variants and a weight loss program for the ability to lose weight in childhood obesity.

More recently, and following the current trends in adult populations, the search for genes involved in early risk markers in children has embraced the use of genome scans. Microsatellite markers were typed on 779 white and 444 black siblings participating in the Bogalusa Heart Study (99). These subjects had been examined serially 2–13 times over an average of 22 y from childhood to adulthood. The total and the incremental areas under the growth curves of lipid traits were calculated and used as measures for long-term concentrations and trends. After adjusting for age, sex, and BMI, heritability estimates of the total area values for all lipid variables were higher than those of a single measurement in either childhood or adulthood. In blacks, significant linkage to the low-density lipoprotein cholesterol (*LDLC*) incremental area was observed on chromosome 1, and suggestive linkage for total area of *LDLC* was observed on chromosome 19. One suggestive linkage on chromosome 2 was identified in whites for the *LDLC* incremental area. Other suggestive linkage was noted for *LDLC* and high-density lipoprotein cholesterol in terms of either total or incremental area on chromosomes 2, 5, 7, and 15 for blacks and whites. Several lipid-related candidate genes such as *LDLR*, LDL receptor–related proteins 3 and 8, *APOE*, *APOA2*, and *APOC2* are located in these regions. Linkage evidence found in this community-based study indicates that regions on these chromosomes may harbor genetic loci affecting a predisposition to developing dyslipidemia in childhood. However, these findings need reinforcement from genomewide association studies and replication in large populations.

SUMMARY

The mechanisms involved in the regulation of plasma lipoprotein concentrations by dietary factors, such as intakes of cholesterol and fatty acids, have been partially elucidated during the past century through the research efforts of scores of investigators, and this knowledge has been translated into therapies to decrease cardiovascular disease. Genetics research has also brought up a number of candidate genes involved in the regulation of the homeostasis of blood lipids. Considering the significant effect of diet on plasma lipids, genetic variation at those loci is expected to explain some of the dramatic interindividual variations in lipoprotein response to dietary change that have been shown to exist among individuals. In fact, the current evidence supports the importance of gene-diet interactions in humans. However, because of conflicting results, more studies will be required to increase our predictive capacity and to reconcile the multiple discordances found in the literature.

At this regard, we have to keep in mind that lipoprotein response to dietary factors is extremely complex, as illustrated by the multiple interrelated pathways and genes discussed here. Therefore, the effects of individual gene variants can be difficult to identify. In fact, the concerted action of differences in gene families may be required to elicit significant interindividual differences in responsiveness to diet. This systems biology approach has been facilitated by the availability of the public information generated by the Human Genome Project and the HapMap (100).

We should also be cautious about the interpretation of studies of the association between allelic variants and common phenotypes. We should direct attention to the population admixture, which can cause an artificial association if a study includes genetically distinct subpopulations, one of which coincidentally displays a higher frequency of disease and allelic variants. Consideration of the ethnic backgrounds of subjects and the use of multiple, independent populations can help avoid this problem.

Another source of concern is multiple-hypothesis testing, which is aggravated by publication bias. Authors who test a single genetic variant for an association with a single phenotype base statistical thresholds for significance on a single hypothesis. But many laboratories search for associations using different variants. Each test represents an independent hypothesis, but only positive results are reported, leading to an overestimate of the significance of any positive associations. Statistical correction for multiple testing is possible, but the application of such thresholds results in loss of statistical power.

