Published in final edited form as:

Eur J Epidemiol. 2009 ; 24(12): 763–774. doi:10.1007/s10654-009-9402-3.

Genetic determinants of serum lipid levels in Chinese subjects: A population-based study in Shanghai, China

Gabriella Andreotti¹, Idan Menashe¹, Jinbo Chen², Shih-Chen Chang³, Asif Rashid⁴, Yu-Tang Gao⁵, Tian-Quan Han⁶, Lori C. Sakoda⁷, Stephen Chanock^{1,8,9}, Philip S. Rosenberg¹, and Ann W. Hsing¹

¹Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, DHHS, Bethesda, MD, USA

² Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

³Department of Discovery Medicine and Epidemiology, AstraZeneca, Wilmington, DE, USA

⁴Department of Pathology, M.D. Anderson Cancer Center, Houston, TX, USA

⁵Department of Epidemiology, Shanghai Cancer Institute, Shanghai, China

⁶Department of Surgery, Ruijin Hospital, Second Medical University, Shanghai, China

⁷Department of Epidemiology, University of Washington, Seattle, WA, USA

⁸Core Genotyping Facility, National Cancer Institute, National Institutes of Health, Gaithersburg, MD, USA

⁹Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA

Abstract

Purpose—We examined the associations between 21 single nucleotide polymorphisms (SNPs) of eight lipid metabolism genes and lipid levels in a Chinese population.

Methods—This study was conducted as part of a population-based study in China with 799 randomly selected healthy residents who provided fasting blood and an in-person interview. Associations between variants and mean lipid levels were examined using a test of trend and least squares mean test in a general linear model.

Results—Four SNPs were associated with lipid levels: *LDLR* rs1003723 was associated with total cholesterol (p-trend=0.002) and LDL (p-trend=0.01), *LDLR* rs6413503 was associated with total cholesterol (p-trend=0.05), *APOB* rs1367117 was associated with apoB (p-trend=0.02), and *ABCB11* rs49550 was associated with total cholesterol (p-trend=0.01), triglycerides (p-trend=0.01), and apoA (p-trend=0.01). We found statistically significant effects on lipid levels for *LDLR* rs6413503 among those with high dairy intake, *LPL* rs263 among those with high allium vegetable intake, and *APOE* rs440446 among those with high red meat intake.

Conclusion—We identified new associations between SNPs and lipid levels in Chinese previously found in Caucasians. These findings provide insight into the role of lipid metabolism genes, as well as the mechanisms by which these genes may be linked with disease.

Keywords

single nucleotide polymorphisms; Chinese; serum lipid levels

Introduction

Serum lipids play an essential role in several metabolic systems, including the hormonal, nervous and circulatory systems (1). Imbalances in serum lipid levels, such as hyperlipidemia, characterized by increased total cholesterol, triglycerides, and low-density-lipoprotein (LDL), and decreased high-density-lipoprotein (HDL), is associated with several chronic diseases, including cardiovascular disease, gallstones, hypertension, and cancer (2-5).

Serum lipids are affected by both lifestyle factors, such as diet, obesity, and physical activity, and genetic factors (6). For example, high fat and low fiber diets have been consistently reported as risk factors for hyperlipidemia (7). In addition, variants of genes involved in lipid metabolism, such as the low density lipoprotein receptor (*LDLR*), which encodes the LDL receptor that regulates the uptake of LDL by the liver and extrahepatic tissue, have been linked to higher serum levels of LDL (8-11) as well as familial hyperlipidemia (12,13), but predominantly in Caucasian populations. Also, *APOB* and *APOE*, which encode the major carrier and binding proteins of LDL, apolipoproteins B and E, have been associated with higher serum levels of total cholesterol, LDL, and apolipoprotein B (apo B), and lower HDL (14-18). Furthermore, several of these variants in the lipid metabolism pathway have been linked with chronic diseases, such as cardiovascular disease (9,11,16,17), cancer (19), and alzheimer's disease (20) indicating the importance of gaining a better understanding of the functional effect of these variants. In this report, we examined the associations between 21 SNPs in eight genes in the lipid metabolism pathway (*ABCB11*, *ALOX5*, *APOB*, *APOE*, *LDLR*, *LPL*, *RXRA*, *RXR*B) and serum lipid (total cholesterol, triglycerides), lipoprotein (HDL, LDL), and apolipoprotein (apo A, apo B) levels in a population-based study, conducted in Shanghai, China.

Methods

Study Participants

Participants for this study were controls selected for a U.S.-China collaborative biliary tract cancer case-control study, which has been previously reported (21-23). Briefly, participants were healthy, permanent residents of urban Shanghai, between 35 and 74 years of age, and were randomly selected from the Resident Registry of Shanghai (includes over 6 million records) between June 1997 and May 2001. The participation rate among eligible subjects was 82%; a total of 799 healthy participants were included in the study. All participants provided written informed consent; and the study protocol was approved by the Institutional Review Boards of the National Cancer Institute and Shanghai Cancer Institute (SCI).

Interview

Information on demographic characteristics, lifestyle behaviors and diet were obtained through in-person interviews conducted by trained interviewers, using a structured questionnaire. All interviews were taped and verified in order to assure accuracy of interview protocol and coding. At interview, weight, height, and waist and hip circumferences were measured. The response rate for interviews was over 82%. In order to assess the reproducibility of interview responses, 5% of the subjects were randomly selected for re-interview three months after the initial interview; the concordance of responses to key questions between the original and follow-up interviews was greater than 90%.

Blood collection and serum lipid assays

Overnight fasting blood samples were collected from over 80% of the participants who gave consent. Within 4 hours of collection, samples were transported to the central processing laboratory at the SCI for processing. Serum levels of total cholesterol, triglycerides, HDL, LDL, apo A and apo B were measured for all subjects who donated overnight fasting blood samples. Measurements were conducted at the Laboratory of Biochemistry, Institute of Cardiovascular Diseases, Zhongshan Hospital, Shanghai Medical University (Fudan University), using the following assays: 1) Total cholesterol: oxidation enzymatic assay using a cholesterol test kit prepared by Shanghai No.18 Pharmaceutical Company and spectrophotometer type 722 (24); 2) Triglycerides: glycerol phosphoric acid oxidase assay using a triglyceride kit prepared by the Shanghai Biochemical Company and spectrophotometer type 722 (24); 3) HDL: phosphotungstate-magnesium assay with the agent and instrument prepared and manufactured by the same companies as the total cholesterol assay (25); 4) Apo A and apo B: immunoturbidimetric assay prepared by Shanghai Technology Company and ultraviolet spectrophotometer type 754 (26); and 5) LDL was not directly measured but calculated by the Friedewald formula (27,28). Spectrophotometers were manufactured by the Shanghai Third Analysis Instrument Company. The sensitivity, specificity, and coefficient of variation of the lipid level assays were evaluated and were found to be satisfactory.

