Original Contribution

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Role of Blood Lipids in the Development of Ischemic Stroke and its Subtypes

A Mendelian Randomization Study

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Background and Purpose—Statin therapy is associated with a lower risk of ischemic stroke supporting a causal role of low-density lipoprotein (LDL) cholesterol. However, more evidence is needed to answer the question whether LDL cholesterol plays a causal role in ischemic stroke subtypes. In addition, it is unknown whether high-density lipoprotein cholesterol and triglycerides have a causal relationship to ischemic stroke and its subtypes. Our aim was to investigate the causal role of LDL cholesterol, high-density lipoprotein cholesterol, and triglycerides in ischemic stroke and its subtypes through Mendelian randomization (MR).

Methods—Summary data on 185 genome-wide lipids-associated single nucleotide polymorphisms were obtained from the Global Lipids Genetics Consortium and the Stroke Genetics Network for their association with ischemic stroke (n=16 851 cases and 32 473 controls) and its subtypes, including large artery atherosclerosis (n=2410), small artery occlusion (n=3186), and cardioembolic (n=3427) stroke. Inverse-variance–weighted MR was used to obtain the causal estimates. Inverse-variance–weighted multivariable MR, MR-Egger, and sensitivity exclusion of pleiotropic single nucleotide polymorphisms after Steiger filtering and MR-Pleiotropy Residual Sum and Outlier test were used to adjust for pleiotropic bias.

Results—A 1-SD genetically elevated LDL cholesterol was associated with an increased risk of ischemic stroke (odds ratio: 1.12; 95% confidence interval: 1.04–1.20) and large artery atherosclerosis stroke (odds ratio: 1.28; 95% confidence interval: 1.10–1.49) but not with small artery occlusion or cardioembolic stroke in multivariable MR. A 1-SD genetically elevated high-density lipoprotein cholesterol was associated with a decreased risk of small artery occlusion stroke (odds ratio: 0.79; 95% confidence interval: 0.67–0.90) in multivariable MR. MR-Egger indicated no pleiotropic bias, and results did not markedly change after sensitivity exclusion of pleiotropic single nucleotide polymorphisms. Genetically elevated triglycerides did not associate with ischemic stroke or its subtypes.

Conclusions—LDL cholesterol lowering is likely to prevent large artery atherosclerosis but may not prevent small artery occlusion nor cardioembolic strokes. High-density lipoprotein cholesterol elevation may lead to benefits in small artery disease prevention. Finally, triglyceride lowering may not yield benefits in ischemic stroke and its subtypes. **(*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.117.019653.)**

Key Words: cholesterol, HDL ■ cholesterol, LDL ■ polymorphism, single nucleotide ■ stroke ■ triglycerides

Circulating lipid and lipoprotein biomarkers have consistently been associated with cardiovascular diseases as myocardial infarction and stroke.[1] A previous meta-analysis of low-density lipoprotein cholesterol (LDLC)–lowering trials has shown risk reduction for ischemic stroke.[2] In addition, the SPARCL trial (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) in secondary stroke prevention demonstrated a significant reduction in recurrent stroke with atorvastatin.[3] Importantly, it is unclear as to whether lipid lowering with statins is beneficial across different ischemic stroke subtypes. Although lipid lowering is likely to be effective in large artery atherosclerosis stroke, the evidence implicating elevated lipids in the small artery occlusion stroke is scant. In the recent J-STARS (Japan Statin Treatment Against Recurrent Stroke) stroke secondary prevention trial, pravastatin reduced large artery atherosclerosis recurrent stroke risk,

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but it had no effect on small artery occlusion risk.[4] In addition, there is insufficient evidence whether high-density lipoprotein cholesterol (HDLC) and triglycerides may be causally involved in the development of ischemic stroke.[5]

Genetic variants are randomly distributed at conception and thus can be used to overcome 2 of the major problems of observational studies, biases because of confounding and reverse causation. Mendelian randomization (MR) is an analytic method that leverages genetic variants associated with heritable risk factors to generate causal estimates between such factors and diseases. This method has recently been used to provide evidence for a causal relationship of LDLC and triglycerides with coronary artery disease (CAD). However, MR studies have not indicated any causality between HDLC and CAD.[6–10]

All MR studies rely on 3 basic assumptions: the genetic instrument (1) should be reliably associated with the exposure, (2) should be associated with the outcome only through the exposure, and (3) should not be associated with other factors that affect the outcome. This means that the genetic variants used as instruments must exert their effects on the outcome exclusively through the exposure of interest and not through alternative pathways. Single genetic variants, as single nucleotide polymorphisms (SNPs), that fulfill the MR assumptions, can be used, but their use may only be meaningful in large studies powerful enough to study the effect of the small proportion of exposures explained by the single variants. However, summary-level data of large meta-analyses of genome-wide association studies (GWAS) are increasingly available and allow the use of combinations of SNPs in MR analyses. However, SNPs may not fulfill the MR assumptions and may lead to bias through pleiotropic effects. Several methods have been recently developed to correct for such bias.[11,12]

We conducted an MR study, using summary-level data from publicly available GWAS of lipids and other cardiometabolic traits, to investigate the causal relationship of LDLC, HDLC, and triglycerides in the development of ischemic stroke as a whole and its 3 main subtypes: cardioembolic, large artery atherosclerosis stroke, and small artery occlusion.

