JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 68, NO. 25, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.10.033

Phenotypic Characterization of Genetically Lowered Human Lipoprotein(a) Levels

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ABSTRACT

BACKGROUND Genomic analyses have suggested that the *LPA* gene and its associated plasma biomarker, lipoprotein(a) (Lp[a]), represent a causal risk factor for coronary heart disease (CHD). As such, lowering Lp(a) levels has emerged as a therapeutic strategy. Beyond target identification, human genetics may contribute to the development of new therapies by defining the full spectrum of beneficial and adverse consequences and by developing a dose-response curve of target perturbation.

OBJECTIVES The goal of this study was to establish the full phenotypic impact of *LPA* gene variation and to estimate a dose-response curve between genetically altered plasma Lp(a) and risk for CHD.

METHODS We leveraged genetic variants at the *LPA* gene from 3 data sources: individual-level data from 112,338 participants in the U.K. Biobank; summary association results from large-scale genome-wide association studies; and *LPA* gene sequencing results from case subjects with CHD and control subjects free of CHD.

RESULTS One SD genetically lowered Lp(a) level was associated with a 29% lower risk of CHD (odds ratio [OR]: 0.71; 95% confidence interval [CI]: 0.69 to 0.73), a 31% lower risk of peripheral vascular disease (OR: 0.69; 95% CI: 0.59 to 0.80), a 13% lower risk of stroke (OR: 0.87; 95% CI: 0.79 to 0.96), a 17% lower risk of heart failure (OR: 0.83; 95% CI: 0.73 to 0.94), and a 37% lower risk of aortic stenosis (OR: 0.63; 95% CI: 0.47 to 0.83). We observed no association with 31 other disorders, including type 2 diabetes and cancer. Variants that led to gain of *LPA* gene function increased the risk for CHD, whereas those that led to loss of gene function reduced the CHD risk.

CONCLUSIONS Beyond CHD, genetically lowered Lp(a) levels are associated with a lower risk of peripheral vascular disease, stroke, heart failure, and aortic stenosis. As such, pharmacological lowering of plasma Lp(a) may influence a range of atherosclerosis-related diseases. (J Am Coll Cardiol 2016;68:2761–72) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CHD = coronary heart disease

CI = confidence interval

CKD = chronic kidney disease

DNA = deoxyribonucleic acid

eGFR = estimated glomerular filtration rate

GWAS = genome-wide association study

HDL = high-density lipoprotein

HF = heart failure

LDL = low-density lipoprotein

Lp(a) = lipoprotein(a)

OR = odds ratio

PVD = peripheral vascular disease

SNP = single nucleotide polymorphism

Lipoprotein(a) (Lp[a]) is a circulating lipoprotein in which the constituent apolipoprotein B on a low-density lipoprotein (LDL) particle is modified by the covalent addition of another protein, namely apolipoprotein(a) (1,2). Higher plasma Lp(a) levels are associated with an increased risk for incident coronary heart disease (CHD) (3), heritable, and largely determined by variation in the *LPA* gene, which encodes apolipoprotein(a) (2). Genetic variants in *LPA* that increase Lp(a) levels also increase CHD risk, suggesting that Lp(a) is a causal risk factor for development of CHD (4-6). Consequently, lowering Lp(a) levels has emerged as a therapeutic strategy to reduce the risk of CHD (2,7).

Beyond identifying a therapeutic target gene, human genetics may help estimate the probable efficacy and safety of pharmacological modulation (8). Although *LPA* variants have been consistently reported to be associated with CHD (5,6) and aortic valve stenosis (9,10), there is uncertainty around the full spectrum of phenotypic consequences. Previous studies have reported conflicting evidence on whether *LPA* variants are associated with other cardiovascular diseases, such as stroke (11,12). In addition, observational epidemiology has associated lower plasma levels of Lp(a) with increased risks of cancer (13) and diabetes (14).

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Deoxyribonucleic acid (DNA) sequence variants might also provide a mechanism to estimate a dose-response curve. In particular, the simultaneous identification of gain-of-function variants as well as loss-of-function variants and an analysis of phenotypic effects can reveal a dose-response curve even before a clinical trial is initiated.

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In the present study, we leveraged genetic variants across the allele frequency spectrum and 3 large data sources to evaluate the phenotypic consequences of genetically lowered Lp(a) levels. The effect of a genetically mediated 1 SD decrease in Lp(a) levels on cardiometabolic disease and range of other disorders was estimated.

METHODS

The overall study design is shown in **Figure 1**. Several data sources were leveraged to provide greater power for estimating the effect of genetically lowered Lp(a) level on cardiometabolic traits and outcomes, to conduct a phenome-wide association study, and to examine the effect of rare loss-of-function variants in the *LPA* gene on risk of CHD.

