Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.
ONLINE-ONLY METHODS

**LPA genetic risk score.**

*LPA* genetic risk scores were calculated using the external weights for 43 single-nucleotide variants (SNVs) described by Burgess et al. (2018) (Online-Only Table 1). Quality control filtering of genotyping individuals from the UK Biobank was performed such that individuals that were a mismatch between genetic and reported sex, outliers for heterozygosity or missing rate, or missing more than 3 SNVs from the *LPA* genetic risk score were excluded. *LPA* genetic risk scores were calculated using the weighted formula $\Sigma [\beta_x \times \text{SNV}_x]$, where $\beta_x$ is the effect size for the lipprotein(a)-associated effect and $\text{SNV}_x$ is the number of effect alleles at that locus for $\text{SNV}_x$ (0, 1, or 2).
**ONLINE-ONLY TABLES**

Online-Only Table 1. Genetic variants used in the *LPA* genetic risk score. External weights for the association between genetic variants and lipoprotein(a) were obtained from Burgess et al. (2018)\(^1\). Values for the association with lipoprotein(a) were converted from mg/dL to nmol/L by multiplying by 2.15.

| Chr:Pos (hg19) | rsID          | Effect allele | Other allele | Conditional association with Lp(a), Beta (nmol/L) | Conditional association with Lp(a), SE (nmol/L) |
|----------------|---------------|---------------|--------------|-------------------------------------------------|---------------------------------------------|
| 6:160997118    | rs74617384    | T             | A            | 91.16                                           | 1.075                                       |
| 6:161013013    | rs140570886   | C             | T            | 172.43                                          | 1.72                                        |
| 6:161017363    | rs73596816    | A             | G            | 41.28                                           | 1.29                                        |
| 6:160891897    | rs182443492   | A             | C            | 79.12                                           | 2.15                                        |
| 6:161032800    | rs369686024   | A             | G            | 41.28                                           | 1.72                                        |
| 6:161089307    | rs56393506    | T             | C            | 26.66                                           | 0.86                                        |
| 6:160831796    | rs151135411   | A             | G            | 149.425                                         | 5.805                                       |
| 6:161292838    | rs145099029   | C             | A            | 38.27                                           | 3.87                                        |
| 6:160998199    | rs41267813    | A             | G            | -126.42                                         | 6.235                                       |
| 6:160890350    | rs6916433     | T             | A            | -10.105                                         | 0.645                                       |
| 6:161137990    | rs783147      | A             | G            | -4.3                                            | 0.645                                       |
| 6:160953137    | rs41266379    | C             | T            | 15.265                                          | 1.505                                       |
| 6:160954800    | rs143461353   | T             | C            | 28.165                                          | 2.15                                        |
| 6:160942926    | rs142126734   | A             | G            | 16.125                                          | 1.075                                       |
| 6:160899049    | rs139609547   | -             | A            | 9.46                                            | 0.86                                        |
| 6:161162290    | rs1835346     | G             | A            | 11.18                                           | 1.505                                       |
| 6:161159366    | rs4252152     | G             | T            | 19.565                                          | 1.935                                       |
| 6:161078894    | rs79246098    | C             | T            | 13.33                                           | 1.935                                       |
| 6:160966559    | rs139145675   | A             | G            | -48.375                                         | 5.16                                        |
| 6:161022107    | rs41259144    | T             | C            | -20.64                                          | 1.72                                        |
| 6:161012805    | rs9456551     | C             | T            | 7.74                                            | 0.43                                        |
| 6:160953642    | rs41267809    | G             | A            | -14.19                                          | 1.29                                        |
| 6:161257953    | rs34371670    | T             | C            | -18.06                                          | 1.505                                       |
| 6:161070653    | rs41269876    | A             | C            | -17.63                                          | 1.29                                        |
| 6:160909667    | rs141834709   | A             | T            | 18.705                                          | 2.15                                        |
| 6:161162406    | rs4252170     | C             | T            | 6.88                                            | 0.86                                        |
| 6:161251940    | rs138491411   | G             | A            | 10.75                                           | 1.72                                        |
| 6:160720804    | rs183815886   | C             | G            | 31.82                                           | 3.87                                        |
| 6:160847571    | rs117446263   | A             | G            | -11.18                                          | 1.29                                        |
| 6:160543317    | rs200684404   | T             | C            | 145.555                                         | 19.78                                       |
| 6:160493099    | rs200144324   | T             | C            | 175.225                                         | 24.295                                      |
| Chromosome | Position | SNP ID     | Allele 1 | Allele 2 | Effect Size | Standard Error |
|------------|----------|------------|----------|----------|-------------|----------------|
| 6          | 16:0817652 | rs77337569 | G        | T        | 11.18       | 1.72           |
| 6          | 16:1214526 | rs186418835 | A        | G        | -20.855     | 3.225          |
| 6          | 16:1177443 | rs117534432 | T        | C        | 7.095       | 1.075          |
| 6          | 16:1011999 | rs200376184 | C        | G        | 37.625      | 5.805          |
| 6          | 16:1189071 | rs11753588 | A        | G        | -5.16       | 0.645          |
| 6          | 16:1285760 | rs4709474  | G        | A        | 3.655       | 0.43           |
| 6          | 16:1031132 | rs191690882 | A        | G        | -28.38      | 4.085          |
| 6          | 16:1255668 | rs182349273 | G        | A        | 73.96       | 12.255         |
| 6          | 16:1108896 | rs75274517 | A        | G        | -13.975     | 2.15           |
| 6          | 16:0825930 | rs143365644 | T        | A        | 7.955       | 1.075          |
| 6          | 16:1135746 | rs139389770 | G        | T        | -11.18      | 1.935          |
| 6          | 16:1250301 | rs140606700 | G        | A        | 13.76       | 2.58           |
### Online-Only Table 1. International Statistical Classification of Diseases and Related Health Problems (ICD) and Office of Population Censuses and Surveys Classification of Interventions and Procedures (OCPS) codes used to define atherosclerotic cardiovascular disease events.