Genotyping

Genes were selected for their role in lipid metabolism and their potential effects on serum lipid levels (*ABCB11*, *ALOX5*, *APOB*, *APOE*, *LDLR*, *LPL*, *RXRA*, *RXRβ*). SNPs were selected based on having a validated assay at the NCI Core Genotyping Facility (CGF) (<http://cgf.nci.nih.gov/home.cfm>) and a variant allele frequency of at least 5% among Asians as reported by NCI's SNP500Cancer Database (<http://snp500cancer.nci.nih.gov>) (29). Overall, the genes we selected are central to the lipid metabolism pathway, and the SNPs have validated assays and good coverage in the Chinese population. The 21 SNPs we examined are listed in the Supplemental Table. Genomic DNA was extracted from buffy coat by the standard phenol chloroform method at the NCI laboratory. Genotyping was conducted at the CGF using the TaqMan assay (Applied Biosystems, Foster City, CA, <http://snp500cancer.nci.nih.gov>). The genotyping failure rate among all samples was less than 2%. The quality and potential misclassification of the genotyping results were assessed by evaluating 20 duplicate DNA samples from 4 quality control subjects (80 total samples) that were randomly placed within the same reaction plates used for study subjects. The concordance between duplicate samples was over 99%. In addition, the 80 QC samples were typed for 20 unique molecular markers, which indicated a high (>99%) reproducibility of the genotyping results.

Statistical Analysis

The Pearson chi-square test was used to determine whether the distributions of the selected characteristics differed between men and women. The lipids examined included, serum lipids (total cholesterol, triglycerides), lipoproteins (HDL, LDL), and apolipoproteins (apo A, apo B), and are henceforth collectively referred to as "lipids." We examined the distribution of lipid levels and determined that total cholesterol and triglycerides were slightly skewed, thus we log transformed these values for statistical analyses. Associations between the selected characteristics and mean serum lipid levels were assessed using the linear test of trend for ordinal variables and the least squares mean test for dichotomous variables in a general linear model (GLM). Characteristics with statistically significant ($p < 0.05$) differences in mean lipid levels were considered potential confounding factors in the analysis of genetic variants and serum lipid levels. Adjusted mean lipid levels were calculated for each of the three genotypes (homozygous common, heterozygous, and homozygous variant), as well as the combined heterozygous and homozygous variant genotypes (reflecting at least one copy of the variant

allele) of every SNP using GLM. Associations between SNPs and mean lipid levels were assessed using a linear test of trend for the three genotypes, and the least squares mean test comparing the combined heterozygous and variant homozygous genotypes to the common homozygous genotype in a GLM. Initially, age group and gender were adjusted for, but additional models were fitted to further adjust for body mass index (BMI: kg/m²), waist-hip-ratio (WHR), hypertension, diabetes, gallstones, smoking status, drinking status, and total calories per day in order to evaluate the potential for confounding by these factors. Associations between SNPs and mean lipid levels were also examined in stratified subgroups of potential modifying factors, and the likelihood ratio test was used to formally test for multiplicative interactions. To consider multiple comparisons, we applied a Bonferroni correction for the associations between the 21 SNPs and the mean value of each lipid type, but did not correct over subgroup comparisons since these analyses are exploratory in nature and should be viewed as hypothesis generating rather than confirmatory.

We also examined the associations between the haplotypes of the three genes for which we had more than one SNP associated with mean lipid levels (*ABCB11*, *APOB* and *LDLR*). Among population controls, linkage disequilibrium (LD) between markers was assessed by calculating pairwise Lewontin's *D'* and *r*² using Haploview version 3.11 (30). Haplotypes were reconstructed from genotype data using PHASE version 2.1, which uses a Bayesian algorithm to estimate haplotype frequencies (31,32). Associations between haplotypes and mean lipid levels were assessed by fitting an additive model in a GLM to estimate the mean lipid level per copy of each haplotype having a frequency of at least 5% or greater compared with the mean for the most common haplotype pair for each gene. The omnibus *F* ratio test was used to determine if any of the mean lipid levels were significantly different between the haplotypes within each gene.

Results

Overall, the majority of the participants were women (61.2%) and over 64 years of age (58%). There were significant differences between men and women in education, cigarette smoking and alcohol drinking status, BMI, WHR, gallstone status, total calories per day and total fats per day (*p*<0.05) (data not shown). Age-adjusted mean levels of total cholesterol, HDL, LDL, apo A and apo B were significantly higher among women than men (*p*<0.05), and remained significantly higher among women after further adjustment for BMI, WHR, hypertension, and gallstones (Table 1). Due to these differences in lipid levels by gender, we calculated mean lipid levels in relation to selected characteristics separately by gender, but found only a few significant interactions, including that women in the oldest age group (65-75 years) had significantly higher total cholesterol and triglycerides than men in the same age group (*p* interaction=0.02), and that women with hypertension (*p* interaction=0.003) or diabetes (*p* interaction=0.02) had significantly higher serum apo B than men (data not shown). Since gender did not significantly modify most of the associations between the selected characteristics and mean lipid levels, we report the mean lipid levels for men and women combined, adjusting for age and gender in order to account for potential confounding (Table 1). Among all subjects, adjusting for age and gender, BMI, and WHR were positively associated with triglycerides and apo B, and inversely associated with HDL (*p* trend ≤ 0.01). Also, subjects with hypertension and gallstone disease had significantly higher triglycerides than subjects without either condition, and diabetic subjects had significantly higher triglycerides and apo B than subjects without diabetes. For the dietary factors, total calories (kcal/day) was positively associated with total cholesterol (*p* trend ≤ 0.02) and LDL (*p* trend ≤ 0.04), and animal and dairy products (g/day) were positively associated with total cholesterol, HDL and apo B. There were no statistically significant associations for total fat, red meat, vegetable, or fruit consumption with mean lipid levels.

Of the 21 SNPs examined, four showed statistically significant linear associations with mean lipid levels (Figure 1, Table 2). For the *LDLR* rs1003723 (IVS9-30C>T) marker, total cholesterol (p trend=0.002) and LDL (p trend=0.01) were higher with each copy of the T allele compared to the CC genotype; and for the *LDLR* rs6413504 (IVS17-42A>G) marker, total cholesterol (p trend=0.05) increased with each copy of the G allele compared to the AA genotype. For the *APOB* rs1367117 (EX4+56C>T) marker, apoB (p trend=0.02) increased with each copy of the T allele compared to the CC genotype. TC and TT carriers of the *APOB* rs1367117 marker had higher serum triglyceride levels (TC+TT: mean=119.6, F test p=0.01) and higher LDL levels (TC+TT: mean=115.5, F test p=0.02) than carriers of the CC genotype, but the linear tests of trend were not statistically significant. For the *ABCB11* rs49550 (EX28-264A>G) marker, total cholesterol (p trend=0.01), triglycerides (p trend=0.01), and apoA (p trend=0.01) were higher with each copy of the G allele compared to the GG genotype. These results changed little and remained statistically significant after further adjustment for age group, gender, BMI, WHR, hypertension, diabetes, gallstones, cigarette smoking, alcohol drinking, and total calories per day. The mean lipid levels for the other SNPs examined are shown in the Supplemental Table. The minor allele frequencies of the SNPs examined ranged from 4% to 39%, and the genotype frequencies showed no deviation from the expected Hardy-Weinberg equilibrium proportions at the $p > 0.01$ level. To consider multiple comparisons, we applied a Bonferroni correction for the 21 SNPs tested, and found that the linear trend association between *LDLR* rs1003723 and total cholesterol remained statistically significant at the $p \leq 0.05$ level (Figure 1).