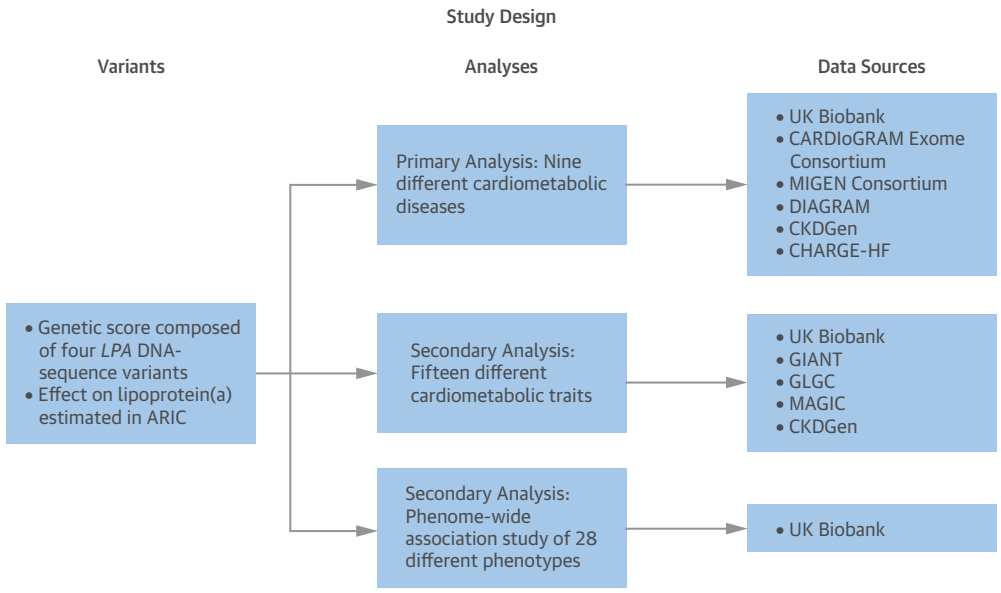
Individual-level data from 112,338 individuals of European ancestry from the U.K. Biobank, a large population-based cohort (Online Appendix), were used (15). Characteristics of individuals are provided in Online Table 1. These individual-level data were supplemented with summary results from 7 genome-wide association study (GWAS) consortia examining blood lipid levels, anthropometric traits, glycemic traits, diabetes, CHD, heart failure (HF), and renal dysfunction, all predominantly containing individuals of European descent (Online Appendix, **Table 1**) (16–23). Our estimates for CHD were derived from the CARDIoGRAM (Coronary Artery Disease Genome wide Replication and Meta-analysis) Exome Consortium analysis of up to 42,335 CHD case subjects and 78,240 control subjects. Finally, *LPA* gene sequences from 15,251 participants of European ancestry from the Myocardial Infarction Genetics (MIGen) Consortium were used.

In the primary analysis, we examined the effect of genetically lowered Lp(a) level on 9 different cardiometabolic diseases: CHD; stroke; HF; atrial fibrillation; aortic stenosis; peripheral vascular disease (PVD); venous thromboembolism; diabetes; and chronic kidney disease (CKD) (Online Table 2). We also examined the effect of genetically lowered Lp(a) level on 15 cardiometabolic quantitative traits (Online Appendix): waist-to-hip ratio; waist circumference; hip circumference; body mass index; systolic blood pressure; diastolic blood pressure; total cholesterol; LDL cholesterol; high-density lipoprotein (HDL) cholesterol; triglyceride levels; fasting glucose; fasting insulin; 2-h glucose; glycosylated hemoglobin; and serum creatinine-derived estimated glomerular filtration rate (eGFR). All traits were standardized (i.e., reported in units of SDs) to allow for comparisons among traits. Using the U.K. Biobank cohort, a phenome-wide association study was also conducted for 28 additional diseases, including endocrine, renal, urological, gastrointestinal, neurological, musculoskeletal, respiratory, and neoplastic disorders.

consulting fees from Merck and Amarin. Dr. Won was supported by Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Science, ICT & Future Planning (2016R1C1B2007920). Dr. Peloso is supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under award number K01HL125751. Dr. Stitziel has received funding from K08HL114642 and R01HL131961; has received a research grant from AstraZeneca; and has received consulting fees from Regeneron. Dr. Farrall has received the British Heart Foundation Centre of Research Excellence, Oxford (RE/13/1/30181), award; the Wellcome Trust core award (090532/Z/09/Z); and funding from the Wellcome Trust Institutional Support Scheme. Dr. Abecasis has served as a consultant for Regeneron. Dr. Rader has received consulting fees from Aegerion Pharmaceuticals, Alnylam Pharmaceuticals, Eli Lilly and Company, Pfizer, Sanofi, and Novartis; is an inventor on a patent related to lomitapide that is owned by the University of Pennsylvania and licensed to Aegerion Pharmaceuticals; and is a cofounder of Vascular Strategies and Staten Biotechnology. Dr. Danesh has served as a consultant for Takeda; has been a member of the Novartis Cardiovascular & Metabolic Advisory Board, the International Cardiovascular and Metabolism Research and Development portfolio committee for Novartis, the Merck Sharp & Dohme UK Atherosclerosis Advisory Board, the Pfizer Population Research Advisory Panel, and the Sanofi Advisory Board; and has received funding from the British Heart Foundation, the BUPA Foundation, diaDexus, European Research Council, the European Union, Evelyn Trust, Fogarty International Centre, GlaxoSmithKline, Merck, the National Heart, Lung, and Blood Institute, the National Health Service Blood and Transplant, the National Institute for Health Research, the National Institute of Neurological Disorders and Stroke, Novartis, Pfizer, Roche, Sanofi, Takeda, The Wellcome Trust, U.K. Biobank, the University of British Columbia, and the U.K. Medical Research Council. Dr. Ardissino has received speaker fees from AstraZeneca, Boehringer Ingelheim, Johnson & Johnson, Bayer, Daiichi-Sankyo, GlaxoSmithKline, Eli Lilly and Company, Boston Scientific, Bristol-Myers Squibb, Menarini Group, Novartis, and Sanofi; and research grants from GlaxoSmithKline, Eli Lilly and Company, Pfizer, and Novartis. Dr. Saleheen has received grants from Pfizer, Regeneron, and the National Institutes of Health. Dr. Kathiresan is supported by a research scholar award from the Massachusetts General Hospital, the Donovan Family Foundation, and R01 HL127564; has received grants from Bayer Healthcare, Aegerion Pharmaceuticals, and Regeneron Pharmaceuticals; has received consulting fees from Merck, Novartis, Sanofi, AstraZeneca, Alnylam Pharmaceuticals, Leerink Partners, Noble Insights, Quest Diagnostics, Genomics PLC, and Eli Lilly and Company; and holds equity in San Therapeutics and Catabasis Pharmaceuticals. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Emdin and Khera contributed equally to this work.