Methods

Data Sources

Summary-level data for 185 genome-wide lipids-associated SNPs were obtained from the publicly available data through the Global Lipids Genetics Consortium.[13] The Global Lipids Genetics Consortium GWAS included 188 577 individuals of primarily European ancestry. The summary-level data for ischemic stroke and its subtypes were obtained from the National Institute of Neurological Disorders and Stroke–Stroke Genetics Network.[14] The Stroke Genetics Network GWAS included 16 851 ischemic stroke cases and 32 473 controls of predominantly European ancestry. Of the ischemic stroke cases, 2410 were subclassified as large artery atherosclerosis stroke, 3186 as small artery occlusion stroke, and 3427 as cardioembolic stroke using the Trial of Org 10172 in Acute Stroke Treatment criteria.[15] The Global Lipids Genetics Consortium summary data were available in the public domain, and an ethics approval was obtained from each contributing study in the original publication.[13] Each study included in the Stroke Genetics Network was approved by the local institutional review board and ethics committee, and all participants provided written informed consent.[14] In line with the Transparency and Openness Promotion Guidelines, data and analytic methods used have been appropriately cited, and the data used for the main analyses are provided in Tables I and II in the online-only Data Supplement.

SNP Selection

We obtained summary estimates for 185 SNPs reported in the most recent lipids GWAS by Willer et al[13] to be associated with LDLC, HDLC, and triglycerides. The 185 SNPs can be considered as independent because of low linkage disequilibrium (maximum r^2<0.2 between any SNPs). Each instrumental variable was constructed from SNPs showing GWAS significant association ($P<5\times10^{-8}$) with the respective trait. The instrumental variables included 76 SNPs for LDLC, 86 SNPs for HDLC, and 51 SNPs for triglycerides. The LDLC, HDLC, and triglycerides instruments explained 6.4%, 5.9%, and 4.6% of the variances in LDLC, HDLC, and triglycerides, respectively, as estimated by the gtx package in R. We then obtained summary estimates for the same set of 185 SNPs from the Stroke Genetics Network GWAS for ischemic stroke and its subtypes, and the effect alleles were matched with all lipid and stroke summary data. Summary data on 2 SNPs (rs1998013 and rs7422339) were missing.

Statistical Analysis

We performed 3 different MR analyses: (1) conventional inverse-variance–weighted MR; (2) multivariable MR to adjust for pleiotropy using summary-level data of other known lipid- and cardiometabolic traits; and (3) MR-Egger to account for all pleiotropic bias from known and unknown factors.

First, we performed inverse-variance–weighted MR (hereafter referred to as conventional MR) using each set of SNPs for each trait as instrumental variables. This method is a weighted linear regression between the instrumental SNP-β estimates of each lipid trait as exposure variables and the stroke β estimates of the same SNPs as outcome variables. This regression is weighted by the inverse-variance of SNP–stroke association, and the regression line is fixed to zero. This method, however, does not correct for pleiotropic bias if present.[16] To correct for that, we performed inverse-variance–weighted multivariable MR (hereafter referred to as multivariable MR) using all 185 SNPs. This method adjusts for pleiotropic effects across the included lipid traits in our analyses using β's from SNP–stroke as outcome variables and β's from SNP-LDLC, SNP-HDLC, and SNP-triglycerides as predictors in 1 multivariable model. The intercept was constrained to zero, and the regression was weighted by the inverse-variance of the SNP–stroke associations.[17] We additionally performed multivariable MR using a total of 343 SNPs (r^2<0.2). In addition to the 185 primarily lipid associated SNPs, we included SNPs that associate primarily with other cardiometabolic traits, including 97 SNPs for body mass index, 49 for waist-to-hip ratio adjusted for body mass index, 36 for fasting plasma glucose, and 26 for fasting plasma insulin, all obtained from publicly available data releases of the latest GWAS meta-analyses.[13,18–20] We additionally performed MR-Egger as previously described.[12] Egger regression was previously developed to detect small-study bias in meta-analyses and can be similarly used to detect bias because of unbalanced pleiotropy in MR studies. In contrast to conventional MR, the regression line is unconstrained, and the intercept represents the average pleiotropic effects across all SNPs, assuming that the distribution of pleiotropic effects is independent from the genetic associations with exposure, also known as the INstrument Strength Independent of Direct Effect assumption. In addition to MR-Egger, we performed sensitivity analyses to minimize biases because of pleiotropy by excluding SNPs exhibiting potential pleiotropy using Steiger filtering. Steiger filtering was performed using the 185 lipid-associated SNPs for each lipid trait. SNPs were excluded if they explained larger variance of any of the other 2 lipid traits compared with the trait of interest. We performed a 2-stage Steiger filtering. The first stage was based solely on the r^2 values of each SNP with respect to the 3 lipid traits. For example, for the LDLC instrument, we included an SNP if it had a larger r^2 value for LDLC compared with HDLC or triglycerides. In a stricter additional stage, SNPs were included only if r^2 values were significantly larger for the trait compared with the other 2 traits (P<0.05), as described before.[21] Finally, analyses were done using instruments that only included SNPs that exclusively associated with the trait of interest and not with the other traits ($P>5\times10^{-8}$). We analyzed all of these instruments for outlier pleiotropy using MR-Pleiotropy

Residual Sum and Outlier test and performed conventional MR and MR-Egger after exclusion of outlier SNPs. Analyses were performed using the MendelianRandomization, TwoSampleMR, and MR-Pleiotropy Residual Sum and Outlier test packages in R version 3.2.[22,23] Bonferroni-corrected 2-sided *P* values (*P*=0.004; 0.05/12) for 12 tests (3 exposures and 4 outcomes) were used.