| Cardiovascular Outcome Category | ICD-9 Diagnosis Codes | ICD-10 Diagnosis Codes | OCPS-4 (operations) |
|---------------------------------|-----------------------|------------------------|---------------------|
| Myocardial infarction           | 410 Acute myocardial infarction  
411 Other acute and subacute forms of ischaemic heart disease  
412 Old myocardial infarction  
42979 Ill-defined descriptions and complications of heart disease - Other | I21 Acute myocardial infarction  
I22 Subsequent myocardial infarction  
I23 Certain current complications following acute myocardial infarction  
I24.1 Dressler syndrome  
I25.2 Old myocardial infarction. | N/A |
| Ischemic stroke                  | 434 Occlusion of cerebral arteries  
436 Acute, but ill-defined, cerebrovascular disease | I63 Cerebral infarction  
I64 Stroke, not specified as haemorrhage or infarction. | N/A |
| Cardiovascular mortality         | N/A | Any diagnosis code for causes of death related to: *Chapter IX Diseases of the circulatory system* | N/A |
| Coronary artery disease          | Myocardial infarction codes | Myocardial infarction codes | K40 Saphenous vein graft replacement of coronary artery  
K41 Other autograft replacement of coronary artery  
K42 Allograft replacement of coronary artery  
K43 Prosthetic replacement of coronary artery  
K44 Other replacement of coronary artery  
K45 Connection of thoracic artery to coronary artery  
K46 Other bypass of coronary artery  
K47 Repair of coronary artery  
K48 Other open operations on coronary artery  
K49 Transluminal balloon angioplasty of coronary artery |
| Category                                                                 | ICD-10 Codes                                                                 |
|-------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Peripheral artery disease (non-coronary or cerebrovascular events)     | • 440 Atherosclerosis  
• 444 Arterial embolism and thrombosis  
• 4438 Other specified peripheral vascular disease  
• 4439 Peripheral vascular disease, unspecified |
|                                                                         | • I70 Atherosclerosis  
• I74 Arterial embolism and thrombosis  
• I73.8 Other specified peripheral vascular diseases  
• I73.9 Peripheral vascular disease, unspecified |
|                                                                         | • L50 Other emergency bypass of iliac artery  
• L51 Other bypass of iliac artery  
• L52 Reconstruction of iliac artery  
• L54 Transluminal operations on iliac artery  
• L58 Other emergency bypass of femoral artery  
• L59 Other bypass of femoral artery  
• L60 Reconstruction of femoral artery  
• L63 Transluminal operations on femoral artery  
• X09 Amputation of leg |
|                                                                       | • K50 Other therapeutic transluminal operations on coronary artery  
• K75 Percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery |
Online-Only Table 3. Spearman's rank correlation between LPA genetic risk score and measured lipoprotein(a) levels for different ethnic groups. Black/African (AFR: Caribbean, African, any other Black background), White/European (EUR: British, Irish, any other White background), East Asian (EAS: Chinese, other Asian background), South Asian (SAS: Indian, Pakistani, Bangladeshi), unknown (other ethnic group, do not know, or prefer not to answer).