Manuscript received July 20, 2016; revised manuscript received September 21, 2016, accepted October 4, 2016.

FIGURE 1 Study Design



This study included 1 primary and 2 secondary analyses to estimate the effect of a lipoprotein(a) (Lp[a]) on a range of outcomes. ARIC = Atherosclerosis Risk in Communities; CARDIoGRAM = Coronary Artery Disease Genome-wide Replication and Meta-analysis; CHARGE-HF = Cohorts for Heart and Aging Research in Genomic Epidemiology-Heart Failure; CKDGen = Chronic Kidney Disease Genetics Consortium; DIAGRAM = Diabetes Genetics Replication and Meta-analysis; DNA = deoxyribonucleic acid; GIANT = Genetic Investigation of Anthropometric Traits; GLGC = Global Lipids Genetics Consortium; MAGIC = Meta-Analyses of Glucose and Insulin-related traits Consortium; MIGen = Myocardial Infarction Genetics.

DNA SEQUENCE VARIANTS. To estimate the effect of genetically lowered Lp(a) level on a wide range of phenotypes, individual-level data from U.K. Biobank were combined with summary-level data from large-scale GWAS. Four single nucleotide polymorphisms (SNPs) in the *LPA* gene were used that have been previously associated with plasma Lp(a) levels: rs10455872, rs3798220, rs41272114, and rs143431368 (Online Table 3). Together, rs10455872 and rs3798220 explain approximately 36% of variation in plasma Lp(a) levels (5); the other 2 (rs41272114 and rs143431368) are loss-of-function variants associated with lower Lp(a) levels.

To standardize the estimates to a 1 SD decrease in Lp(a) levels, estimates of the effect of each variant on Lp(a) levels from the ARIC (Atherosclerosis Risk In Communities) study were used (Online Table 3, Online Appendix). ARIC is a community-based study of 15,792 white and black participants, ages 45 to 64 years, who were first enrolled in 1987 (24). The analysis was restricted to 2,758 individuals of European ancestry in the ARIC cohort who had Lp(a) levels measured at the baseline visit by using a double-antibody enzyme-linked immunosorbent assay (25). Participants fasted for 12 to 24 h before blood collection. Plasma was separated from cells with centrifugation within 1 h of collection and stored at -70°C. Analyses were performed within 2 weeks. The assay was shown to have high internal reliability in a validation study in ARIC ($r = 0.90$) and in a separate comparison versus a newer assay calibrated by using International Federation of Clinical Chemistry reference material ($r = 0.88$) (26). Linear regression was used, adjusting for age, sex, and 5 principal components of ancestry, to estimate the association between each variant and Lp(a) level in an additive model. Because Lp(a) levels were non-normally distributed, log-transformed Lp(a) levels were used, as previously described (5).

STATISTICAL ANALYSIS. For analyses of both U.K. Biobank and summary-level data, a gene variant score was created out of the 4 SNPs. For each variant, we modeled the Lp(a)-lowering allele and weighted by the effect of each SNP on log-transformed Lp(a) levels in SD units (Online Table 3). The effect of this gene variant score on each trait and outcome was then

examined, standardized per SD decrease in log-transformed Lp(a) levels.

For U.K. Biobank, an *LPA* gene variant score was generated in units of SD Lp(a) by multiplying each variant by its effect on Lp(a) levels. This gene variant score was then included in a logistic regression analysis adjusting for age, sex, 10 principal components of ancestry, and a dummy variable for array type. For the summary-level data, this approach is equivalent to an inverse variance-weighted, fixed effects meta-analysis of the effect of each variant on a trait or outcome of interest, divided by the effect of each variant on Lp(a) levels (27).

For the primary outcomes (the 9 cardiometabolic diseases), a Bonferroni-adjusted level of significance of $p = 0.05/9 = 0.0056$ was set. For the secondary analysis of cardiometabolic traits, which included 15 traits, a level of significance of $p = 0.05/15 = 0.003$ was set. For the phenome-wide association study of 28 phenotypes, a level of significance of $p = 0.05/28 = 0.0018$ was set.

LOSS-OF-FUNCTION VARIANT ANALYSIS. To examine whether loss-of-function variants in the *LPA* gene influence CHD risk, whole exome sequencing data from the MIGen Consortium were used (Online Appendix). This consortium is composed of 10 coronary artery disease case-control studies (28,29). Loss-of-function variants were defined as follows: 1) nonsense mutations that resulted in early termination of the apolipoprotein(a) protein; 2) frameshift mutations due to insertions or deletions of DNA; or 3) splice-site mutations that resulted in an incorrectly spliced protein. These loss-of-function variants in the MIGen Consortium were combined with loss-of-function variants that were genotyped (either directly or imputed) in the U.K. Biobank. Variants are provided in Online Tables 4 and 5. We analyzed rare variants (<1%) separately to a common loss-of-function variant in the *LPA* gene (rs41272114, allele frequency of 3.8% in U.K. Biobank) (30,31).

We tested for the association of CHD with the presence of a loss-of-function variant using logistic regression. In the MIGen Consortium, the analysis was adjusted for sex, 5 principal components of ancestry, and a dummy variable for each cohort. We did not adjust for age in the MIGen Consortium because cases in some cohorts were selected for early-onset myocardial infarction, resulting in age being significantly and inversely associated with the presence of CHD. In the U.K. Biobank, the analysis was adjusted for age, sex, 10 principal components of ancestry, and array type.