Table 3 shows the statistically significant findings ($P \leq 0.05$) from the analysis examining the statistical interactions between the genetic variants and dietary factors on mean serum lipid levels adjusting for age group, gender, BMI, WHR, hypertension, diabetes, gallstone status, cigarette smoking, alcohol consumption, and total calories per day. We found that carriers of the G allele of the *LDLR* rs6413504 marker who had high dairy intake (≥ 124 g/day), had on average, 26% higher serum triglycerides levels (mean=137.5 mg/dl, F test p=0.03, p interaction=0.05) compared to carriers of the AA genotype. Also, carriers of the T allele of the *LPL* rs6413504 marker who had high allium vegetable intake (≥ 10 g/day), had on average, 27.4% lower serum triglycerides levels (mean=99.3 mg/dl, F test p=0.01, p interaction=0.04) compared to carriers of the CC genotype. We also found that carriers of the G allele of the *APOE* rs440446 (IVS1+69C>G) marker who had high red meat intake (≥ 30 g/day), had on average, 9.5% lower total serum cholesterol levels (mean=174.5 mg/dl, F test p=0.05, p interaction=0.02) and 15.9% lower serum LDL levels (mean=96.5 mg/dl, F test p=0.04, p interaction=0.02) compared to carriers of the CC genotype.

BMI significantly modified the association between the *LPL* rs6413504 marker and mean HDL levels (p interaction=0.04), however, due to the small sample size of the variant genotype of the *LPL* rs6413504 marker by BMI category, we had limited statistical power to accurately assess this interaction. Gender did not significantly modify the associations between the markers and mean serum lipid levels examined. Although we did not observe effect modification by WHR, hypertension, smoking, or alcohol consumption on the associations between the markers and the serum lipid levels, we had limited statistical power to accurately assess these interactions. There were no significant associations between the haplotypes of *ABCB11*, *APOB* and *LDLR* and serum lipid levels.

Discussion

In this population-based study of healthy Chinese subjects, variants of *LDLR*, *APOB*, *ABCB11*, *LPL*, and *APOE* were associated with serum lipid levels. These results indicate that these lipid metabolism genes which have been associated with serum lipid levels predominantly in Caucasian populations, also have significant effects on serum lipid levels among Chinese.

Furthermore, our results also suggest that these genetic variants modify established associations between dietary factors and serum lipid levels.

Our finding of the association between two *LDLR* variants (rs1003723, rs6413504) with total cholesterol and particularly LDL are consistent with previous studies of other *LDLR* polymorphisms (8-11). For example, two *LDLR* markers, rs6511720 and rs228671, (not examined in our study) showed significant associations with LDL levels in recent genome-wide association studies conducted in Caucasian populations (8-10). These two markers are not polymorphic in Chinese and are not in LD ($D' < 0.4$) with the two *LDLR* markers reported in our study in Caucasians (33). Therefore, it is likely that other causative variants are responsible for the effects observed in our study. We also found that another *LDLR* variant (rs6413504) was associated with increased serum triglyceride levels among subjects with a high dairy intake. Although no previous studies of *LDLR* have shown an interaction with dairy intake, an earlier study of a different coding variant, *LDLR* T1773C (rs688), reported significantly higher serum triglyceride levels among African American carriers of the T1773C allele (34). This variant is in moderate to high LD with both *LDLR* markers noted in this study (D' with rs6413504 = 0.71, D' with rs1003723 = 0.89) (33). Our findings together with results from previous studies suggest that *LDLR* has an important role on lipid levels in different ethnic populations. Previous studies have reported that decreased LDL receptor activity is associated with increased levels of triglycerides, LDL, and total cholesterol (35-37). Given the LDL receptor's role as the primary binding site for serum LDL and triglycerides, and its regulation of the clearance of LDL and triglyceride-rich lipoproteins from circulation (35), the association between the *LDLR* markers and total cholesterol, LDL, and triglycerides is biologically plausible.

Of special interest is that the T allele of the *LDLR* rs1003723 marker that was associated with high total cholesterol and LDL in this study, was previously shown to confer a 1.5-fold risk of bile duct cancer in the same study population (19). We also previously showed that elevated total cholesterol and LDL were linked to bile duct cancer risk (5), therefore it is plausible that the association between *LDLR* rs1003723 and bile duct cancer is in part related to its effect on total cholesterol and LDL. It is worthy to note that *LDLR* rs1003723 was the only variant that remained statistically significant after controlling for multiple comparisons, which further highlights the importance of this marker.

Our finding of an association between the *APOB* rs1367117 marker and apoB is consistent with previous studies of other *APOB* variants reporting higher levels of serum apoB (38,39). Our finding is biologically plausible as the *APOB* gene encodes for apolipoprotein B, the major carrier and binding protein of LDL. In our earlier study on biliary tract cancer, we found another *APOB* marker, rs520354 (IVS6+360C>T), which is in LD with rs1367117 ($D'=0.81$) (33), was associated with a 2-fold risk of bile duct cancer among men (19). We also found that the *APOB* rs520354 - rs1367117 haplotype was associated with a 1.6-fold risk of bile duct cancer (19). Since bile duct cancer was linked with high serum apoB in this population (5), this finding indicates that the *APOB* variants might linked to bile duct cancer through their effects on apoB.

We also observed positive associations between the *ABCB11* rs49550 marker and total cholesterol, triglycerides, and apoA. *ABCB11* is a highly conserved member of the multi-drug resistance (MDR) gene family of adenosine triphosphate (ATP) binding cassette transporters. It is expressed in hepatocytes and is involved in the secretion of bile salts from the liver (40). Mutations in *ABCB11* have been associated with familial intrahepatic cholestasis (41,42). Although familial intrahepatic cholestasis is usually not associated with abnormal cholesterol levels, little is known about the effects of *ABCB11* variants on lipid levels. In lipid-lowering trials, bile acid binding agents, have been shown to lower glucose levels by reducing triglyceride levels (43). Thus, given *ABCB11*'s role in bile acid secretions, it is plausible that

the gene may also have an effect on lipid levels (44), although future studies are needed to confirm this hypothesis.

Our finding that the T allele of *LPL* rs6413504 was associated with lower triglycerides among those who had high allium vegetable intake (≥ 10 g/day) has not been previously reported. *LPL* encodes the lipoprotein lipase enzyme, which functions as the rate-determining enzyme for the clearance of chylomicrons and very low density lipoproteins (VLDL) from circulation (45, 46). Increased lipoprotein lipase activity has been linked with lower triglyceride and higher HDL in humans (47,48) and laboratory animals (49,50), suggesting that the effect of *LPL* and allium vegetables on triglycerides may be linked to their impact on lipoprotein lipase activity. Allium vegetables, particularly garlic, have been shown to have lipid lowering effects in animals and humans (51). The mechanism by which garlic reduces lipid levels in humans is uncertain, however, animal studies have shown that dietary garlic supplementation depressed lipogenic and cholesterologenic hepatic enzymes (52,53). It is worth noting that the median consumption of allium vegetables (10 g/day) in our Chinese population may be higher than the consumption in most U.S. populations (54,55), which may have allowed us to detect the significant interaction with the *LPL* variant.