| Ethnic Group       | n     | Correlation Co-efficient | p-value          |
|-------------------|-------|--------------------------|------------------|
| Admixed           | 2,340 | 0.483                    | < 2.2 x10^{-16}  |
| Black/African (AFR)| 6,521 | 0.070                    | 1.76 x10^{-8}    |
| East Asian (EAS)  | 2,774 | 0.281                    | < 2.2 x10^{-16}  |
| White/European (EUR)| 350,903 | 0.717                  | < 2.2 x10^{-16}  |
| South Asian (SAS) | 6,203 | 0.371                    | < 2.2 x10^{-16}  |
| Unknown           | 5,358 | 0.437                    | < 2.2 x10^{-16}  |
Online-Only Table 4. Enrollment characteristics of UK Biobank study participants not using cholesterol-lowering medication and without prevalent atherosclerotic cardiovascular disease at study enrollment. High-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C).

| Characteristic                      | Measure          | White/European and Non-White/European | European          |
|-------------------------------------|------------------|---------------------------------------|-------------------|
| n                                   | no.              | 300839                                | 283540            |
| Age (years)                         | mean (SD)        | 56.6 (8.0)                            | 56.8 (8.0)        |
| Female sex                          | no. (%)          | 174555 (58.0)                         | 164734 (58.1)     |
| Ethnicity - Admixed                 | no. (%)          | 1991 (0.7)                            | 0 (0.0)           |
| Ethnicity - African/Black           | no. (%)          | 5163 (1.7)                            | 0 (0.0)           |
| Ethnicity - East Asian              | no. (%)          | 2105 (0.7)                            | 0 (0.0)           |
| Ethnicity - European                | no. (%)          | 283540 (94.2)                         | 283540 (100.0)    |
| Ethnicity - South Asian             | no. (%)          | 4275 (1.4)                            | 0 (0.0)           |
| Ethnicity - Unknown                 | no. (%)          | 3765 (1.3)                            | 0 (0.0)           |
| Total cholesterol (mg/dL)           | mean (SD) / n    | 229.3 (41.2) / 300650                 | 230.1 (41.1) / 283360 |
| Direct LDL-C (mg/dL)                | mean (SD) / n    | 144.5 (31.5) / 300167                 | 145.0 (31.4) / 282907 |
| Triglycerides (mg/dL)               | median (IQR) / n | 127.0 (93.4) / 300636                 | 127.6 (93.4) / 283346 |
| HDL-C (mg/dL)                       | mean (SD) / n    | 57.4 (14.7) / 275219                  | 57.6 (14.7) / 259349 |
| Lipoprotein(a) (nmol/L)             | median (IQR) / n | 24.1 (73.6)                           | 23.1 (72.9)       |
| Lipoprotein(a) ≥ 120 nmol/L         | no. (%)          | 53960 (17.9)                          | 50961 (18.0)      |
| C-reactive protein (g/L)            | median (IQR) / n | 1.3 (2.1) / 300037                   | 1.3 (2.0) / 282779 |
| Hemoglobin A1c (mmol/mol)           | median (IQR) / n | 34.9 (4.7) / 300037                  | 34.7 (4.7) / 270823 |
| Antihypertensive medication         | no. (%) / n      | 36255 (12.1) / 300839                 | 33493 (11.8) / 283540 |
| Hypertension                        | no. (%) / n      | 59447 (19.8) / 300344                 | 55562 (19.6) / 283140 |
| Diabetes mellitus                   | no. (%) / n      | 43218 (1.4) / 300237                  | 3525 (1.2) / 283088 |
| Body mass index (kg/m²)             | mean (SD) / n    | 27.0 (4.6) / 299831                   | 26.9 (4.6) / 282759 |
| Current smoker                      | no. (%) / n      | 30628 (10.2) / 299851                 | 28527 (10.1) / 282669 |
Online-Only Table 5. Risk discrimination models for incident atherosclerotic cardiovascular disease events for individuals of European and non-European ethnicity using cardiovascular risk calculators. The risk prediction of QRISK3 and the Pooled Cohort Equations were compared for the overall study cohort of 300,839 individuals of European and non-European ethnicities. 11,731 individuals experienced a myocardial infarction, an ischemic stroke, or cardiovascular mortality event over a median follow-up of 11.1 years (interquartile range 1.4 years). The area under the receiver operating characteristic curve (AUROC) and the Harrell’s C-statistic for Cox proportional-hazards models are shown for QRISK3 and the PCE. Models were compared using A DeLong’s test for receiver operating characteristic curves and an analysis of variance test for Cox proportional-hazard models.