We performed conventional MR analyses for LDLC using variants in genes encoding targets for LDLC lowering (*HMGCR*, *PCSK9*, and *NPC1L1*) or HDLC elevation (*CETP*). Variants in these genes were previously selected using r^2<0.4, and thus we incorporated covariance matrices in all MR analyses.[8,24]

Odds ratio (OR) thresholds were calculated for all stroke subtypes given the case count, sample size, instrument strength, and 80% minimum power.[25] For ischemic stroke, we had 80% power to detect associations with ORs as low as 1.11 with an instrument explaining 6.4% of the exposure and as high as 1.26 with instruments explaining 1.2% of the exposure. The OR range was 1.24 to 1.56 for large artery atherosclerosis stroke, 1.21 to 1.49 for small artery occlusion stroke, and 1.20 to 1.48 for cardioembolic stroke (Table III in the online-only Data Supplement).

Results

The associations between LDLC and ischemic stroke and subtypes are shown in Figure 1. Genetically predicted LDLC was associated with higher risk for ischemic stroke (OR: 1.12; 95% confidence interval [CI]: 1.01–1.24; per 1-SD elevation of LDLC) by conventional MR. MR-Egger showed a stronger association (OR: 1.22; 95% CI: 1.05–1.43), and the intercept did not indicate pleiotropic bias (*P* intercept=0.14). In addition, conventional MR suggested a direct association between genetically elevated LDLC and large artery atherosclerosis stroke (OR: 1.28; 95% CI: 1.07–1.53). Fully adjusted multivariable MR and MR-Egger showed stronger associations (OR: 1.36; 95% CI: 1.17–1.57 and OR: 1.40; 95% CI: 1.06–1.86, respectively), and MR-Egger intercept showed no pleiotropy (*P*=0.39). After Bonferroni correction, only multivariable MR analyses remained significant. Genetically predicted LDLC did not associate with small artery occlusion nor with cardioembolic stroke.

Genetically predicted elevations in HDLC levels were associated with lower risk of small artery occlusion stroke (OR: 0.79; 95% CI: 0.67–0.93; per 1-SD elevation of HDLC) using conventional MR (Figure 2). Similar associations were observed using multivariable MR. MR-Egger showed no evidence of pleiotropic bias (*P* intercept=0.33). Multivariable MR analyses showed a weaker evidence of association between HDLC and ischemic stroke as it did not pass Bonferroni correction. In addition, the MR-Egger estimate showed a null association (OR: 1.01; 95% CI: 0.87–1.18). No associations were observed for HDLC with large artery atherosclerosis or cardioembolic strokes. Finally, genetically elevated triglycerides did not associate with ischemic stroke or any of its subtypes (Figure 3).

In sensitivity analyses, MR-Pleiotropy Residual Sum and Outlier test showed outlier pleiotropy between LDLC and ischemic stroke. After excluding outlier SNPs, LDLC remained associated with ischemic stroke (OR: 1.14; 95% CI: 1.06–1.24; *P*=0.0009; Table IV in the online-only Data Supplement). The 2-stage Steiger filtering resulted in 66- and 61-SNP LDLC

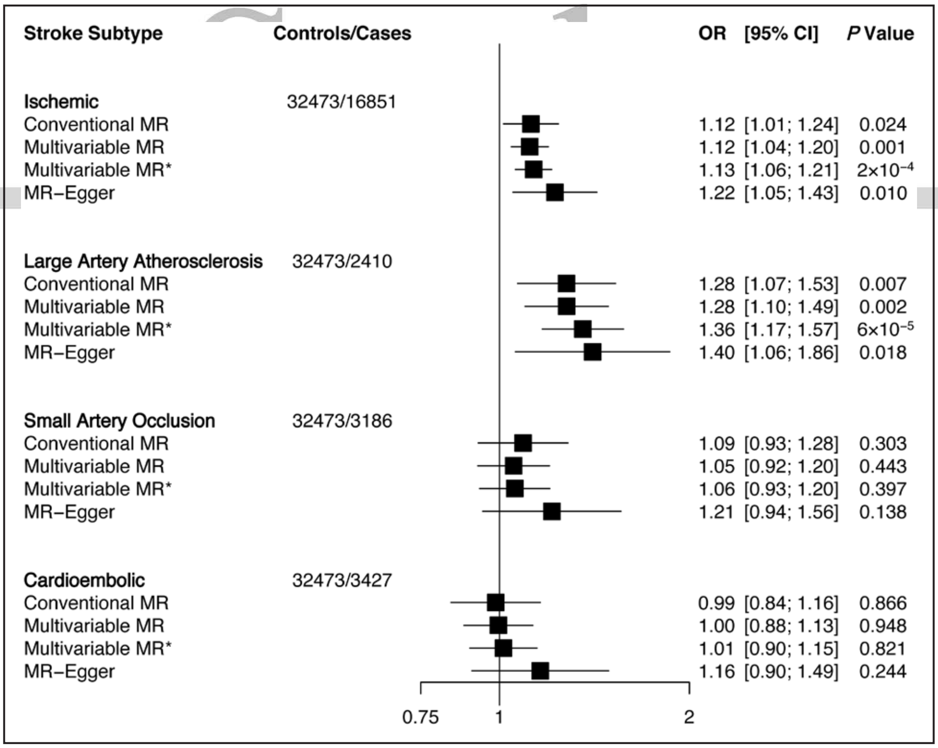

Figure 1. Association of low-density lipoprotein cholesterol with ischemic stroke and subtypes using different Mendelian randomization (MR) analyses. Odds ratio (OR) of ischemic stroke per 1-SD increase in each lipid trait. Conventional MR estimates were derived from 2-sample MR that forces the intercept of the slope line to zero and does not account for pleiotropy. Multivariable MR adjusts for other lipid traits and MR-Egger adjusts for unbalanced pleiotropy. *Multivariable MR analysis using summary estimates of 343 single nucleotide polymorphisms that adjusts for lipid traits, body mass index (BMI), waist hip ratio adjusted for BMI, fasting plasma glucose, and fasting plasma insulin. CI indicates confidence interval.