We also observed that carriers of the G allele of *APOE* rs440446 who had a high red meat intake had lower total cholesterol and LDL. Since high red meat consumption is typically associated with elevated cholesterol (7), it is unclear why we found lower total cholesterol and LDL among this group. A large cohort study examining the same *APOE* marker among Caucasians also reported lower LDL levels among carriers of the G allele, although the association was not statistically significant (56). The mechanism by which *APOE* rs440446 may be linked with lower LDL levels is unclear; however previous studies of another *APOE* variant have suggested that lower LDL levels may be linked to delayed catabolic rate of lipoprotein metabolism and decreased binding of LDL to the LDL receptor (56-58). Additional experimental or large replication studies addressing the interaction between genetic variants and dietary factors in humans are required.

Notable strengths of this study include its population-based design, random selection of participants, and the high response rate. Also, misclassification of genotypes is minimal given the high reproducibility of genotype data. Measurement error of serum lipids is likely to be small given the high sensitivity and specificity, and small coefficient of variation of the lipid level assays. We also had the unique ability to examine the associations between variants and lipid levels for variants previously associated with biliary tract cancer, thereby providing insight into the etiologic mechanisms of these cancers.

Limitations of the study should also be noted. Since SNP selection was not based on complete sequencing data, coverage of the genes was limited, thus, we may have missed the effect of some important markers. Also, since SNPs for this study were selected before results from other recent studies were available, we could not exactly examine the same markers in these other studies, limiting inter-study comparisons. Furthermore, we cannot conclude that the observed associations are causal since the functional effect of the SNPs are unclear; however, the observed SNP effects can be considered markers for other functional SNPs in LD with those examined in this study. Our statistical power to evaluate gene-gene and gene-environment interactions was limited. We had no information on use of cholesterol-lowering medication, which could have caused a decrease in serum lipid levels in subjects taking these medications. However, after excluding subjects with a history of hypertension, heart disease or diabetes (n=377), (those who would be the most likely to be taking lipid-lowering medications), the observed main effect associations remained statistically significant at the $p<0.05$ level, suggesting minimal impact of lipid-lowering drugs on our results.

In conclusion, this population-based study showed that variants of the *LDLR*, *APOB*, *ABCB11*, *LPL*, and *APOE* genes are associated with serum lipid levels in a healthy middle-aged and elderly Chinese population. In this Chinese population we identified new SNPs within genes previously associated with lipid levels in Caucasians, and showed that these variants modified established associations between dietary factors and lipid levels, suggesting the importance of these genes in different ethnic populations. Our findings also provided insight into the mechanisms by which these variants may be linked with chronic diseases, such as cancer. Future studies with a more comprehensive coverage of these genes are needed in different ethnic populations to provide further insight into the effect of these genes on serum lipid levels and other diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by the Intramural Research Program of the NIH, National Cancer Institute; National Center on Minority Health, NIH; and Center to Reduce Cancer Disparities, NCI, NIH.

References

1. Trayhurn P, Beattie JH. Physiological role of adipose tissue: white adipose tissue as an endocrine and secretory organ. *Proc Nutr Soc* 2001;60:329–39. [PubMed: 11681807]
2. Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 1986;256:2823–8. [PubMed: 3773199]
3. Wuermli L, Joerger M, Henz S, et al. Hypertriglyceridemia as a possible risk factor for prostate cancer. *Prostate Cancer Prostatic Dis* 2005;8:316–20. [PubMed: 16158078]
4. Ruixing Y, Fengping H, Shangling P, et al. Prevalence of hyperlipidemia and its risk factors for the middle-aged and elderly in the Guangxi Hei Yi Zhuang and Han populations. *J Investig Med* 2006;54:191–200.
5. Andreotti G, Chen J, Gao YT, et al. Serum lipid levels and the risk of biliary tract cancers and biliary stones: A population-based study in China. *Int J Cancer* 2008;122:2322–9. [PubMed: 18076041]
6. Heller DA, de Faire U, Pedersen NL, Dahlén G, McClearn GE. Genetic and environmental influences on serum lipid levels in twins. *N Engl J Med* 1993;328:1150–6. [PubMed: 8455681]
7. Report of the National Cholesterol Education Program expert panel on detection, evaluation and treatment of high blood cholesterol in adults. *Arch Intern Med* 1988;148:36–69. [PubMed: 3422148]
8. Kathiresan S, Melander O, Guiducci C, et al. Six new loci associated with blood low-density lipoprotein cholesterol, high-density lipoprotein cholesterol or triglycerides in humans. *Nat Genet* 2008;40:189–97. [PubMed: 18193044]
9. Willer CJ, Sanna S, Jackson AU, et al. Newly identified loci that influence lipid concentrations and risk of coronary artery disease. *Nat Genet* 2008;40:161–9. [PubMed: 18193043]
10. Sandhu MS, Waterworth DM, Debenham SL, et al. LDL-cholesterol concentrations: a genome-wide association study. *Lancet* 2008;371:483–91. [PubMed: 18262040]
11. Linsel-Nitschke P, Götz A, Erdmann J, et al. Lifelong reduction of LDL-cholesterol related to a common variant in the LDL-receptor gene decreases the risk of coronary artery disease—a Mendelian Randomisation study. *PLoS ONE* 2008;3:e2986. [PubMed: 18714375]
12. Humphries SE, Kessling AM, Horsthemke B, et al. A common DNA polymorphism of the low-density lipoprotein (LDL) receptor gene and its use in diagnosis. *Lancet* 1985;1:1003–5. [PubMed: 2859461]
13. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. *Science* 1986;232:34–47. [PubMed: 3513311]