| Features                  | AUROC (95% CI) [p-value] | Harrell’s C-statistic (SE) [p-value] |
|---------------------------|--------------------------|-------------------------------------|
| Pooled Cohort Equations   | 0.742 (0.738-0.747) [reference] | 0.741 (0.002) [reference] |
| QRISK3                    | 0.749 (0.745-0.754) [3.31x10^{-15}] | 0.748 (0.002) [p<2.2x10^{-16}] |
Online-Only Table 6. Additional value of lipoprotein(a) metrics to atherosclerotic cardiovascular disease risk discrimination among individuals of White/European ethnicity defined as borderline-to-intermediate risk by QRISK3 using only complete data. This subgroup included 121,428 individuals classified as having borderline-intermediate ASCVD risk without prevalent ASCVD, diabetes mellitus, severe hypercholesterolemia, or use of cholesterol-lowering medication (10-year risk of 5-20%). 4,585 individuals experienced a myocardial infarction, an ischemic stroke, or cardiovascular mortality event over a median follow-up of 11.0 years (interquartile range 1.4 years). The area under the receiver operating characteristic curve (AUROC) and the Harrell’s C-statistic for Cox proportional-hazards models are shown for the Pooled Cohort Equations (PCE) with and without the addition of continuous measured lipoprotein(a) and LPA genetic risk score (GRS). Models were compared relative to the QRISK3 model using an analysis of variance test for Cox proportional-hazard models or DeLong’s test for receiver operating characteristic curves. Standard error (SE).

| Features                   | AUROC (SE) [p-value] | Harrell’s C-statistic (SE) [p-value] |
|----------------------------|----------------------|-------------------------------------|
| QRISK3                     | 0.640 (0.632-0.648) [ref.] | 0.639 (0.004) [ref.] |
| QRISK3 & Lp(a)             | 0.642 (0.634-0.650) [p=0.02] | 0.641 (0.004) [p=3.54x10⁻⁸] |
| QRISK3 & LPA GRS           | 0.642 (0.634-0.650) [p=0.02] | 0.641 (0.004) [p=1.20x10⁻⁸] |
| QRISK3 & Lp(a) & LPA GRS   | 0.642 (0.634-0.650) [p=0.01] | 0.641 (0.004) [p=1.95x10⁻⁸] |
Online-Only Table 7. Additional value of lipoprotein(a) metrics to atherosclerotic cardiovascular disease risk discrimination among individuals of White/European ethnicity defined by the Pooled Cohort Equations as borderline-intermediate risk using complete and imputed data. This subgroup included 113,703 individuals classified as having borderline-intermediate ASCVD risk without prevalent ASCVD, diabetes mellitus, severe hypercholesterolemia, or use of cholesterol-lowering medication (10-year risk of 5-20%). 5,938 individuals experienced a myocardial infarction, an ischemic stroke, or cardiovascular mortality event over a median follow-up of 11.1 years (interquartile range 1.5 years). The area under the receiver operating characteristic curve (AUROC) and the Harrell’s C-statistic for Cox proportional-hazards models are shown for the Pooled Cohort Equations (PCE) with and without the addition of continuous measured lipoprotein(a) and \( LPA \) genetic risk score (GRS). Models were compared relative to the PCE model using an analysis of variance test for Cox proportional-hazard models or DeLong’s test for receiver operating characteristic curves. Standard error (SE).