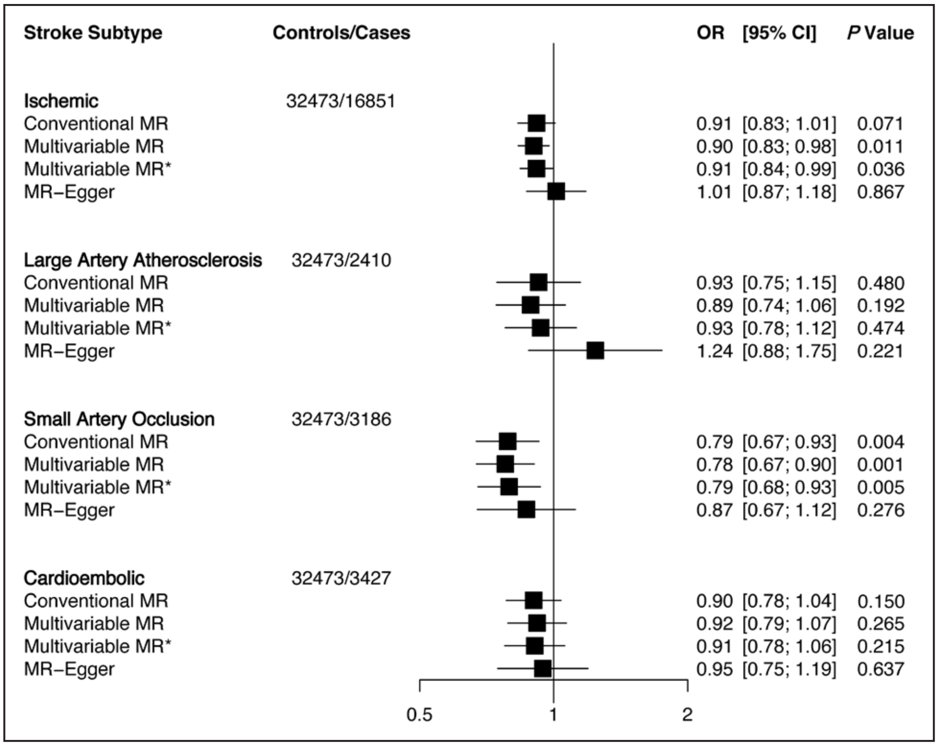

Figure 2. Association of high-density lipoprotein cholesterol with ischemic stroke and subtypes using different Mendelian randomization (MR) analyses. Odds ratio (OR) of ischemic stroke per 1-SD increase in each lipid trait. Conventional MR estimates were derived from 2-sample MR that forces the intercept of the slope line to zero and does not account for pleiotropy. Multivariable MR adjusts for other lipid traits and MR-Egger adjusts for unbalanced pleiotropy. *Multivariable MR analysis using summary estimates of 343 single nucleotide polymorphisms that adjust for lipid traits, body mass index (BMI), waist hip ratio adjusted for BMI, fasting plasma glucose, and fasting plasma insulin. CI indicates confidence interval.

instruments (explaining 5.9% and 5.6% of LDLC variance, respectively) that indicated direct association between LDLC and ischemic stroke (P=0.0001). Excluding SNPs associated with HDLC and triglycerides resulted in a 55-SNP instrument (explaining 3.6% of LDLC variance), which showed direct association with ischemic stroke (OR: 1.20; 95% CI: 1.08–1.34). All LDLC instruments after Steiger filtering and exclusion of HDLC and triglycerides SNPs showed direct association with large artery atherosclerosis stroke with ORs ranging between 1.32 and 1.36 using conventional MR.

MR-Pleiotropy Residual Sum and Outlier test showed outlier pleiotropy between HDLC and small artery atherosclerosis stroke (Table V in the online-only Data Supplement). Removal of outlier SNPs did not change our results (OR: 0.81; 95% CI: 0.70–0.93; P=0.003). Two-stage Steiger filtering resulted in 76- and 50-SNP HDLC instruments (explaining 4.9% and 4.2% of HDLC variance, respectively), which also showed nominal associations (P=0.014 and 0.010, respectively). Excluding LDLC- and triglycerides-associated SNPs resulted in a 50-SNP instrument (explaining 1.9% of HDLC variance) that did not show a significant association (OR: 0.82; 95% CI: 0.65–1.04; P=0.11).