14. Lopez-Miranda J, Ordovas JM, Ostos MA, et al. Dietary fat clearance in normal subjects is modulated by genetic variation at the apolipoprotein B gene locus. *Arterioscler Thromb Vasc Biol* 1997;17:1765–73. [PubMed: 9327775]
15. Pablos-Méndez A, Mayeux R, Ngai C, Shea S, Berglund L. Association of apo E polymorphism with plasma lipid levels in a multiethnic elderly population. *Arterioscler Thromb Vasc Biol* 1997 Dec;17(12):3534–41. [PubMed: 9437203]
16. Aalto-Setälä K, Palomaki H, Miettinen H, et al. Genetic risk factors and ischaemic cerebrovascular disease: role of common variation of the genes encoding apolipoproteins and angiotensin-converting enzyme. *Ann Med* 1998;30:224–33. [PubMed: 9667803]
17. Boekholdt SM, Peters RJ, Fountoulaki K, Kastelein JJ, Sijbrands EJ. Molecular variation at the apolipoprotein B gene locus in relation to lipids and cardiovascular disease: a systematic meta-analysis. *Hum Genet* 2003;113:417–25. [PubMed: 12942366]
18. Liao YC, Lin HF, Rundek T, et al. Multiple genetic determinants of plasma lipid levels in Caribbean Hispanics. *Clin Biochem* 2008;41:306–12. [PubMed: 18078817]
19. Andreotti G, Chen J, Gao YT, et al. Polymorphisms of genes in the lipid metabolism pathway and risk of biliary tract cancers and stones: a population-based case-control study in Shanghai, China. *Cancer Epidemiol Biomarkers Prev* 2008;17:525–34. [PubMed: 18296645]
20. Licastro F, Porcellini E, Caruso C, Lio D, Corder EH. Genetic risk profiles for Alzheimer's disease: integration of APOE genotype and variants that up-regulate inflammation. *Neurobiol Aging* 2007;28:1637–43. [PubMed: 16930778]
21. Hsing AW, Bai Y, Andreotti G, et al. Family history of gallstones and the risk of biliary tract cancer and gallstones: A population-based study in Shanghai, China. *Int J Cancer* 2007;121:832–8. [PubMed: 17450525]
22. Hsing AW, Gao YT, McGlynn KA, et al. Biliary tract cancer and stones in relation to chronic liver conditions: A population-based study in Shanghai, China. *Int J Cancer* 2007;120:1981–5. [PubMed: 17278101]
23. Sakoda LC, Gao YT, Chen BE, et al. Prostaglandin-endoperoxide synthase 2 (PTGS2) gene polymorphisms and risk of biliary tract cancer and gallstones: a population-based study in Shanghai, China. *Carcinogenesis* 2006;27:1251–6. [PubMed: 16361272]
24. Smith L, Lucas D, Lehnus G. Automated measurement of total cholesterol and triglycerides, in “tandem,” on the discrete sample analyzer, Gilford System 3500. *Clin Chem* 1979;25:439–42. [PubMed: 262187]
25. National Institutes of Health, National Heart, Lung, and Blood Institute. National Cholesterol Education Program, Recommendations on Lipoprotein Measurement From the Working Group on Lipoprotein Measurement. U.S.A.: Sep. 1995 p. 103 NIH Publication No. 95-3044
26. Labeur C, Shepherd J, Rosseneu M. Immunological assays of apolipoproteins in plasma: methods and instrumentation. *Clin Chem* 1990;36:591–7. [PubMed: 2182220]
27. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499–502. [PubMed: 4337382]
28. Rifai N, Warnick GR, McNamara JR, Belcher JD, Grinstead GF, Frantz ID Jr. Measurement of low-density-lipoprotein cholesterol in serum: a status report. *Clin Chem* 1992;38:150–60. [PubMed: 1733589]
29. Packer BR, Yeager M, Burdett L, et al. SNP500Cancer: a public resource for sequence validation, assay development, and frequency analysis for genetic variation in candidate genes. *Nucleic Acids Res* 2006;34(Database issue):D617–21. [PubMed: 16381944]
30. Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. *Bioinformatics* 2005;21:263–5. [PubMed: 15297300]
31. Stephens M, Donnelly P. A comparison of Bayesian methods for haplotype reconstruction. *American Journal of Human Genetics* 2003;73:1162–9. [PubMed: 14574645]
32. Stephens M, Smith NJ, Donnelly P. A new statistical method for haplotypes reconstruction from population data. *American Journal of Human Genetics* 2003;68:978–9. [PubMed: 11254454]
33. The International HapMap Consortium. The International HapMap Project. *Nature* 2003;426:789–96. [PubMed: 14685227]

34. Davis CL, Wang X, Snieder H, Treiber FA. Genetic and environmental determinants of lipid profile in black and white youth: a study of four candidate genes. *Ethn Dis* 2005;15:568–77. [PubMed: 16259478]
35. Espirito Santo SM, Rensen PC, Goudriaan JR, et al. Triglyceride-rich lipoprotein metabolism in unique VLDL receptor, LDL receptor, and LRP triple-deficient mice. *J Lipid Res* 2005;46:1097–102. [PubMed: 15772433]
36. Tacke PJ, Teusink B, Jong MC, et al. LDL receptor deficiency unmasks altered VLDL triglyceride metabolism in VLDL receptor transgenic and knockout mice. *J Lipid Res* 2000;41:2055–62. [PubMed: 11108739]
37. Brown MS, Goldstein JL. How LDL receptors influence cholesterol and atherosclerosis. *Sci Am* 1984;251:58–66. [PubMed: 6390676]
38. Pallaud C, Gueguen R, Sass C, et al. Genetic influences on lipid metabolism trait variability within the Stanislas Cohort. *J Lipid Res* 2001;42:1879–90. [PubMed: 11714857]
39. Boland LL, Folsom AR, Boerwinkle E. Apolipoprotein E genotype and gallbladder disease risk in a large population-based cohort. *Ann Epidemiol* 2006;16:763–9. [PubMed: 16882462]
40. Kullak-Ublick GA, Stieger B, Meier PJ. Enterohepatic bile salt transporters in normal physiology and liver disease. *Gastroenterology* 2004;126:322–42. [PubMed: 14699511]
41. Strautnieks SS, Bull LN, Knisely AS, et al. A gene encoding a liver-specific ABC transporter is mutated in progressive familial intrahepatic cholestasis. *Nat Genet* 1998;20:233–8. [PubMed: 9806540]
42. Noe J, Kullak-Ublick GA, Jochum W, et al. Impaired expression and function of the bile salt export pump due to three novel ABCB11 mutations in intrahepatic cholestasis. *J Hepatol* 2005;43:536–43. [PubMed: 16039748]
43. Staels B, Kuipers F. Bile acid sequestrants and the treatment of type 2 diabetes mellitus. *Drugs* 2007;67:1383–92. [PubMed: 17600387]
44. Chen WM, Erdos MR, Jackson AU, et al. Variations in the G6PC2/ABCB11 genomic region are associated with fasting glucose levels. *J Clin Invest* 2008;118:2620–8. [PubMed: 18521185]
45. Heizmann C, Kirchgessner T, Kwiterovich PO, et al. DNA polymorphism haplotypes of the human lipoprotein lipase gene: possible association with high density lipoprotein levels. *Hum Genet* 1991;86:578–84. [PubMed: 1673959]
46. Merkel M, Eckel RH, Goldberg IJ. Lipoprotein lipase: genetics, lipid uptake, and regulation. *J Lipid Res* 2002;43:1997–2006. [PubMed: 12454259]
47. Emi M, Hata A, Robertson M, Iverius PH, Hegele R, Lalouel JM. Lipoprotein lipase deficiency resulting from a nonsense mutation in exon 3 of the lipoprotein lipase gene. *Am J Hum Genet* 1990;47:107–11. [PubMed: 2349938]
48. Minnich A, Kessling A, Roy M, et al. Prevalence of alleles encoding defective lipoprotein lipase in hypertriglyceridemic patients of French Canadian descent. *J Lipid Res* 1995;36:117–24. [PubMed: 7706936]
49. Tsutsumi K, Inoue Y, Shima A, Iwasaki K, Kawamura M, Murase T. The novel compound NO-1886 increases lipoprotein lipase activity with resulting elevation of high density lipoprotein cholesterol, and long-term administration inhibits atherogenesis in the coronary arteries of rats with experimental atherosclerosis. *J Clin Invest* 1993;92:411–7. [PubMed: 8326009]
50. Yin W, Tsutsumi K. Lipoprotein lipase activator NO-1886. *Cardiovasc Drug Rev* 2003;21:133–42. [PubMed: 12847564]
51. Yeh YY, Liu L. Cholesterol-lowering effect of garlic extracts and organosulfur compounds: human and animal studies. *J Nut* 2001;131:989S–93S.
52. Qureshi AA, Abuirmeileh N, Din ZZ, Elson CE, Burger WC. Inhibition of cholesterol and fatty acid biosynthesis in liver enzymes and chicken hepatocytes by polar fractions of garlic. *Lipids* 1983;18:343–8. [PubMed: 6877039]
53. Yeh YY, Yeh SM. Garlic reduces plasma lipids by inhibiting hepatic cholesterol and triacylglycerol synthesis. *Lipids* 1994;29:189–93. [PubMed: 8170288]
54. Steinmetz KA, Kushi LH, Bostick RM, Folsom AR, Potter JD. Vegetables, fruit, and colon cancer in the Iowa Women's Health Study. *Am J Epidemiol* 1994;139:1–15. [PubMed: 8296768]