TABLE 1 Characteristics of Genome-Wide Association Studies Utilized

Consortium (Ref. #)	Outcome/Trait	Sample Size	Genotyping
GLGC (17)	LDL cholesterol HDL cholesterol Total cholesterol Triglycerides	Up to 188,587 individuals	37 studies using Metabochip, 23 studies using various arrays
MAGIC (18)	Fasting glucose Fasting insulin 2-h glucose HbA_{1c}	Up to 133,010 individuals	Various arrays, imputation to 2.5 million SNPs using HapMap reference panel
GIANT (37,38)	Waist-to-hip ratio Waist circumference Hip circumference Body mass index	Up to 322,154 individuals	Various arrays, imputation to 2.5 million SNPs using HapMap reference panel
CKDGen (39)	Serum estimated glomerular filtration rate Chronic kidney disease	Up to 133,413 individuals	Various arrays, imputation to 2.5 million SNPs using HapMap reference panel
CARDIoGRAM Exome Consortium (22)	Coronary heart disease	Up to 42,335 case subjects/ 78,240 control subjects	Illumina HumanExome BeadChip array or the Illumina OmniExome array
DIAGRAM (20)	Diabetes	Up to 34,840 case subjects/ 114,981 control subjects	37 studies using Illumina Metabochip, 23 studies various arrays, imputation to 2.5 million SNPs using HapMap reference panel
CHARGE-HF (23)	Heart failure	Up to 2,526 case subjects/ 18,400 control subjects	Various arrays, imputation to 2.5 million SNPs using HapMap reference panel

CARDIoGRAM = Coronary Artery Disease Genome-wide Replication and Meta-analysis; CHARGE-HF = Cohorts for Heart and Aging Research in Genomic Epidemiology-Heart Failure; CKDGen = Chronic Kidney Disease Genetics Consortium; DIAGRAM = Diabetes Genetics Replication and Meta-analysis; GIANT = Genetic Investigation of Anthropometric Traits; GLGC = Global Lipids Genetics Consortium; HbA_{1c} = glycosylated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MAGIC = Meta-Analyses of Glucose and Insulin-related traits Consortium; SNP = single nucleotide polymorphism.

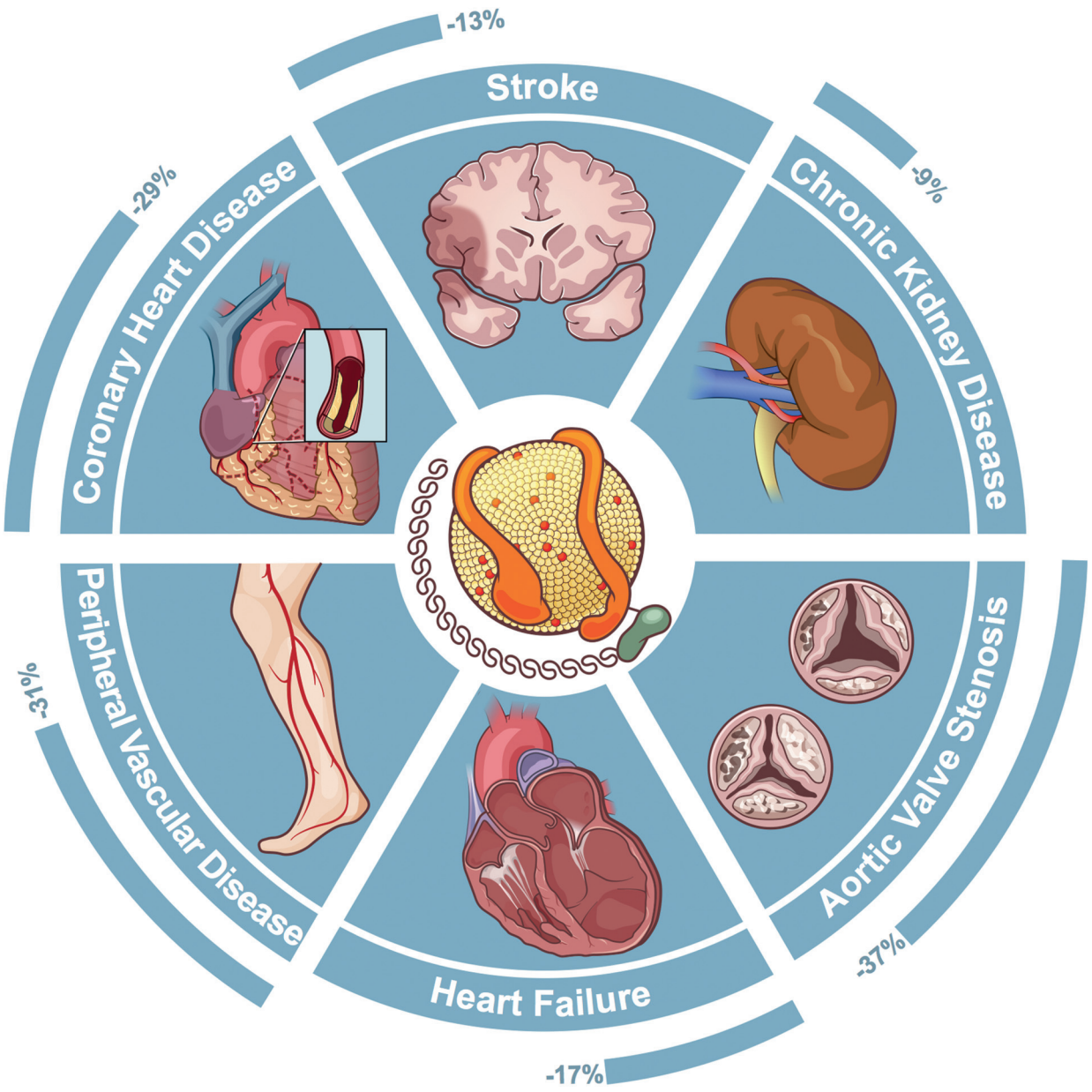
All analyses were performed by using R version 3.2.3 software (The R Project for Statistical Computing, Vienna, Austria).