Finally, an LDLC-lowering instrument created by SNPs in the *LDLR* gene supported a causal role of LDLC in ischemic (OR: 0.78; 95% CI: 0.63–0.96; per 1-SD lower LDLC) and large artery stroke (OR: 0.66; 95% CI: 0.45–0.98). Although, the *HMGCR* LDLC instrument showed lower risk of ischemic stroke (OR: 0.70; 95% CI: 0.50–0.99), no association was observed with large artery stroke, but a strong association was observed with small artery occlusion stroke (OR: 0.41; 95% CI: 0.21–0.81). The *PCSK9* LDLC instrument showed an unexpected higher risk of cardioembolic stroke with lower LDLC but no association with all ischemic or the other stroke subtypes. The *NPC1L1* instrument showed lower risk of ischemic (OR: 0.61; 95% CI: 0.37–0.99), large artery atherosclerosis (OR: 0.18; 95% CI: 0.06–0.53), and small artery occlusion (OR: 0.22; 95% CI: 0.08–0.56) strokes. Finally, a *CETP* instrument for higher HDLC suggested lower risk of ischemic (OR: 0.94; 95% CI: 0.88–1.00) and small artery occlusion stroke (OR: 0.88; 95% CI: 0.78–1.00; Figure I in the online-only Data Supplement).

Discussion

This MR study provides evidence for a direct relationship between LDLC and ischemic stroke that is likely driven by an association with large artery atherosclerosis stroke. There was no evidence of association of LDLC with small artery occlusion or cardioembolic stroke. In addition, results from this study provide evidence for an inverse association between HDLC and small artery occlusion stroke. Finally, this study does not provide any support for association of genetically higher triglycerides with ischemic, large artery atherosclerosis, small artery occlusion, or cardioembolic strokes.

Observational studies have provided discrepant results concerning the relationship of LDLC, HDLC, and triglycerides with ischemic stroke. Most but not all observational studies

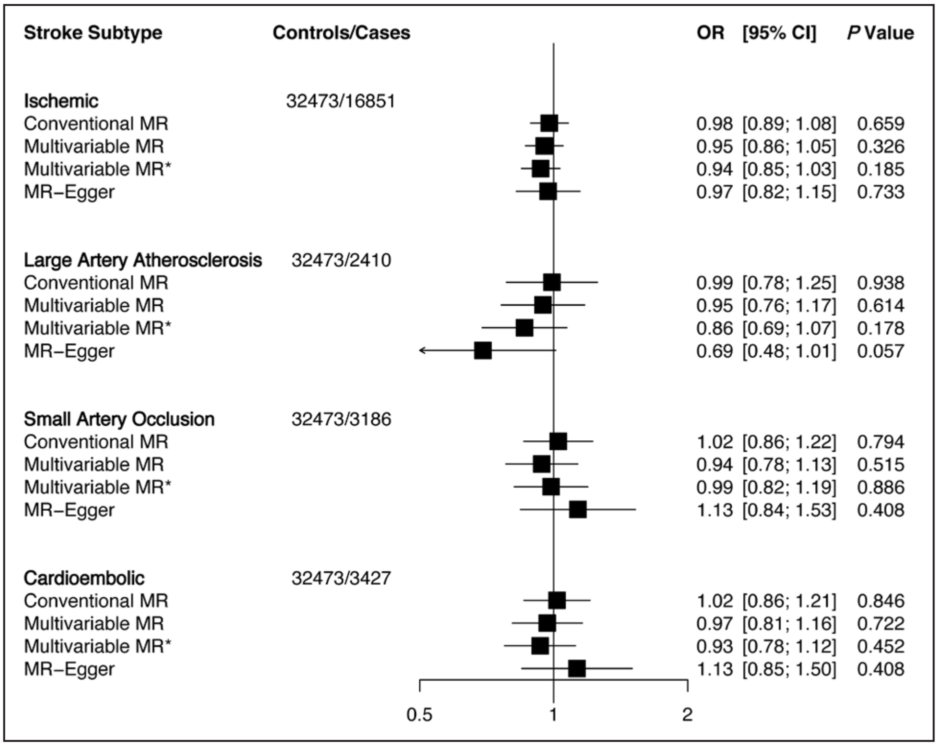

Figure 3. Association of triglycerides with ischemic stroke and subtypes using different Mendelian randomization (MR) analyses. Odds ratio (OR) of ischemic stroke per 1-SD increase in each lipid trait. Conventional MR estimates were derived from 2-sample MR that forces the intercept of the slope line to zero and does not account for pleiotropy. Multivariable MR adjusts for other lipid traits and MR-Egger adjusts for unbalanced pleiotropy. *Multivariable MR analysis using summary estimates of 343 single nucleotide polymorphisms that adjust for lipid traits, body mass index (BMI), waist hip ratio adjusted for BMI, fasting plasma glucose, and fasting plasma insulin. CI indicates confidence interval.

support a direct association between elevated total and LDLC and ischemic stroke.[1,26,27] In addition, most studies report an inverse relationship between HDLC and ischemic stroke[27–30] and a direct relationship between triglycerides and ischemic stroke.[1,27–31] However, most observational studies have not performed subtyping of ischemic stroke into different pathophysiological stroke subtypes. Few studies have shown direct association between total cholesterol and large artery atherosclerosis stroke.[32] However, the association between LDLC and small artery occlusion stroke has not been consistent among studies.[1,33,34] Randomized controlled trials (RTCs) have provided evidence for a causal association between LDLC and ischemic stroke while such evidence is lacking for HDLC and triglycerides. Statins have consistently shown benefits in terms of cardiovascular risk reduction including stroke.[2,35] However, there is insufficient evidence from HDLC and triglyceride-targeted trials concerning if elevation of HDLC or lowering of triglycerides decreases the risk of ischemic stroke. In a meta-analysis of clinical trials, none of 3 HDLC raising agents reduced ischemic stroke risk in patients treated with statins, which could potentially be related to off-target effects by these drugs.[5]