55. Le Marchand L, Hankin JH, Wilkens LR, Kolonel LN, Englyst HN, Lyu LC. Dietary fiber and colorectal cancer risk. *Epidemiology* 1997;8:658–65. [PubMed: 9345666]
56. Chasman DI, Kozlowski P, Zee RY, Kwiatkowski DJ, Ridker PM. Qualitative and quantitative effects of APOE genetic variation on plasma C-reactive protein, LDL-cholesterol, and apoE protein. *Genes Immun* 2006;7:211–19. [PubMed: 16511556]
57. Weisgraber KH, Innerarity TL, Mahley RW. Abnormal lipoprotein receptor-binding activity of the human E apoprotein due to cysteine-arginine interchange at a single site. *J Biol Chem* 1982;257:2518–21. [PubMed: 6277903]
58. Kowal RC, Herz J, Weisgraber KH, Mahley RW, Brown MS, Goldstein JL. Opposing effects of apolipoproteins E and C on lipoprotein binding to low density lipoprotein receptor-related protein. *J Biol Chem* 1990;265:10771–9. [PubMed: 2355022]

Figure 1. Associations between 21 SNPs in genes in the lipid metabolism pathway and serum lipid levels. Black dashed line indicates a $p\text{-trend} = 0.05$, and the red dashed line indicates $p = 0.05$ after Bonferroni correction for the 21 SNPs examined

Table 1
Mean Serum Lipid Levels in relation to Selected Characteristics

Serum Lipids													
Selected Characteristics	N	Total Cholesterol (mg/dl)		Triglyceride (mg/dl)		HDL (mg/dl)		LDL (mg/dl)		Apo A (mg/dl)		Apo B (mg/dl)	
		Mean ¹	(SE) ¹	Mean ¹	(SE) ¹	Mean ¹	(SE) ¹	Mean ¹	(SE) ¹	Mean ¹	(SE) ¹	Mean ¹	(SE) ¹
All Subjects	779	183.1	(1.7)	109.6	(2.5)	46.3	(0.6)	108.9	(1.6)	113.9	(0.8)	86.1	(0.9)
Gender													
Male	302	176.2	(2.5)	107.8	(3.6)	43.6	(0.9)	104.2	(2.5)	111.2	(1.3)	84.3	(1.3)
Female	477	190.2	(2.2)	111.5	(3.3)	49.0	(0.8)	114.0	(2.1)	116.4	(1.1)	87.9	(1.2)
<i>p</i> ²		<.0001		0.46		<.0001		0.003		0.001		0.04	
Age at interview (yrs)													
34-54	105	175.8	(3.8)	104.1	(5.3)	46.0	(1.3)	103.1	(3.7)	114.0	(1.9)	83.6	(2.0)
55-64	222	189.2	(2.7)	110.1	(4.0)	46.5	(0.9)	115.6	(2.6)	114.7	(1.3)	89.0	(1.4)
65-75	452	184.7	(1.9)	115.0	(2.9)	46.4	(0.7)	108.6	(1.8)	113.3	(0.9)	85.8	(0.9)
<i>P trend</i> ³			0.11		0.02		0.98		0.62		0.57		0.69
Ever Smoked Cigarettes ⁴													
No	545	183.3	(2.4)	107.2	(3.4)	46.9	(0.8)	110.8	(2.4)	114.8	(1.2)	85.7	(1.3)
Yes	234	182.4	(3.8)	120.4	(6.1)	43.9	(1.3)	106.0	(3.7)	115.1	(1.9)	86.9	(2.0)
<i>p</i> ²			0.85		0.05		0.06		0.28		0.90		0.62
Ever Drank Alcohol													
No	620	182.8	(2.0)	110.0	(3.0)	45.8	(0.7)	109.8	(2.0)	113.5	(1.0)	86.4	(1.1)
Yes	159	179.0	(4.7)	99.3	(6.2)	48.2	(1.6)	104.5	(4.6)	112.6	(2.3)	82.9	(2.5)
<i>p</i> ²			0.47		0.14		0.18		0.29		0.72		0.19
Body Mass Index ⁵ (kg/m ²)													
<18.5	66	182.3	(5.8)	79.9	(6.0)	51.8	(2.0)	108.5	(5.6)	113.2	(2.9)	79.7	(3.0)
18.5-22.9	313	185.6	(2.5)	105.4	(3.4)	48.2	(0.8)	110.5	(2.4)	115.3	(1.2)	86.3	(1.3)
23.0-24.9	163	180.2	(3.6)	116.8	(5.5)	45.2	(1.2)	105.7	(3.5)	111.4	(1.8)	84.8	(1.9)
25.0-29.9	204	182.0	(3.8)	122.5	(6.0)	41.9	(1.3)	111.1	(3.6)	113.5	(1.9)	88.1	(2.0)
≥30	33	186.2	(12.3)	113.8	(18.3)	42.6	(4.2)	119.2	(12.0)	116.3	(6.2)	84.0	(6.5)

Serum Lipids												
Selected Characteristics	Total Cholesterol (mg/dl)		Triglyceride (mg/dl)		HDL (mg/dl)		LDL (mg/dl)		Apo A (mg/dl)		Apo B (mg/dl)	
	N	Mean ^I (SE) ^I	Mean ^I (SE) ^I	Mean ^I (SE) ^I	Mean ^I (SE) ^I	Mean ^I (SE) ^I	Mean ^I (SE) ^I	Mean ^I (SE) ^I	Mean ^I (SE) ^I	Mean ^I (SE) ^I	Mean ^I (SE) ^I	
<i>P trend</i> ³												
Waist to Hip Ratio ⁶												
<0.80	145	181.3 (4.4)	84.5 (4.8)	51.8 (1.5)	108.8 (4.3)	114.9 (2.2)	80.4 (2.3)					
0.80-0.83	134	181.2 (4.0)	100.6 (5.2)	47.8 (1.4)	105.5 (3.9)	115.2 (2.0)	84.0 (2.1)					
0.84-0.87	175	184.4 (3.7)	114.1 (5.5)	46.9 (1.3)	110.2 (3.6)	112.8 (1.8)	85.4 (1.9)					
0.88-0.91	176	184.7 (3.6)	123.6 (5.8)	44.5 (1.2)	109.4 (3.6)	112.9 (1.8)	88.3 (1.9)					
≥0.92	149	187.3 (4.4)	126.4 (7.2)	42.5 (1.5)	113.6 (4.3)	116.8 (2.2)	92.5 (2.3)					
<i>P trend</i> ³												
Hypertension												
No	444	181.1 (2.0)	102.7 (2.7)	47.5 (0.7)	108.0 (2.0)	113.8 (1.0)	84.6 (1.1)					
Yes	335	187.3 (3.3)	117.0 (5.0)	45.1 (1.1)	111.0 (3.2)	113.0 (1.6)	86.5 (1.37)					
<i>p</i> ²		0.11	0.01	0.07	0.44		0.67		0.35			
Diabetes												
No	714	183.4 (1.7)	108.0 (2.5)	46.4 (0.6)	109.4 (1.7)	114.1 (0.9)	85.5 (0.9)					
Yes	65	174.0 (8.8)	143.1 (16.8)	46.6 (3.1)	96.6 (9.9)	113.0 (4.4)	99.1 (4.6)					
<i>p</i> ²		0.30	0.02	0.95	0.20		0.80		0.004			
Gallstones												
No	586	184.0 (1.8)	107.2 (2.6)	46.9 (0.6)	110.0 (1.8)	114.0 (0.9)	85.9 (0.9)					
Yes	193	183.7 (4.8)	128.0 (8.1)	43.8 (1.7)	106.0 (4.7)	114.4 (2.4)	88.1 (2.5)					
<i>p</i> ²		0.96	0.01	0.09	0.42		0.88		0.42			
Total Calories (kcal/day)												
0-1,796	194	181.1 (4.2)	106.5 (6.0)	47.18 (1.47)	106.7 (4.10)	114.8 (2.1)	86.1 (2.2)					
1,797-2,133	194	183.0 (3.3)	106.9 (4.7)	49.11 (1.16)	108.4 (3.25)	114.7 (1.6)	84.8 (1.7)					
2,134-2,584	193	182.4 (3.5)	116.4 (5.4)	44.56 (1.22)	109.9 (3.40)	114.0 (1.7)	88.3 (1.8)					
≥ 2,585	194	185.7 (3.3)	108.7 (4.8)	45.74 (1.16)	110.5 (3.22)	113.8 (1.6)	85.6 (1.7)					
<i>P trend</i> ³												
Total Fats (g/day)												

