## Materials and Methods

### ApoE genotyping

*APOE* genotypes were measured in 431,239 patients who had concomitant Lp(a) mass levels, LDL-C, apoB, triglyceride and HDL-C levels. *APOE* genotypes were measured at the Health Diagnostic Laboratory using methods as previously described.[1-3]

### Lipid and Lipoprotein Measurements

Fasting blood was drawn and serum and EDTA-anticoagulant tubes were collected and stored at -70$^{o}$C, using a standardized protocol.[4] LDL-C and HDL-C were measured using direct enzymatic assays (Beckman-Coulter Biomedical Ltd, Co Clare, Ireland), and fasting triglycerides were measured using a standard enzymatic method (Roche Diagnostics, Indianapolis, IN). Cholesterol within small dense LDL (15.0 nm-20.0 nm) was measured using an automated homogenous assay (Denka Seiken Co., Ltd., 3-4-2 Nihonbashi-Kayabacho, Chuo-Ku, Tokyo) and analyzed on a Roche/Hitachi Modular P Chemistry Analyzer, coefficient of variance of 3.2%.[4] Additionally, lipoprotein particle number (VLDL, LDL, HDL) was measured at LipoScience (Raleigh, NC) by nuclear magnetic resonance spectroscopy using the LipoProfile-3 algorithm.[4] Lp(a)-cholesterol [Lp(a)-C] was measured as previously described.[5] For Lp(a)-C measurements, plasma was available in 147,970, for small dense LDL in 420,724 and for hsCRP in 403,457 individuals. LDL-C corrected for the content of Lp(a) cholesterol (LDL-C corr), which constitutes approximately 30% of Lp(a) mass, was calculated as previously described.[6]
Plasma levels of apoE protein were not available in this dataset. Additionally, since this is a dataset from a referral laboratory, clinical variables and lipid treatment variables were not available.

### Statistical Analysis

Variables are presented as mean (standard deviation) or median (interquartile range) if not normally distributed. Analysis of variance was used to determine differences in lipid, lipoprotein and laboratory variables. We also examined the relationship of *APOE* isoforms in patients with LDL-C ≥190 mg/dl and ≥250 mg/dL on Lp(a) levels to derive insights into possible relationship of the LDL receptor (LDLR) in patients that are more likely to have LDLR deficiency. We additionally examined the relationship of ε2/ε2 isoforms in patients with dysbetalipoproteinemia, using triglyceride cutoffs of >150, >200 and >500 mg/dL on Lp(a) levels
A $p<0.05$ was considered significant. Correlations between variables were determined by Spearman's rho. Analyses were performed with SPSS version 24.

References


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