Clinical trials have previously shown that statins, and more recently PCSK9 inhibitors, provide comparable risk reduction in both ischemic stroke and CAD.[2,36] Attributable to a lifelong genetic exposure to lower LDLC, MR studies have demonstrated higher risk reduction in CAD compared with RCTs (≈70% versus ≈25% per 1 mmol/L lower LDLC).[2,6,36] Given the comparable effects of LDL lowering drugs in RCTs, one would expect MR studies with LDLC to provide a similar magnitude of risk increase for ischemic stroke as earlier shown for CAD. However, our study indicated only a 12% increased risk of ischemic stroke and 28% increased risk of large artery atherosclerosis stroke with 1 mmol/L higher LDLC. Although the MR-Egger estimates provided larger estimates (22% and 40%, respectively), they remained below the expected effect of lifelong exposure to elevated LDLC. One explanation for lower estimates could lie in the pathophysiological heterogeneity of ischemic stroke. In addition, it may be partially attributed to differences in the characteristics of the stroke cases in RCTs compared with those in our study or other MR studies. It is likely that lipid-lowering RCTs are enriched for lipid-related cardiovascular disease and that the incident stroke cases may carry more of a large artery atherosclerosis phenotype, that is, patients with higher risk by LDLC in our study compared with any ischemic stroke. Finally, prolonged exposure to elevated LDLC could have different consequences in stroke versus CAD.

As discussed above, our results suggest that genetic contribution of LDLC-related mechanisms in large artery stroke may be of lower magnitude compared with CAD despite sharing an atherosclerotic pathogenic origin. In fact, a recent study reported that a *PCSK9* loss-of-function variant was not associated with ischemic nor large artery atherosclerosis stroke.[37] Similarly, no association between lower LDLC by the *PCSK9* variants and ischemic stroke or large artery atherosclerosis stroke was observed in our study. In addition, our study indicated a weaker effect of LDLC lowering through *HMGCR* and *NPC1L1* variants on ischemic stroke (OR: 0.70 and 0.61 per 1 mmol/L lower LDLC) compared with previously reported effect by the same instruments on CAD (OR: ≈0.50 per 1 mmol/L lower LDLC).[8] In line with these observations, previous GWAS studies have indicated enrichment of lipid pathways in CAD but not in ischemic stroke pathogenesis.[37,38]

Our study does not provide support for a causal relationship between LDLC and small artery occlusion or cardioembolic stroke. However, it is important to remember that our results cannot exclude a weaker causal association. We were 80% powered to detect a minimum OR of 1.2 for both of these outcomes, and lack of evidence in these MR analyses could be a consequence of insufficient statistical power. In contrast, the lower risk of ischemic stroke by *HMGCR*-mediated lower LDLC in our study appeared to be solely mediated through its effect on small artery occlusion. This is in contrast to the J-STARS trial that found a lower risk of large artery atherosclerosis but not small artery occlusion or cardioembolic stroke among individuals in the pravastatin arm of the trial.[4] However, both the *HMGCR* instrument and the J-STARS trial were underpowered to detect associations with stroke subtypes, and therefore these results should not be taken as conclusive evidence. Finally, our study indicated a larger effect of *NPC1L1*-mediated lower LDLC on ischemic, large artery atherosclerosis, and small artery occlusion, which is in line with reported larger risk reduction of ischemic stroke (21%) compared with myocardial infarction (13%) by ezetimibe in the IMPROVE-IT trial (Improved Reduction of Outcomes: Vytorin Efficacy International Trial).[39]

The relationship between HDLC and ischemic stroke seems to be less clear as compared with LDLC in our study. Estimates from conventional and multivariable MR indicated nominal evidence for a weak inverse association, which vanished in the MR-Egger analysis. However, the MR-Egger intercept was not significant, and the MR-Egger analysis is less powerful compared with the inverse-variance–weighted methods.[12] A recent Framingham study investigated the role of 47 HDLC SNPs in ischemic stroke and reported no association. However, that study included 301 ischemic stroke cases compared with 16 851 in the present study.[40] Evidence from previous MR studies does not support a causal role between HDLC and CAD,[6,41] which is also consistent with our results of no association between genetically elevated HDLC and large artery atherosclerosis stroke. However, our study suggests an inverse association between HDLC and small artery occlusion stroke supported by both conventional and multivariable MR analyses but not by the less-powered MR-Egger. In addition, *CETP*-mediated higher HDLC provided some evidence for lower risk of small artery occlusion stroke. This needs to be further investigated in future MR studies with larger numbers and MRI-confirmed cases of small artery occlusion stroke. The putative role of HDLC in small artery occlusion or lacunar strokes has been reported in few previous studies. Higher serum HDLC has previously been found to associate with higher cerebral vasculature CO_2 reactivity that reflects the function of smaller intracerebral arteries.[42] There is also some evidence that HDLC may affect endothelial dysfunction or brain soluble amyloid levels, which are probable pathogenic mechanisms in small artery occlusion stroke.[43–45]

Our study does not support a causal role of triglycerides in ischemic stroke. This in contrast to recent MR studies that support a direct causal role between triglycerides and CAD.[6,7,46] Indeed, these results provide further support for a differential role of lipids in stroke and CAD, as discussed above. Our results are in line with those from clinical trials that have not been able to provide evidence that triglyceride lowering would affect stroke risk. In addition, our study does not show any direct causal relationship between triglycerides and large artery atherosclerosis stroke even though it shares common pathogenic mechanisms with CAD.