An additional caveat about the published literature relates to the fact that most studies were not initially designed to examine gene-diet interactions, but they are a reanalysis of previously obtained data using new information from genetic analysis carried out a posteriori. Future studies need to be carefully designed in terms of sample size, taking into consideration the frequencies of the alleles examined. Moreover, we do not really know the specific dietary factors responsible for most of the effects already reported. Therefore, baseline and intervention diets should be carefully controlled in terms of dietary cholesterol, individual fatty acids, concentrations of fat, as well as fiber and other minor components of the diet such as phytosterols. It is also important to emphasize that some allele effects may be apparent primarily during situations of metabolic stress, such as the postprandial state. Therefore, studies should be designed to test gene-diet interactions in both the fasting and the fed state. As indicated above, the most plausible scenario is that multiple genes will determine the response to dietary manipulation. Consequently, attention should be paid to gene-gene interactions. However, the large number of study subjects required and the subsequent costs involved may make such studies infeasible. Two alternatives for examining these complex interactions in humans are possible: the first selects study participants on the basis of their genetic variants and the second makes better use of the large cohort studies for which dietary information has been or will be collected. Both approaches combined will enable us to take the

concept of gene-diet interactions beyond the research laboratory into the real world. However, we need to keep in mind that most efforts to identify genetic markers of disease and gene-diet interaction are to provide early risk detection and to apply early behavioral changes that will facilitate disease prevention. In this regard, it is important to highlight that most of the information currently available in the literature has been generated by using adult cohorts and that the findings are extrapolated to childhood without adequate testing and confirmation of findings. However, we need to be careful about when and with whom we may implement more personalized prevention because the balance between risk and benefits may be different at different ages. In this regard, the ''antagonistic pleiotropy'' theory, based in population genetics, proposes that certain alleles that are favored because of beneficial early effects also have deleterious later effects (101). Therefore, we need to make sure that the proper studies are carried out in children to evaluate the balance between optimal early development and healthy aging for individual genomes.

Despite the current uncertainties and limitations, the concept of gene-environment interactions modulating common disease risk factors is well founded and in the future should provide the scientific knowledge to address the major health problems in the population by using molecular and more individually targeted approaches to disease prevention and therapy. (Other articles in this supplement to the Journal include references 102–109.)