RESULTS

We first estimated the effect of *LPA* gene variant score on plasma Lp(a) levels in ARIC participants. Variants rs3798220 and rs10455872 altered Lp(a) levels by 0.98 and 0.91 SD, respectively, whereas rs41272114 and rs143431368 altered Lp(a) levels by 0.62 SD and 0.92 SD (Online Table 3). In this study, 1 SD in Lp(a) levels equaled 28 mg/dl. The distribution of *LPA* gene variant score in the U.K. Biobank is provided (Online Table 6).

We examined the effect of genetically lowered Lp(a) level on 9 different cardiometabolic diseases (**Central Illustration**). Genetically lowered Lp(a), a 1 SD genetic decrease, was associated with a 29%

CENTRAL ILLUSTRATION **Impact of Genetically Mediated Lp(a) Reduction (1 SD) on Disease Risk**



Emdin, C.A. et al. J Am Coll Cardiol. 2016;68(25):2761–72.

The goal of this study was to establish the full phenotypic impact of *LPA* gene variation and to estimate a dose-response curve between genetically altered plasma lipoprotein a (Lp[a]) and risk for coronary heart disease. Estimates were derived in U.K. Biobank using logistic regression, adjusted for age, sex, 10 principal components and array type, with the exception of chronic kidney disease (CKD), which was derived by using summary statistics from the Chronic Kidney Disease Genetics Consortium, and heart failure, which was derived in both UK Biobank and the Cohorts for Heart and Aging Research in Genomic Epidemiology Heart Failure Consortium. One SD genetically lowered Lp(a) level was associated with reduced risk of 5 cardiometabolic diseases. Although the estimate for CKD did not reach Bonferroni-adjusted significance, it was included as a significant outcome because the underlying trait (estimated glomerular filtration rate) was significantly associated with Lp(a) ($p = 2 \times 10^{-5}$). OR = odds ratio.

lower risk of CHD (odds ratio [OR]: 0.71; 95% confidence interval [CI]: 0.69 to 0.73; $p = 3.2 \times 10^{-90}$). Genetically lowered Lp(a) had similar strengths of association with CHD across subpopulations (Online Figure 1). Beyond CHD, genetically lowered Lp(a) level was associated with a 31% lower risk of PVD (OR: 0.69; 95% CI: 0.59 to 0.80; $p = 1.9 \times 10^{-6}$), a 13% lower risk of stroke (OR: 0.87; 95% CI: 0.79 to 0.96; $p = 0.004$), a 37% lower risk of aortic stenosis (OR: 0.63; 95% CI: 0.47 to 0.83; $p = 0.0011$), and a 17% lower risk of HF (OR: 0.83; 95% CI: 0.73 to 0.94; $p = 0.0045$).

Although genetically lowered Lp(a) levels were only nominally associated with a 9% lower risk of CKD (OR: 0.91; 95% CI: 0.81 to 1.00; $p = 0.043$), it was highly significantly associated with the underlying quantitative trait (eGFR), as described later. Genetically lowered Lp(a) level was not associated with diabetes, venous thromboembolism, or atrial fibrillation. To examine if the association of genetically lowered Lp(a) with HF and aortic stenosis was mediated by CHD, we excluded participants with CHD in the U.K. Biobank (n = 4,461). After exclusion, a 1 SD genetic decrease in Lp(a) levels had similar strengths of association with HF (OR: 0.84; 95% CI: 0.66 to 1.07; n = 107,877) and aortic stenosis (OR: 0.70; 95% CI: 0.49 to 0.99; n = 107,877). A sensitivity analysis excluding those with prevalent aortic stenosis (n = 193) yielded a similar strength for the association between a 1 SD decrease in Lp(a) levels and HF (OR: 0.85; 95% CI: 0.72 to 1.02; n = 112,145).

In contrast to the effects of Lp(a) on cardiometabolic disorders, we found no association of genetically lowered Lp(a) with any of 28 different disorders, including 4 gastrointestinal disorders, 3 endocrine disorders, 2 renal/urological disorders, 3 psychiatric disorders, 4 musculoskeletal disorders, 4 respiratory disorders, and 8 different cancers (all $p > 0.01$) (**Figure 2**).

We next estimated the effect of *LPA* gene variant score on 15 quantitative traits (**Figure 3**). A significant association of genetically lowered Lp(a) with improved kidney function was observed: a 0.04 SD (95% CI: 0.02 to 0.05) increase in eGFR per SD genetically lowered Lp(a) ($p = 1.4 \times 10^{-5}$). This scenario corresponds to an approximate 2.0 ml/min increase in eGFR per SD lower Lp(a). As expected, a 1 SD genetically lowered Lp(a) was associated with total cholesterol and LDL cholesterol (0.14 SD decrease in total cholesterol [95% CI: 0.11 to 0.16; $p = 3.5 \times 10^{-27}$) and a 0.14 SD decrease in LDL cholesterol (95% CI: 0.11 to 0.16; $p = 4.7 \times 10^{-27}$). These estimates correspond, approximately, to a 5.6 mg/dl decrease in total cholesterol and a 4.9 mg/dl decrease in LDL cholesterol. We found no significant association of *LPA* genetic risk score with waist-to-hip ratio, waist circumference, hip circumference, body mass index, systolic blood pressure, diastolic blood pressure, HDL cholesterol, triglycerides, fasting glucose, fasting insulin, 2-h glucose, or glycosylated hemoglobin ($p > 0.05$ for each). *LPA* gene variant risk score remained unassociated with systolic and diastolic blood pressures when use of antihypertensive therapy was not accounted for (0 SD [95% CI: -0.02 to 0.01] and 0 SD [95% CI: -0.01 to 0.02] per SD lower Lp[a], respectively).