| Features                  | AUROC (SE) [p-value] | Harrell’s C-statistic (SE) [p-value] |
|---------------------------|----------------------|-------------------------------------|
| PCE                       | 0.608 (0.601-0.615) [ref.] | 0.609 (0.004) [ref.]                |
| PCE & Lp(a)               | 0.611 (0.603-0.618) [p=0.01]  | 0.611 (0.004) [3.71x10^{-14}]     |
| PCE & \( LPA \) GRS       | 0.611 (0.603-0.617) [p=0.03]  | 0.611 (0.004) [5.48x10^{-10}]     |
| PCE & Lp(a) & \( LPA \) GRS | 0.611 (0.603-0.617) [p=0.01]  | 0.611 (0.004) [3.03x10^{-13}]     |
Online-Only Table 8. Additional value of lipoprotein(a) metrics to atherosclerotic cardiovascular disease risk discrimination among individuals of White/European ethnicity defined by the Pooled Cohort Equations as borderline-intermediate risk using complete data. This subgroup included 96,260 individuals classified as having borderline-intermediate ASCVD risk without prevalent ASCVD, diabetes mellitus, severe hypercholesterolemia, or use of cholesterol-lowering medication (10-year risk of 5-20%). 5,436 individuals experienced a myocardial infarction, an ischemic stroke, or cardiovascular mortality over a median follow-up of 11.0 years (interquartile range 1.5 years). The area under the receiver operating characteristic curve (AUROC) and the Harrell’s C-statistic for Cox proportional-hazards models are shown for the Pooled Cohort Equations (PCE) with and without the addition of continuous measured lipoprotein(a) and LPA genetic risk score (GRS). Models were compared relative to the PCE model using an analysis of variance test for Cox proportional-hazard models or DeLong’s test for receiver operating characteristic curves. Standard error (SE).