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REFERENCES

1. Ordovas JM, Shen J. Gene-environment interactions and susceptibility to metabolic syndrome and other chronic diseases. J Periodontol 2008; 79:1508–13.
2. National Cholesterol Education Program. Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). Circulation 1994;89: 1333–445.
3. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection. Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143–421.
4. Grundy SM, Cleeman JI, Merz CN, et al. A summary of implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Arterioscler Thromb Vasc Biol 2004;24:1329–30.
5. Stone NJ, Bilek S, Rosenbaum S. Recent National Cholesterol Education Program Adult Treatment Panel III update: adjustments and options. Am J Cardiol 2005;96:53E–9E.
6. Corella D, Ordovas JM. Integration of environment and disease into 'omics' analysis. Curr Opin Mol Ther 2005;7:569–76.
7. Rubenstrunk A, Hanf R, Hum DW, Fruchart JC, Staels B. Safety issues and prospects for future generations of PPAR modulators. Biochim Biophys Acta 2007;1771:1065–81.
8. Backes JM, Gibson CA, Ruisinger JF, Moriarty PM. Fibrates: what have we learned in the past 40 years? Pharmacotherapy 2007;27: 412–24.
9. Brown WV. Expert commentary: the safety of fibrates in lipid-lowering therapy. Am J Cardiol 2007;99:19C–21C.
10. Wierzbicki AS. Fibrates after the FIELD study: some answers, more questions. Diab Vasc Dis Res 2006;3:166–71.
11. Bots ML, Visseren FL, Evans GW, et al. Torcetrapib and carotid intima-media thickness in mixed dyslipidaemia (RADIANCE 2 study): a randomised, double-blind trial. Lancet 2007;370:153–60.
12. Schmitz G, Schmitz-Madry A, Ugocsai P. Pharmacogenetics and pharmacogenomics of cholesterol-lowering therapy. Curr Opin Lipidol 2007;18:164–73.
13. Freund CL, Clayton EW. Pharmacogenomics and children: meeting the ethical challenges. Am J Pharmacogenomics 2003;3:399–404.
14. Anderson JT, Grande F, Keys A. Essential fatty acids, degree of unsaturation, and effect of corn (maize) oil on the serum-cholesterol level in man. Lancet 1957;272:66–8.
15. Ahrens EH Jr. Seminar on atherosclerosis: nutritional factors and serum lipid levels. Am J Med 1957;23:928–52.
16. Keys A, Anderson JT, Grande F. Prediction of serum-cholesterol responses of man to changes in fats in the diet. Lancet 1957;273:959–66.
17. 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.
18. Mensink RP, Katan MB. Effect of dietary fatty acids on serum lipids and lipoproteins. A meta-analysis of 27 trials. Arterioscler Thromb 1992;12:911–9.
19. Cobb MM, Teitlebaum H. Determinants of plasma cholesterol responsiveness to diet. Br J Nutr 1994;71:271–82.
20. 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.