Serum Lipids

Selected Characteristics		Total Cholesterol (mg/dl)		Triglyceride (mg/dl)		HDL (mg/dl)		LDL (mg/dl)		Apo A (mg/dl)		Apo B (mg/dl)		
		N	Mean ^I (SE) ^I	Mean ^I (SE) ^I	Mean ^I (SE) ^I	Mean ^I (SE) ^I	Mean ^I (SE) ^I	Mean ^I (SE) ^I	Mean ^I (SE) ^I	Mean ^I (SE) ^I	Mean ^I (SE) ^I			
Animal products (g/day)														
0-22 23-29 30-34 ≥ 35	P trend ³	193	182.9	3.6	111.3	5.3	44.1	1.3	107.3	3.5	113.6	1.8	87.0	1.9
		194	188.6	3.4	115.3	5.2	46.9	1.2	114.5	3.3	115.7	1.7	87.2	1.8
		194	183.2	3.4	111.2	5.1	48.3	1.2	106.2	3.3	113.2	1.7	87.1	1.8
		194	177.6	3.2	111.7	4.4	46.8	1.1	107.4	3.2	112.6	1.6	87.8	1.7
		0.07		0.42		0.15		0.69		0.21		0.92		
Red Meat (g/day)														
0-16 17-29 30-52 ≥ 53	P trend ³	195	179.1	4.1	99.0	5.4	46.5	1.4	107.3	4.0	109.0	2.0	82.7	2.2
		191	181.7	3.5	118.5	5.6	45.6	1.2	106.8	3.4	113.6	1.8	84.3	1.9
		195	183.1	3.2	111.4	4.8	45.1	1.1	111.1	3.2	115.0	1.6	88.6	1.7
		194	187.5	3.1	108.4	4.4	49.4	1.1	110.1	3.0	116.7	1.5	87.5	1.6
		0.04		0.46		0.02		0.37		0.04		0.04		
Dairy products (g/day)														
0-67 68-123 124-256 ≥ 257	P trend ³	192	182.1	4.6	106.7	6.5	46.5	1.6	106.6	4.5	114.0	2.3	85.4	2.4
		195	184.3	3.8	106.9	5.4	48.6	1.3	111.0	3.7	112.5	1.9	88.0	2.0
		199	177.4	3.1	111.4	4.7	45.5	1.1	103.8	3.0	113.2	1.6	84.7	1.7
		189	187.9	3.1	108.7	4.5	45.7	1.1	114.6	3.0	115.9	1.5	86.5	1.6
		0.91		0.69		0.49		0.66		0.46		0.94		
All vegetables (g/day)														
0-476 477-716 717-1040	P trend ³	195	179.3	4.5	106.4	6.4	45.7	1.6	107.8	4.4	112.4	2.2	83.7	2.4
		192	181.0	3.1	108.6	4.6	45.6	1.1	108.9	3.1	112.0	1.6	85.6	1.7
		196	182.8	3.2	113.9	4.9	46.3	1.1	109.1	3.1	114.7	1.6	85.4	1.7
		192	188.4	3.3	108.5	4.7	49.1	1.1	109.9	3.2	116.4	1.6	89.2	1.7
		0.03		0.64		0.02		0.82		0.20		0.03		
All vegetables (g/day)														
0-476 477-716 717-1040		194	182.7	3.6	107.2	5.2	46.2	1.3	109.0	3.5	114.8	1.8	82.0	1.9
		192	179.4	3.3	109.1	4.8	47.5	1.2	106.1	3.2	113.8	1.6	86.6	1.7
		196	184.2	3.3	111.4	4.9	46.6	1.2	109.9	3.2	113.2	1.6	87.6	1.7

Serum Lipids														
Selected Characteristics		Total Cholesterol (mg/dl)		Triglyceride (mg/dl)		HDL (mg/dl)		LDL (mg/dl)		Apo A (mg/dl)		Apo B (mg/dl)		
		N	Mean ^I (SE) ^I	Mean ^I (SE) ^I	Mean ^I (SE) ^I	Mean ^I (SE) ^I	Mean ^I (SE) ^I	Mean ^I (SE) ^I	Mean ^I (SE) ^I	Mean ^I (SE) ^I	Mean ^I (SE) ^I			
≥ 1041		193	184.8	3.4	109.1	4.9	45.7	1.2	109.8	3.3	113.8	1.7	87.5	1.8
<i>P trend</i> ³				0.28		0.57		0.42		0.12		0.51		0.42
Allium vegetables (g/day)														
0-4		178	183.0	3.7	105.5	5.3	47.2	1.3	107.3	3.6	112.3	1.9	85.2	2.0
5-9		227	185.8	3.2	113.3	4.8	45.7	1.1	114.1	3.1	115.4	1.6	86.0	1.7
10-17		174	180.5	3.6	111.2	5.4	45.9	1.3	107.2	3.5	113.7	1.8	84.4	1.9
≥ 18		196	182.2	3.2	109.0	4.6	47.4	1.1	105.8	3.1	114.1	1.6	87.8	1.7
<i>P trend</i> ³				0.74		0.17		0.41		0.74		0.09		0.61
All fruits (g/day)														
0-313		193	186.8	4.0	111.0	5.9	46.5	1.4	112.6	3.9	111.7	2.0	84.3	2.1
314-655		195	179.5	3.5	105.9	5.0	47.5	1.2	105.4	3.4	114.2	1.8	84.8	1.9
656-1136		194	183.3	3.3	112.0	4.9	47.1	1.2	109.3	3.2	114.7	1.6	88.2	1.7
≥ 1137		193	185.7	3.2	111.6	4.8	44.9	1.1	111.7	3.1	114.0	1.6	86.8	1.7
<i>P trend</i> ³				0.05		0.74		0.90		0.54		0.52		0.05

¹ Adjusted for age and gender

² Least squares mean test for the difference in mean lipid levels between dichotomous characteristics