| Features               | AUROC (SE) [p-value] | Harrell’s C-statistic (SE) [p-value] |
|------------------------|----------------------|--------------------------------------|
| PCE                    | 0.614 (0.609-0.624) [reference] | 0.617 (0.004) [reference] |
| PCE & Lp(a)            | 0.619 (0.611-0.627) [p=0.03] | 0.619 (0.004) [p=1.44x10^-11] |
| PCE & LPA GRS          | 0.619 (0.611-0.626) [p=0.02] | 0.619 (0.004) [p=2.20x10^-8] |
| PCE & Lp(a) & LPA GRS  | 0.619 (0.611-0.627) [p=0.02] | 0.619 (0.004) [p=1.03x10^-10] |
Online-Only Figure 1. Self-reported ethnicity subgroups cluster with genetic principal components of ancestry. Individuals of admixed, Black/African (AFR: Caribbean, African, any other Black background), White/European (EUR: British, Irish, any other White background), East Asian (EAS: Chinese, other Asian background), South Asian (SAS: Indian, Pakistani, Bangladeshi), and unknown (other ethnic group, do not know, or prefer not to answer) self-reported ethnicity are depicted based on the first 2 principal components of genetic ancestry.
Online-Only Figure 2. Distributions of measured lipoprotein(a) and LPA genetic risk scores. The distributions of (A) measured lipoprotein(a) [Lp(a)], (B) lipoprotein(a) genetic risk score (GRS), and (C) residuals of measured lipoprotein(a) – LPA genetic risk score are depicted for ethnic groupings. Black/African (AFR: Caribbean, African, any other Black background), White/European (EUR: British, Irish, any other White background), East Asian (EAS: Chinese, other Asian background), South Asian (SAS: Indian, Pakistani, Bangladeshi), unknown (other ethnic group, do not know, or prefer not to answer).
Online-Only Figure 3. Association of measured lipoprotein(a) and LPA genetic risk score with risk of incident, composite atherosclerotic cardiovascular events. The risk of incident atherosclerotic cardiovascular disease (ASCVD) events, stratified by self-reported ethnicity is depicted as hazard ratios and 95% confidence intervals for the composite endpoints of peripheral arterial disease, ischemic stroke, coronary artery disease, myocardial infarction, and cardiovascular disease mortality for individuals not using cholesterol-lowering medication and without prevalent ASCVD at enrollment. Hazard ratios are scaled to depict a 120 nmol/L increase in (A) measured lipoprotein(a) (Lp(a)) or (B) LPA genetic risk score (GRS) levels. Cox proportional hazard models included age, sex, assessment centre, genotyping batch, and the first five principal components of ancestry. Black/African (AFR: Caribbean, African, any other Black background), White/European (EUR: British, Irish, any other White background), East Asian (EAS: Chinese, other Asian background), South Asian (SAS: Indian, Pakistani, Bangladeshi), unknown (other ethnic group, do not know, or prefer not to answer).
Online-Only Figure 4. Measured lipoprotein(a) and LPA genetic risk score (GRS) associate with incident atherosclerotic cardiovascular disease among individuals of White/European ethnicity using cholesterol lowering medication. The risk of incident atherosclerotic cardiovascular disease (ASCVD) events is depicted as hazard ratios and 95% confidence intervals for peripheral arterial disease, ischemic stroke, coronary artery disease, myocardial infarction, cardiovascular disease (CVD) mortality, and composite ASCVD for 43,829 individuals without prevalent ASCVD, but using cholesterol-lowering medication at enrollment. Hazard ratios are scaled to depict a 120 nmol/L increase in measured lipoprotein(a) (Lp(a)) or LPA genetic risk score (GRS) levels. All Cox proportional hazard models included age, sex, assessment centre, genotyping batch, and the first five principal components of ancestry.
Online-Only Figure 5. Measured lipoprotein(a) has stronger associations with composite atherosclerotic cardiovascular disease events at the extremes of elevated lipoprotein(a) than the LPA genetic score. (A) The incidence rate of composite atherosclerotic cardiovascular disease (ASCVD) per 1000 person years (± 95% CIs), (B) measured levels of lipoprotein(a) (± interquartile range), and (C) probability of composite ASCVD by 75 years-of-age are displayed for each percentile of measured lipoprotein(a) and LPA genetic risk score (GRS). Dashed lines correspond to the 80th percentile of measured lipoprotein and LPA GRS (approximately 120 nmol/L). Associations with incidence rates were determined from 283,540 individuals of White/European ethnicity not using cholesterol-lowering medication and without prevalent ASCVD at enrollment. Alternatively, associations with measured lipoprotein(a) and probability of ASCVD were determined from 350,903 individuals of White/European ethnicity regardless of cholesterol-lowering medication use or prevalent ASCVD at enrollment.
Online-Only Figure 6. Distributions of atherosclerotic cardiovascular disease risk determined by clinical risk calculators. The distribution of 10-year atherosclerotic cardiovascular disease (ASCVD) risk determined by (A) QRISK3 and (B) the Pooled Cohort Equations is displayed for 300,839 individuals of White/European and non-White/European individuals not using cholesterol-lowering medication and without prevalent ASCVD at enrollment. Data are displayed using complete data only (QRISK3: 254,315; PCE: n=255,510) and complete and imputed data (QRISK3 and QRISK3: n=300,839). The dashed black lines depict 5% (low-to-borderline) and 20% (intermediate-to-high) ASCVD risk thresholds.
ONLINE-ONLY REFERENCES

1. Burgess S, Ference BA, Staley JR, Freitag DF, Mason AM, Nielsen SF, et al. Association of LPA variants with risk of coronary disease and the implications for lipoprotein(a)-lowering therapies: a Mendelian randomization analysis. *JAMA Cardiol.* 2018;3(7):619-627.