21. Okey R. Dietary blood and cholesterol in normal women. J Biol Chem 1933;99:717–27.
22. 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.
23. Jacobs DR Jr, Anderson JT, Hannan P, Keys A, Blackburn H. Variability in individual serum cholesterol response to change in diet. Arteriosclerosis 1983;3:349–56.
24. O'Hanesian MA, Rosner B, Bishop LM, Sacks FM. Effects of inherent responsiveness to diet and day-to-day diet variation on plasma lipoprotein concentrations. Am J Clin Nutr 1996;64:53–9.
25. Cobb MM, Risch N. Low-density lipoprotein cholesterol responsiveness to diet in normolipidemic subjects. Metabolism 1993;42:7–13.
26. Lefevre M, Champagne CM, Tulley RT, Rood JC, Most MM. Individual variability in cardiovascular disease risk factor responses to low-fat and low-saturated-fat diets in men: body mass index, adiposity, and insulin resistance predict changes in LDL cholesterol. Am J Clin Nutr 2005;82:957–63 (quiz 1145–6).
27. Mahaney MC, Blangero J, Rainwater DL, et al. Pleiotropy and genotype by diet interaction in a baboon model for atherosclerosis: a multivariate quantitative genetic analysis of HDL subfractions in two dietary environments. Arterioscler Thromb Vasc Biol 1999;19:1134–41.
28. Rainwater DL, Kammerer CM, Carey KD, et al. Genetic determination of HDL variation and response to diet in baboons. Atherosclerosis 2002;161:335–43.
29. Rainwater DL, Kammerer CM, Cox LA, et al. A major gene influences variation in large HDL particles and their response to diet in baboons. Atherosclerosis 2002;163:241–8.
30. Rainwater DL, Kammerer CM, VandeBerg JL. Evidence that multiple genes influence baseline concentrations and diet response of Lp(a) in baboons. Arterioscler Thromb Vasc Biol 1999;19:2696–700.
31. Corella D, Ordovas JM. Single nucleotide polymorphisms that influence lipid metabolism: interaction with dietary factors. Annu Rev Nutr 2005;25:341–90.
32. Ordovas JM, Corella D. Genetic variation and lipid metabolism: modulation by dietary factors. Curr Cardiol Rep 2005;7:480–6.
33. Brunner EJ, Thorogood M, Rees K, Hewitt G. Dietary advice for reducing cardiovascular risk. Cochrane Database Syst Rev 2005; CD002128.
34. Hooper L, Summerbell CD, Higgins JP, et al. Reduced or modified dietary fat for preventing cardiovascular disease. Cochrane Database Syst Rev 2001;CD002137.
35. Howard BV, Van Horn L, Hsia J, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA 2006;295:655–66.
36. Tinker LF, Bonds DE, Margolis KL, et al. Low-fat dietary pattern and risk of treated diabetes mellitus in postmenopausal women: the Women's Health Initiative randomized controlled dietary modification trial. Arch Intern Med 2008;168:1500–11.
37. Weiss LA, Pan L, Abney M, Ober C. The sex-specific genetic architecture of quantitative traits in humans. Nat Genet 2006;38:218–22.