The main advantages of our study include the large number of ischemic stroke cases and the availability of data on ischemic stroke subtypes. In addition, we have used the most up-to-date summary-level genetic data on lipids and other cardiometabolic traits. Finally, we have used several methods to correct for a possible pleiotropic bias (multivariable MR, MR-Egger, Steiger filtering, and exclusion of pleiotropic SNPs). However, our study still has several limitations. Although the number of ischemic stroke cases was relatively large, the numbers of ischemic stroke subtypes were still relatively low, and therefore lack of evidence in some of our MR analyses could be a consequence of insufficient statistical power. However, most estimates were consistent using different MR approaches, which indicates that the observed associations are not likely to be by chance observations. Finally, we cannot rule out bias because of population stratification. However, all the SNP trait and SNP disease estimates were obtained from predominantly studies of European ancestry, which indicates that the cases, controls, and lipid measurements were obtained from comparable or similar populations.

Our results suggest that elevated LDLC levels increase the risk for ischemic stroke, indicating that further LDLC reduction is likely to result in further risk reduction in ischemic stroke. Our study further suggests that the LDLC-lowering effect may be of particular importance for risk reduction of large atherosclerosis stroke. However, elevated triglycerides do not increase the risk for ischemic stroke or any of its subtypes, indicating that future triglyceride-targeted therapies may not lead to beneficial effects in terms of decreasing the risk of ischemic stroke although they will likely lead to beneficial coronary effects.[46] Finally, our results provide some evidence of lower small artery occlusion stroke risk by elevated HDLC, but this needs to be confirmed by adequately powered future studies.

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Disclosures

None.

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Role of Blood Lipids in the Development of Ischemic Stroke and its Subtypes: A Mendelian Randomization Study

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SUPPLEMENTAL MATERIAL

Supplemental Table I. Association of 185 lipid-associated single nucleotide polymorphisms with lipid traits in the Global Lipids Genetics Consortium genome-wide association meta-analysis.

			LDL cholesterol			HDL cholesterol			Triglycerides		
SNP	A1	A2	beta	se	p	beta	se	p	beta	se	p
rs10019888	G	A	0.018	0.005	3.23E-04	-0.027	0.005	4.90E-08	0.023	0.005	2.28E-06
rs10029254	T	C	0.006	0.004	2.05E-01	-0.009	0.004	4.87E-02	0.027	0.004	7.55E-09
rs1010167	G	C	0.025	0.004	6.22E-11	-0.004	0.004	3.96E-01	0.002	0.004	8.08E-01
rs10102164	A	G	0.032	0.005	3.74E-11	-0.001	0.004	7.97E-01	0.011	0.004	6.87E-03
rs10282707	C	T	0.008	0.004	4.23E-02	0.025	0.004	1.03E-11	-0.009	0.003	6.52E-03
rs103294	T	C	0.007	0.005	1.23E-01	0.052	0.004	4.00E-30	-0.002	0.004	7.52E-01
rs1035744	T	C	0.007	0.004	1.58E-01	-0.006	0.004	1.55E-01	0.021	0.004	1.45E-07
rs10401969	T	C	0.118	0.007	2.65E-54	-0.013	0.007	1.02E-01	0.121	0.007	9.70E-70
rs10493326	A	G	0.021	0.004	1.91E-06	-0.001	0.004	6.73E-01	0.031	0.004	2.00E-15
rs10513688	A	G	0.022	0.006	2.18E-03	-0.005	0.006	6.08E-01	0.031	0.006	1.54E-07
rs10773105	T	C	0.006	0.004	1.22E-01	-0.036	0.004	3.20E-24	0.004	0.003	5.09E-01
rs10790162	A	G	0.076	0.007	1.09E-23	-0.095	0.007	9.91E-40	0.231	0.007	1.10E-249
rs10832962	T	C	0.032	0.004	6.62E-14	0.004	0.004	3.33E-01	0.011	0.004	5.18E-03
rs10861661	C	A	0.000	0.005	9.29E-01	-0.022	0.004	5.05E-07	0.023	0.004	2.60E-07
rs10903129	G	A	0.033	0.004	3.03E-17	0.001	0.003	8.59E-01	0.008	0.003	5.88E-03
rs11045163	A	G	0.006	0.004	1.63E-01	-0.022	0.004	3.20E-09	0.010	0.003	2.85E-03
rs11220462	A	G	0.059	0.006	6.61E-21	-0.016	0.006	8.75E-03	0.019	0.005	1.32E-03
rs11246602	C	T	0.002	0.006	5.26E-01	0.034	0.005	1.68E-10	-0.009	0.005	1.92E-01
rs11563251	T	C	0.035	0.006	4.50E-08	0.006	0.006	3.65E-01	0.008	0.006	8.26E-02
rs11660468	T	C	0.011	0.004	3.41E-03	0.039	0.003	3.60E-27	-0.001	0.003	8.80E-01
rs1169288	C	A	0.038	0.004	6.45E-21	0.010	0.004	9.13E-03	0.003	0.004	4.20E-01
rs1186380	C	T	0.024	0.004	8.46E-08	0.000	0.004	8.69E-01	-0.003	0.004	5.21E-01
rs12133576	A	G	0.010	0.004	3.83E-03	0.024	0.004	6.15E-11	-0.009	0.003	1.19E-02
rs12145743	T	G	0.004	0.004	3.38E-01	-0.020	0.004	1.80E-08	0.012	0.004	5.56E-04
rs12226802	G	A	0.000	0.005	6.19E-01	0.033	0.005	1.29E-09	-0.007	0.005	2.30E-01
rs1250229	C	T	0.024	0.004	3.13E-08	-0.003	0.004	4.04E-01	0.009	0.004	1.39E-02
rs12525163	T	C	0.004	0.004	2.56E-01	-0.022	0.004	1.52E-07	0.009	0.004	3.70E-02
rs1260326	T	C	0.021	0.004	1.51E-07	-0.011	0.004	1.74E-03	0.115	0.003	2.29E-239
rs12670798	C	T	0.034	0.004	4.81E-14	-0.001	0.004	7.33E-01	0.010	0.004	1.68E-02
rs12678919	A	G	0.008	0.006	5.05E-01	-0.155	0.006	1.38E-149	0.170	0.006	1.82E-199
rs12801636	A	G	0.008	0.005	1.45E-01	0.024	0.004	3.15E-08	-0.018	0.004	1.35E-05
rs13107325	C	T	0.016	0.008	5.74E-02	0.071	0.008	1.07E-15	-0.031	0.008	3.98E-05
rs13326165	G	A	0.004	0.005	2.67E-01	-0.029	0.004	9.04E-11	0.021	0.004	2.96E-06
rs1341267	A	C	0.002	0.004	8.87E-01	0.002	0.003	8.59E-01	-0.018	0.003	8.30E-07
rs1367117	A	G	0.119	0.004	9.48E-183	-0.022	0.004	7.59E-09	0.025	0.004	1.06E-11
rs1482852	A	G	0.003	0.004	5.75E-01	-0.021	0.004	6.34E-08	0.013	0.004	3.68E-04
rs1515110	T	G	0.006	0.004	9.36E-02	-0.032	0.004	8.04E-18	0.027	0.003	8.54E-14
rs1532085	A	G	0.003	0.004	6.47E-01	0.107	0.004	1.24E-188	0.031	0.003	2.32E-18