³ Linear test of trend for ordinal characteristics

⁴ Ever smoke cigarettes for at least 6 consecutive months

⁵ Body mass index = weight/(height²); distribution based on WHO classification for obesity among Asians

⁶ Cutoffs for waist and hip circumference, and waist-to-hip-ratio based on quintiles among population controls

Table 2
Mean Serum Lipid Levels of Variants of Genes in the Lipid Metabolism Pathway

Serum Lipids													
Genotype	N	Total Cholesterol (mg/dl)		Triglycerides (mg/dl)		HDL (mg/dl)		LDL (mg/dl)		Apo A (mg/dl)		Apo B (mg/dl)	
		Mean ^I	(SE) ^I	Mean ^I	(SE) ^I	Mean ^I	(SE) ^I	Mean ^I	(SE) ^I	Mean ^I	(SE) ^I	Mean ^I	(SE) ^I
LDLR													
IVS9-30C>T(rs1003723)													
CC	565	176.8	1.8	108.2	2.8	46.6	0.7	107.1	1.9	114.3	1.0	85.5	1.0
TC	199	185.3	3.4	113.3	5.3	46.4	1.2	114.2	3.4	113.1	1.8	87.5	1.9
TT	14	185.3	15.4	107.0	22.6	45.9	5.6	114.9	15.4	113.3	7.9	76.7	8.3
p ²			0.002		0.87		0.54		0.01		0.56		0.18
TC+TT	213	186.0	3.3	113.1	5.2	46.5	1.2	114.6	3.3	113.0	1.7	87.3	1.8
p ³			0.02		0.41		0.97		0.05		0.53		0.39
IVS17-42A>G (rs6413504)													
AA	411	177.1	2.1	108.5	3.3	47.1	0.8	106.8	2.2	114.5	1.1	85.5	1.2
GA	291	180.8	2.7	113.8	4.3	45.9	1.0	110.4	2.7	113.7	1.4	87.0	1.5
GG	67	187.9	6.3	102.1	8.7	48.4	2.3	116.7	6.2	111.2	3.2	84.6	3.4
p ²			0.05		0.78		0.74		0.07		0.93		0.39
GA+GG	358	181.6	2.4	111.7	3.8	46.3	0.9	111.0	2.5	113.3	1.3	86.5	1.3
p ³			0.16		0.52		0.50		0.20		0.48		0.59
APOB													
EX4+56C>T (rs1367117)													
CC	564	177.4	1.9	105.6	2.8	46.8	0.7	106.8	2.0	113.8	1.0	85.0	1.1
TC	192	183.3	3.2	119.1	5.2	46.1	1.2	115.0	3.2	113.7	1.6	89.2	1.7
TT	10	198.7	28.3	83.1	29.7	53.6	9.5	137.2	26.3	109.7	13.4	89.4	14.1
p ²			0.10		0.08		0.71		0.13		0.74		0.02
TC+TT	202	184.1	3.1	119.6	5.1	46.2	1.1	115.5	3.2	113.9	1.6	89.3	1.7
p ³			0.07		0.01		0.66		0.02		0.96		0.03
ABCB11													

Serum Lipids													
Genotype	N	Total Cholesterol (mg/dl)		Triglycerides (mg/dl)		HDL (mg/dl)		LDL (mg/dl)		Apo A (mg/dl)		Apo B (mg/dl)	
		Mean ¹	(SE) ¹	Mean ¹	(SE) ¹	Mean ¹	(SE) ¹	Mean ¹	(SE) ¹	Mean ¹	(SE) ¹	Mean ¹	(SE) ¹
Ex28-264A>G (rs49550)													
AA	287	171.9	2.5	99.6	3.7	47.0	1.0	103.3	2.7	110.2	1.4	83.9	1.5
AG	349	181.5	2.4	114.5	3.9	45.5	0.9	112.4	2.5	116.1	1.3	87.2	1.3
GG	121	192.6	4.4	118.7	6.9	49.3	1.5	112.9	4.2	116.7	2.2	88.6	2.3
<i>p</i> ²			0.01		0.01		0.43		0.58		0.01		0.42
AG+GG	470	184.1	2.1	115.4	3.3	46.6	0.8	112.5	2.1	116.2	1.1	87.3	1.2
<i>p</i> ³			0.0002		0.002		0.74		0.01		0.001		0.07

¹ Adjusted for age group, gender

² Test of trend

³ Least squares mean test for difference in mean lipid levels between the absence and presence of the variant allele

Table 3
Mean Serum Lipid Levels in relation to Variants of Genes in the Lipid Metabolism Pathway and Food Groups

LDLR	Triglycerides (mg/dl)				
	Dairy products				
	0-123 g/day		≥ 124 g/day		
	N	Mean ^I (SE) ^I	N	Mean ^I (SE) ^I	(SE) ^I
IVS17-42A>G (rs6413504)					
AA	199	125.0 (12.8)	210	108.9 (7.2)	
GA	146	158.9 (21.1)	143	127.8 (10.9)	
GG	38	88.8 (18.5)	29	198.6 (46.2)	
GA+GG	184	133.2 (14.4)	172	137.5 (10.8)	
<i>p</i> ²				0.66	0.03
<i>P</i> interaction					0.05

LPL	Triglycerides (mg/dl)				
	Allium Vegetables				
	< 10 g/day		≥ 10 g/day		
	N	Mean ^I (SE) ^I	N	Mean ^I (SE) ^I	(SE) ^I
IVS5-540C>T (rs263)					
CC	262	120.5 (10.1)	221	136.8 (9.4)	
TC	127	118.4 (13.7)	126	101.5 (10.2)	
TT	13	110.6 (61.6)	22	60.8 (32.7)	
TC+TT	140	118.4 (12.6)	148	99.3 (9.2)	
<i>p</i> ²				0.96	0.01
<i>P</i> interaction					0.04

Total cholesterol (mg/dl)						
APOE	Red Meat					
	0-29 g/day			≥ 30 g/day		
	N	Mean ^I	(SE) ^I	N	Mean ^I	(SE) ^I
	IVS1+69C>G (rs440446)					
CC	156	179.3	(8.6)	161	192.9	(7.0)
GC	170	183.3	(7.0)	184	175.7	(6.4)
GG	56	169.5	(20.0)	39	176.9	(15.2)
GC+GG	226	178.4	(6.3)	223	174.5	(5.8)
<i>p</i> ²				0.94	0.05	
<i>P interaction</i>						
0.02						
LDL (mg/dl)						
APOE	Red Meat					
	0-29 g/day			≥ 30 g/day		
	N	Mean ^I	(SE) ^I	N	Mean ^I	(SE) ^I
	IVS1+69C>G (rs440446)					
CC	156	105.2	(8.7)	161	114.7	(6.7)
GC	170	99.8	(7.2)	184	97.5	(6.1)
GG	56	104.0	(20.1)	39	103.1	(14.5)
GC+GG	226	99.1	(6.5)	223	96.5	(5.5)
<i>p</i> ²				0.57	0.04	
<i>P interaction</i>						
0.02						

^I Adjusted for age group, gender, body mass index, waist-hip-ratio, hypertension, diabetes, gallstones, cigarette smoking, alcohol drinking, and total calories per day

² Least squares mean test for difference in mean lipid levels between the absence and presence of the variant allele