38. Mahley RW. Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. Science 1988;240:622–30.
39. Beisiegel U, Weber W, Ihrke G, Herz J, Stanley KK. The LDL-receptor-related protein, LRP, is an apolipoprotein E-binding protein. Nature 1989;341:162–4.
40. Hatters DM, Peters-Libeu CA, Weisgraber KH. Apolipoprotein E structure: insights into function. Trends Biochem Sci 2006;31:445–54.
41. Eichner JE, Dunn ST, Perveen G, Thompson DM, Stewart KE, Stroehla BC. Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review. Am J Epidemiol 2002;155:487–95.
42. Schaefer EJ, Gregg RE, Ghiselli G, et al. Familial apolipoprotein E deficiency. J Clin Invest 1986;78:1206–19.
43. Ordovas JM, Litwack-Klein L, Wilson PW, Schaefer MM, Schaefer EJ. Apolipoprotein E isoform phenotyping methodology and population frequency with identification of apoE1 and apoE5 isoforms. J Lipid Res 1987;28:371–80.
44. Schaefer EJ, Lamon-Fava S, Johnson S, et al. Effects of gender and menopausal status on the association of apolipoprotein E phenotype with plasma lipoprotein levels. Results from the Framingham Offspring Study. Arterioscler Thromb 1994;14:1105–13.
45. Davignon J, Gregg RE, Sing CF. Apolipoprotein E polymorphism and atherosclerosis. Arteriosclerosis 1988;8:1–21.
46. Masson LF, McNeill G. The effect of genetic variation on the lipid response to dietary change: recent findings. Curr Opin Lipidol 2005;16: 61–7.
47. Brown AJ, Roberts DC. The effect of fasting triacylglyceride concentration and apolipoprotein E polymorphism on postprandial lipemia. Arterioscler Thromb 1991;11:1737–44.
48. Kesaniemi YA, Ehnholm C, Miettinen TA. Intestinal cholesterol absorption efficiency in man is related to apoprotein E phenotype. J Clin Invest 1987;80:578–81.
49. Weintraub MS, Eisenberg S, Breslow JL. Dietary fat clearance in normal subjects is regulated by genetic variation in apolipoprotein E. J Clin Invest 1987;80:1571–7.
50. Nikkilä M, Solakivi T, Lehtimaki T, Koivula T, Laippala P, Astrom B. Postprandial plasma lipoprotein changes in relation to apolipoprotein E phenotypes and low density lipoprotein size in men with and without coronary artery disease. Atherosclerosis 1994;106:149–57.
51. Superko HR, Haskell WL. The effect of apolipoprotein E isoform difference on postprandial lipoprotein in patients matched for triglycerides, LDL-cholesterol, and HDL-cholesterol. Artery 1991;18:315–25.
52. Talmud PJ, Waterworth DM, Humphries SE. Effect of genetic variation on the postprandial response. Results from the European Atherosclerosis Research Study II. World Rev Nutr Diet 2001;89:53–60.
53. Cardona F, Morcillo S, Gonzalo-Marin M, Tinahones FJ. The apolipoprotein E genotype predicts postprandial hypertriglyceridemia in patients with the metabolic syndrome. J Clin Endocrinol Metab 2005; 90:2972–5.
54. Boerwinkle E, Brown S, Sharrett AR, Heiss G, Patsch W. Apolipoprotein E polymorphism influences postprandial retinyl palmitate but not triglyceride concentrations. Am J Hum Genet 1994;54:341–60.
55. Reznik Y, Pousse P, Herrou M, et al. Postprandial lipoprotein metabolism in normotriglyceridemic non-insulin-dependent diabetic patients: influence of apolipoprotein E polymorphism. Metabolism 1996;45:63–71.
56. Orth M, Wahl S, Hanisch M, Friedrich I, Wieland H, Luley C. Clearance of postprandial lipoproteins in normolipemics: role of the apolipoprotein E phenotype. Biochim Biophys Acta 1996;1303:22–30.
57. 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.
58. Viiri LE, Loimaala A, Nenonen A, et al. The association of the apolipoprotein E gene promoter polymorphisms and haplotypes with serum lipid and lipoprotein concentrations. Atherosclerosis 2005;179:161–7.
59. Moreno JA, Lopez-Miranda J, Marin C, et al. The influence of the apolipoprotein E gene promoter (-219G/T) polymorphism on postprandial lipoprotein metabolism in young normolipemic males. J Lipid Res 2003;44:2059–64.
60. Moreno JA, Perez-Jimenez F, Marin C, et al. Apolipoprotein E gene promoter -219G->T polymorphism increases LDL-cholesterol concentrations and susceptibility to oxidation in response to a diet rich in saturated fat. Am J Clin Nutr 2004;80:1404–9.
61. Moreno JA, Perez-Jimenez F, Marin C, et al. The apolipoprotein E gene promoter (-219G/T) polymorphism determines insulin sensitivity in response to dietary fat in healthy young adults. J Nutr 2005;135: 2535–40.