Figure 4 provides a dose-response curve for CHD derived from gain and loss-of-function variants at the *LPA* gene locus. The impact of *LPA* variation on CHD risk is directly proportional to its effect on circulating Lp(a) levels. The Lp(a)-increasing alleles of common variants rs3798220 and rs10455872, which increased Lp(a) levels by 0.98 and 0.91 SD, respectively, increased risk of CHD by 57% (OR: 1.57; 95% CI: 1.46 to 1.69) and 38% (OR: 1.38; 95% CI: 1.33 to 1.43). Rare synonymous variants, which had no significant effect on Lp(a) levels, also had no significant effect on CHD (OR: 0.98; 95% CI: 0.86 to 1.12). A common loss-of-function variant rs41272114, which decreased Lp(a) levels by 0.62 SD, was associated with a 12% lower risk of CHD (OR: 0.88; 95% CI: 0.84 to 0.93; $p = 3.4 \times 10^{-7}$). Presence of a rare (allele frequency <1%) loss-of-function variant in the *LPA* gene was associated with a 24% lower risk of CHD (OR: 0.76; 95% CI: 0.59 to 0.98; p = 0.033) (Online Figure 2).

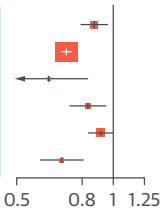
DISCUSSION

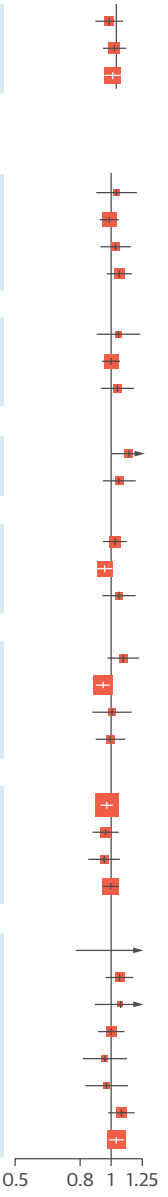
To evaluate the phenotypic consequences of genetically lowered Lp(a) levels, we leveraged the following: 1) 4 DNA sequence variants that alter plasma Lp(a) level; 2) individual-level genotype and phenotype data from >100,000 participants in the U.K. Biobank; 3) summary genetic association results from 7 large-scale GWAS; and 4) *LPA* gene sequences in >15,000 participants. We found that 1 SD genetically lowered Lp(a) was associated with a range of atherosclerosis-related diseases, including CHD, PVD, stroke, HF, and aortic stenosis, but was not associated with 31 other different diseases in a phenome-wide association study.

These data allow for several conclusions. First, using naturally occurring DNA sequence variation, a dose-response relationship between perturbation of Lp(a) and risk for CHD was provided. We examined the effects of both common and rare variants, as

FIGURE 2 Associations of Genetically Lowered Lp(a) With a Range of Diseases

Outcome	Cases	Controls	OR per SD Lower LPA	P-value
Cardiometabolic Disease: Significant Associations				
Stroke	2066	110272	0.87 [0.79; 0.96]	0.004
Coronary Heart Disease	46792	186109	0.71 [0.69; 0.73]	<0.0001
Aortic Valve Stenosis	193	112145	0.63 [0.47; 0.83]	0.0011
Heart Failure	2279	127690	0.83 [0.73; 0.94]	0.0045
Chronic Kidney Disease*	12385	117165	0.91 [0.83; 1.00]	0.043*
Peripheral Vascular Disease	698	111640	0.69 [0.59; 0.80]	<0.0001
Cardiometabolic Disease: Nonsignificant Associations				
Atrial Fibrillation	2204	110134	0.95 [0.86; 1.04]	0.29
Venous Thromboembolism	3305	109033	0.99 [0.91; 1.07]	0.74
Diabetes	40581	227319	0.97 [0.92; 1.03]	0.35
Other Phenotypes: Nonsignificant Associations				
Gastrointestinal disease				
Inflammatory bowel disease	1021	111317	1.04 [0.90; 1.19]	0.60
Gastric reflux	4881	107457	0.99 [0.92; 1.05]	0.67
Gallstones	1831	110507	1.03 [0.93; 1.15]	0.54
Irritable bowel syndrome	2679	109659	1.06 [0.97; 1.16]	0.18
Endocrine				
Hyperthyroidism	868	111470	1.05 [0.90; 1.23]	0.50
Hypothyroidism	5433	106905	1.00 [0.94; 1.06]	0.94
Gout	1612	110726	1.05 [0.93; 1.17]	0.44
Urological				
Enlarged Prostate	1573	110765	1.14 [1.01; 1.28]	0.03
Uterine Fibroids	1634	110704	1.06 [0.95; 1.19]	0.32
Neurological/psychiatric				
Migraine	3161	109177	1.03 [0.95; 1.11]	0.51
Depression	6667	105671	0.95 [0.90; 1.01]	0.08
Anxiety	1545	110793	1.06 [0.94; 1.18]	0.35
Muscoskeletal				
Osteoporosis	1740	110598	1.09 [0.97; 1.22]	0.13
Osteoarthritis	9693	102645	0.94 [0.90; 0.99]	0.014
Sciatica	1035	111303	1.00 [0.88; 1.15]	0.95
Prolapsed disc	1856	110482	0.99 [0.90; 1.10]	0.91
Respiratory				
Asthma	13941	98397	0.97 [0.93; 1.01]	0.10
COPD/Emphysema	2363	109975	0.96 [0.88; 1.05]	0.37
Pneumonia	1581	110757	0.95 [0.85; 1.06]	0.36
Hayfever	6263	106075	1.00 [0.94; 1.06]	0.91
Cancer				
Lung Cancer	115	112223	1.20 [0.78; 1.84]	0.42
Breast Cancer	2383	109955	1.06 [0.96; 1.16]	0.23
Colorectal Cancer	616	111722	1.07 [0.89; 1.28]	0.46
Skin Cancer	2482	109856	1.00 [0.91; 1.09]	0.99
Prostate Cancer	840	111498	0.96 [0.82; 1.11]	0.56
Cervical Cancer	872	111466	0.97 [0.83; 1.12]	0.66
Other Cancer	2409	109929	1.07 [0.98; 1.18]	0.13
Any Cancer	9530	102808	1.04 [0.99; 1.09]	0.13