62. Stengård JH, Frikke-Schmidt R, Tybjaerg-Hansen A, Nordestgaard BG, Sing CF. Variation in 5′ promoter region of the APOE gene contributes to predicting ischemic heart disease (IHD) in the population at large: the Copenhagen City Heart Study. Ann Hum Genet 2007;71:762–71.
63. Fulton JE, Dai S, Grunbaum JA, Boerwinkle E, Labarthe DR. Apolipoprotein E affects serial changes in total and low-density lipoprotein cholesterol in adolescent girls: Project HeartBeat! Metabolism 1999; 48:285–90.
64. Srinivasan SR, Ehnholm C, Elkasabany A, Berenson G. Influence of apolipoprotein E polymorphism on serum lipids and lipoprotein changes from childhood to adulthood: the Bogalusa Heart Study. Atherosclerosis 1999;143:435–43.
65. Szalai C, Czinner A, Csaszar A. Influence of apolipoprotein E genotypes on serum lipid parameters in a biracial sample of children. Eur J Pediatr 2000;159:257–60.
66. Isasi CR, Shea S, Deckelbaum RJ, et al. Apolipoprotein epsilon2 allele is associated with an anti-atherogenic lipoprotein profile in children: the Columbia University BioMarkers Study. Pediatrics 2000;106: 568–75.
67. Couch SC, Isasi CR, Karmally W, et al. Predictors of postprandial triacylglycerol response in children: the Columbia University Biomarkers Study. Am J Clin Nutr 2000;72:1119–27.
68. Tammi A, Ronnemaa T, Rask-Nissila L, et al. Apolipoprotein E phenotype regulates cholesterol absorption in healthy 13-month-old children: the STRIP study. Pediatr Res 2001;50:688–91.
69. Vohl MC, Szots F, Lelievre M, et al. Influence of LDL receptor gene mutation and apo E polymorphism on lipoprotein response to simvastatin treatment among adolescents with heterozygous familial hypercholesterolemia. Atherosclerosis 2002;160:361–8.
70. Rask-Nissila L, Jokinen E, Viikari J, et al. Impact of dietary intervention, sex, and apolipoprotein E phenotype on tracking of serum lipids and apolipoproteins in 1- to 5-year-old children: the Special Turku Coronary Risk Factor Intervention Project (STRIP). Arterioscler Thromb Vasc Biol 2002;22:492–8.
71. Garcés C, Benavente M, Lasuncion MA, Ortega H, Najera G, de Oya M. Gender-specific effects of apolipoprotein E genotype on plasma lipid levels in a population-based sample of 6–7-year-old children in Spain. Acta Paediatr 2002;91:1039–43.
72. Garcés C, Benavente M, Ortega H, et al. Influence of birth weight on the apo E genetic determinants of plasma lipid levels in children. Pediatr Res 2002;52:873–8.
73. Tammi A, Ronnemaa T, Miettinen TA, et al. Effects of gender, apolipoprotein E phenotype and cholesterol-lowering by plant stanol esters in children: the STRIP study. Special Turku Coronary Risk Factor Intervention Project. Acta Paediatr 2002;91:1155–62.
74. Wiegman A, Sijbrands EJ, Rodenburg J, et al. The apolipoprotein epsilon4 allele confers additional risk in children with familial hypercholesterolemia. Pediatr Res 2003;53:1008–12.
75. Guerra A, Rego C, Castro EM, Seixas S, Rocha J. Influence of apolipoprotein E polymorphism on cardiovascular risk factors in obese children. Ann Nutr Metab 2003;47:49–54.
76. Rump P, Mensink RP, Hornstra G. Interaction between a common variant of the cholesteryl ester transfer protein gene and the apolipoprotein E polymorphism: effects on plasma lipids and lipoproteins in a cohort of 7-year-old children. Nutr Metab Cardiovasc Dis 2002;12: 317–24.
77. Nghiem NT, Ta TT, Ohmori R, et al. Apolipoprotein E polymorphism in Vietnamese children and its relationship to plasma lipid and lipoprotein levels. Metabolism 2004;53:1517–21.
78. Medina-Urrutia AX, Cardoso-Saldana GC, Zamora-Gonzalez J, Liria YK, Posadas-Romero C. Apolipoprotein E polymorphism is related to plasma lipids and apolipoproteins in Mexican adolescents. Hum Biol 2004;76:605–14.
79. Garcés C, Cantos M, Benavente M, et al. Variations in APOE genotype distribution in children from areas with different adult cardiovascular disease mortality in Spain. Hum Biol 2004;76:615–21.
80. Ortega H, Castilla P, Gomez-Coronado D, et al. Influence of apolipoprotein E genotype on fat-soluble plasma antioxidants in Spanish children. Am J Clin Nutr 2005;81:624–32.
81. Callas N, Poveda E, Baracaldo C, Hernandez P, Castillo C, Guerra M. [Genetic polymorphism of the E apolipoprotein in school age children:

comparison with levels of plasma lipids and apolipoproteins.] Biomedica 2007;27:526–36 (in Spanish).
82. De França E, Alves JG, Hutz MH. Apolipoprotein E polymorphism and its association with serum lipid levels in Brazilian children. Hum Biol 2004;76:267–75.
83. Gronroos P, Raitakari OT, Kahonen M, et al. Influence of apolipoprotein E polymorphism on serum lipid and lipoprotein changes: a 21-year follow-up study from childhood to adulthood. The Cardiovascular Risk in Young Finns Study. Clin Chem Lab Med 2007;45: 592–8.
84. Gronroos P, Raitakari OT, Kahonen M, et al. Relation of apolipoprotein E polymorphism to markers of early atherosclerotic changes in young adults: the Cardiovascular Risk in Young Finns Study. Circ J 2008;72: 29–34.
85. Bertram L, Tanzi RE. Thirty years of Alzheimer's disease genetics: the implications of systematic meta-analyses. Nat Rev Neurosci 2008;9: 768–78.
86. Goldman JS, Hou CE. Early-onset Alzheimer disease: when is genetic testing appropriate? Alzheimer Dis Assoc Disord 2004;18: 65–7.
87. Becher JC, Keeling JW, McIntosh N, Wyatt B, Bell J. The distribution of apolipoprotein E alleles in Scottish perinatal deaths. J Med Genet 2006;43:414–8.
88. Descamps OS, Bruniaux M, Guilmot PF, Tonglet R, Heller FR. Lipoprotein metabolism of pregnant women is associated with both their genetic polymorphisms and those of their newborn children. J Lipid Res 2005;46:2405–14.
89. Corbo RM, Ulizzi L, Scacchi R, Martinez-Labarga C, De Stefano GF. Apolipoprotein E polymorphism and fertility: a study in pre-industrial populations. Mol Hum Reprod 2004;10:617–20.
90. Wright RO, Hu H, Silverman EK, et al. Apolipoprotein E genotype predicts 24-month bayley scales infant development score. Pediatr Res 2003;54:819–25.
91. Kirkwood TB, Austad SN. Why do we age? Nature 2000;408:233–8.
92. Szitányi P, Pistulkova H, Hubacek JA, Stuchlikova H, Poledne R. Apolipoprotein E/intrauterine undernutrition interaction and hypercholesterolemia in children. Physiol Res 2009;57:965–8.
93. Lagou V, Scott RA, Manios Y, et al. Impact of peroxisome proliferator-activated receptors gamma and delta on adiposity in toddlers and preschoolers in the GENESIS Study. Obesity (Silver Spring) 2008;16:913–8.
94. Cecil JE, Palmer CN, Fischer B, et al. Variants of the peroxisome proliferator-activated receptor gamma- and beta-adrenergic receptor genes are associated with measures of compensatory eating behaviors in young children. Am J Clin Nutr 2007;86:167–73.
95. Duffy VB. Variation in oral sensation: implications for diet and health. Curr Opin Gastroenterol 2007;23:171–7.
96. Dedoussis GV, Theodoraki EV, Manios Y, et al. The Pro12Ala polymorphism in PPARgamma2 gene affects lipid parameters in Greek primary school children: a case of gene-to-gender interaction. Am J Med Sci 2007;333:10–5.
97. Johansson LE, Danielsson P, Norgren S, Marcus C, Ridderstrale M. Interaction between PPARG Pro12Ala and ADIPOQ G276T concerning cholesterol levels in childhood obesity. Int J Pediatr Obes 2008;Jul 21:1–7.
98. Santoro N, Perrone L, Cirillo G, et al. Effect of the melanocortin-3 receptor C17A and G241A variants on weight loss in childhood obesity. Am J Clin Nutr 2007;85:950–3.
99. Chen W, Li S, Srinivasan SR, Boerwinkle E, Berenson GS. A genome scan for loci influencing levels and trends of lipoprotein lipid-related traits since childhood: the Bogalusa Heart Study. Atherosclerosis 2007; 190:248–55.
100. Frodsham AJ, Higgins JP. Online genetic databases informing human genome epidemiology. BMC Med Res Methodol 2007;7:31.
101. Kirkwood TB, Rose MR. Evolution of senescence: late survival sacrificed for reproduction. Philos Trans R Soc Lond B Biol Sci 1991;332: 15–24.
102. Atkinson SA. Introduction to the workshop. Am J Clin Nutr 2009; 89(suppl):1485S–7S.
103. Zeisel SH. Epigenetic mechanisms for nutrition determinants of later health outcomes. Am J Clin Nutr 2009;89(suppl):1488S–93S.
104. Bouchard C. Childhood obesity: are genetic differences involved? Am J Clin Nutr 2009;89(suppl):1494S–501S.
105. Koletzko B, von Kries R, Monasterolo RC, et al. Can infant feeding choices modulate later obesity risk? Am J Clin Nutr 2009;89(suppl): 1502S–8S.
106. Symonds ME, Stephenson T, Budge H. Early determinants of cardiovascular disease: the role of early diet in later blood pressure control. Am J Clin Nutr 2009;89(suppl):1518S–22S.
107. Carlson SE. Early determinants of development: a lipid perspective. Am J Clin Nutr 2009;89(suppl):1523S–9S.
108. Rai D, Larson B. Driving research in infant and children's nutrition: a perspective on industry. Am J Clin Nutr 2009;89(suppl):1530S–2S.
109. Field CJ. Summary of the workshop. Am J Clin Nutr 2009; 89(suppl):1533S–9S.