Although 1 SD genetically lowered Lp(a) level was significantly associated with reduced risk of coronary heart disease, stroke, aortic stenosis, heart failure, chronic kidney disease, and peripheral vascular disease, there was no significant association seen for 3 other cardiometabolic disorders or 28 other diseases. *Nominally but not Bonferroni-adjusted significant. COPD = chronic obstructive pulmonary disease; OR = odds ratio; other abbreviations as in Figure 1.

well as gain-of-function variants that increase Lp(a) levels and loss-of-function variants that decrease Lp(a) levels. The effects of these different variants on CHD were consistently proportional to their effect on Lp(a). Consistent with 2 recent reports (30,32), a low-frequency loss-of-function variant (rs41272114) and a burden of rare loss-of-function variants in *LPA* protected against CHD. In combination, these results suggest that greater pharmacological reductions in Lp(a) levels should produce proportionally greater reductions in CHD risk, thus supporting intensive Lp(a) lowering.

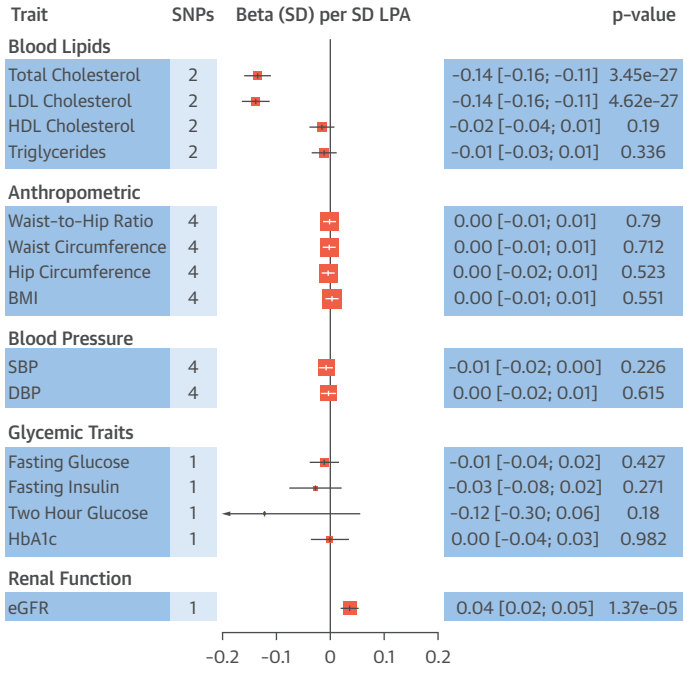
Second, these results suggest that Lp(a) inhibition may be a viable therapeutic strategy to prevent a range of diseases beyond CHD. This study extends previous research demonstrating that *LPA* variants are associated with cardiovascular disease (5,6,11,12,33,34). In a report of up to 12,716 individuals from 35 case-control studies, *LPA* variants were associated with peripheral arterial disease, ischemic stroke, and coronary artery disease (11). In contrast, in an analysis of 14,465 individuals in the Heart Protection Study, *LPA* variants were associated with PVD but not with stroke (12). Our results suggest that *LPA* variants are associated with PVD, stroke, and HF. Furthermore, our report of a significant association with aortic stenosis is consistent with recent analyses demonstrating a significant effect of *LPA* variants on aortic valve calcification and stenosis (9,10). Inclusion of these diseases in composite endpoints of trials of Lp(a)-reducing therapies (in addition to CHD) may increase the likelihood of a positive trial outcome, highlighting the potential benefits of genetic analyses for trial design and clinical drug development.

Third, a surprising finding of this study was that genetically lowered Lp(a) was associated with a modest but significant improvement in kidney function as assessed by 2 phenotypes—eGFR and prevalence of CKD. This lower risk of CKD may be mediated through a reduction in renal atherosclerotic burden. These findings are consistent with a recent GWAS of metabolites that revealed a strong association between *LPA* rs10455872 and creatinine levels (35). These results implicate Lp(a) metabolism in the development of CKD.

STUDY LIMITATIONS. This study's major strength was the scale and variety of data sources, which improved our power to detect an effect of genetically lowered Lp(a) on a wide range of diseases and cardiometabolic traits. Our use of the largest available cohorts provided requisite power to demonstrate that genetic Lp(a) lowering was associated with a lower risk of PVD, stroke, HF, and CKD. Our use of the U.K. Biobank allowed us to examine the association of genetic *LPA* variants across a wide range of noncardiovascular diseases, for which we failed to find an association.

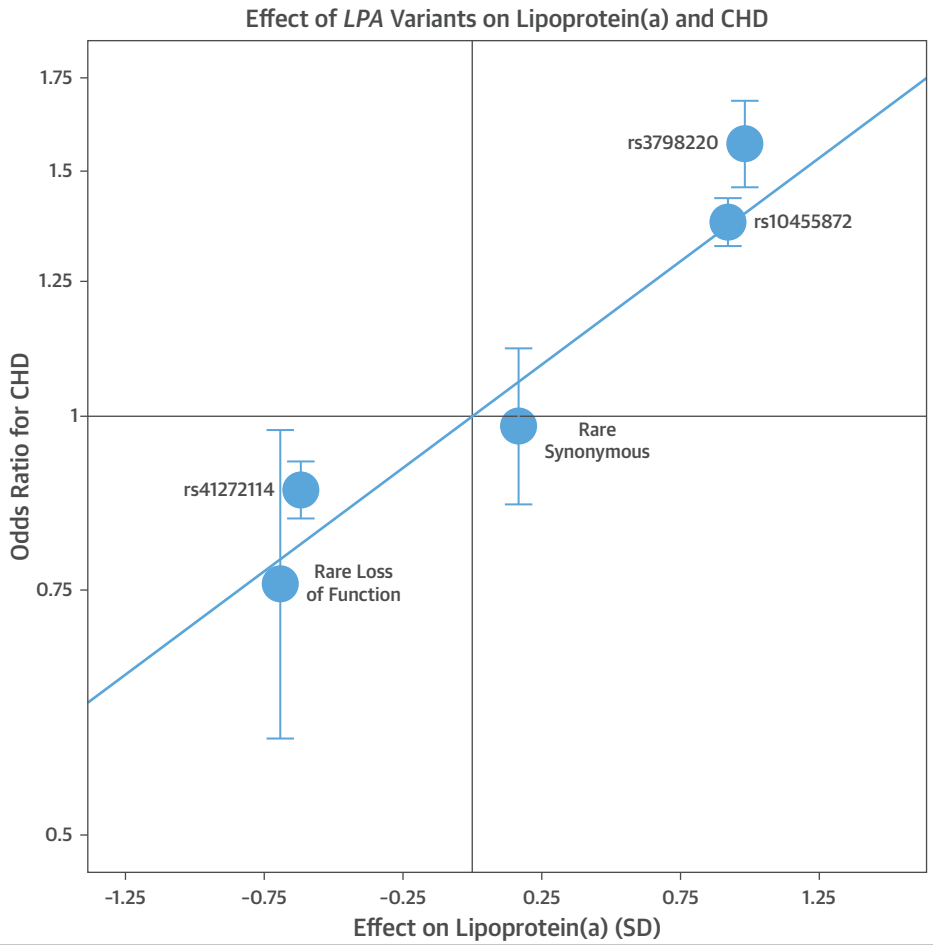
Several study limitations deserve mention. First, our use of a 2-sample design, with exposure estimates from ARIC and outcome estimates from the U.K. Biobank and various GWAS, prevented us from examining whether the effect of *LPA* variants differed according to baseline levels of Lp(a). Second, our phenome-wide association study might have been underpowered to detect a significant effect of Lp(a) on many of the outcomes. Because the U.K. Biobank develops validated phenotypes and accumulates a greater number of events, a phenome-wide association study may be better-powered to detect an effect on different disorders.

FIGURE 3 Association of Genetically Lowered Lp(a) (1 SD Decrease) With Cardiometabolic Quantitative Traits



Genetically lowered Lp(a) level was associated with reductions in total and low-density lipoprotein (LDL) cholesterol as well as improved kidney function. There were no other significant associations seen between 1 SD decrease in Lp(a) and other traits measured. BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HbA_{1c} = glycosylated hemoglobin; HDL = high-density lipoprotein; Lp(a) = lipoprotein a; SBP = systolic blood pressure; SNP = single nucleotide polymorphism.

FIGURE 4 Effect of *LPA* Variants on Lp(a) and CHD



Variant rsID	Variant Class	Protein Change	Minor Allele (Frequency)	Normalized Lp(a) Beta	CHD Odds Ratio	P Value (CHD)
rs3798220	Missense	Ile4399Met	C (0.051)	0.98	1.57	3.0E-35
rs10455872	Intronic	--	G (0.022)	0.92	1.38	1.4E-56
Rare Synonymous	Synonymous	--	(0.02)	0.16	0.98	0.80
rs41272114	Splice Donor	--	T (0.02)	-0.62	0.88	3.4E-7
Rare Loss of Function	Premature Stop/Splice site/Frameshift	--	(0.007)	-0.69	0.76	0.033

Logistic regression was used to test the association of coronary heart disease (CHD) as an outcome and DNA sequence variant as a predictor, adjusting for sex and principal components of ancestry, with additional adjustment for array type and age in U.K. Biobank. The impact of *LPA* variation on CHD risk is directly proportional to its effect on circulating Lp(a) levels. Lp(a) = lipoprotein(a).

Third, we used prevalent events based on a verbal interview with a nurse for our phenome-wide association study of 28 different disorders. Although these events are likely to be of greater specificity than coded hospitalization data, they have not been independently validated. Finally, our population was limited to individuals of European ancestry, and our results may not be generalizable to individuals of different ancestry. Indeed, both Lp(a) levels and the number of Kringle IV domains in Lp(a) have been shown to vary substantially with ancestry, suggesting that the impact of Lp(a) on cardiovascular disease may also differ by ancestry (36).

CONCLUSIONS

Genetically decreased Lp(a) was associated with a range of cardiometabolic disorders, including CHD, stroke, PVD, aortic stenosis, HF, and renal dysfunction. Pharmacological lowering of Lp(a) levels may reduce the risk of these disorders.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: A genetic predisposition to lower blood levels of Lp(a) was associated with protection from coronary artery disease, stroke, PVD, aortic stenosis, HF, and CKD but was not associated with type 2 diabetes, gastrointestinal disorders, or specific cancers.

TRANSLATIONAL OUTLOOK: Further research should be conducted to determine whether more intensive lowering of Lp(a) levels results in proportionally greater reductions in cardiovascular risk.

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KEY WORDS coronary heart disease, genetics, phenome-wide association study, single nucleotide polymorphism

APPENDIX For an expanded Methods section, as well as supplemental tables and figures, please see the online version of this article.