rs1535	A	G	0.053	0.004	7.77E-41	0.039	0.004	5.74E-27	-0.046	0.004	5.49E-40
rs1564348	C	T	0.048	0.005	2.76E-21	-0.008	0.005	1.68E-01	0.016	0.005	4.91E-04
rs16831243	T	C	0.038	0.006	9.06E-12	0.011	0.005	3.90E-02	-0.001	0.005	9.87E-01
rs1688030	C	T	0.016	0.008	3.73E-02	0.009	0.007	2.46E-01	0.038	0.007	1.99E-07
rs1689797	A	C	0.014	0.004	4.92E-04	-0.036	0.004	2.85E-21	0.011	0.004	2.42E-02
rs16942887	A	G	0.001	0.005	7.98E-01	0.083	0.005	8.28E-54	-0.012	0.005	2.96E-02
rs17145738	T	C	0.004	0.006	5.43E-01	0.041	0.005	4.95E-13	-0.115	0.005	9.42E-99
rs17173637	C	T	0.007	0.006	3.81E-01	-0.036	0.006	1.90E-08	0.021	0.006	1.04E-03
rs17286602	T	A	0.003	0.004	4.24E-01	-0.021	0.003	2.93E-07	0.006	0.003	1.62E-01
rs17345563	A	G	0.036	0.006	2.04E-09	-0.014	0.005	4.62E-03	0.015	0.005	3.90E-03
rs174532	A	G	0.035	0.004	3.13E-16	0.021	0.004	6.93E-08	-0.016	0.004	3.44E-05
rs17508045	T	C	0.049	0.007	4.91E-12	-0.009	0.006	4.66E-02	-0.008	0.006	4.00E-01
rs17695224	G	A	0.011	0.004	1.25E-02	0.029	0.004	2.42E-13	-0.012	0.004	1.13E-02
rs17788930	A	G	0.005	0.004	2.18E-01	0.036	0.004	1.53E-22	-0.011	0.004	2.80E-03
rs17789218	T	C	0.024	0.004	3.26E-07	-0.004	0.004	1.35E-01	0.006	0.004	6.65E-02
rs1781930	G	A	0.010	0.005	5.70E-02	0.002	0.005	6.25E-01	0.031	0.004	2.51E-11
rs1800562	G	A	0.062	0.008	8.25E-14	0.007	0.007	2.42E-01	-0.013	0.007	1.72E-01
rs1800961	C	T	0.069	0.011	6.03E-10	0.127	0.010	1.64E-34	0.002	0.009	7.02E-01
rs181362	C	T	0.007	0.005	7.93E-02	0.038	0.004	9.24E-18	0.009	0.004	2.81E-02
rs1883025	C	T	0.030	0.004	6.14E-11	0.070	0.004	1.50E-65	0.022	0.004	2.91E-07
rs1998013	C	T	0.381	0.022	3.02E-48	-0.035	0.020	4.13E-01	-0.009	0.020	6.57E-01
rs2000999	A	G	0.065	0.005	4.22E-41	0.002	0.004	9.52E-01	0.019	0.004	7.49E-07
rs2030746	T	C	0.021	0.004	8.61E-09	-0.003	0.004	3.06E-01	0.003	0.004	4.91E-01
rs205262	A	G	0.009	0.004	3.13E-02	0.028	0.004	3.88E-13	-0.003	0.004	8.03E-01
rs2068888	G	A	0.017	0.004	3.89E-05	-0.019	0.004	2.15E-06	0.024	0.003	1.68E-11
rs2073547	G	A	0.049	0.005	1.92E-21	-0.005	0.005	3.10E-01	0.015	0.004	3.39E-03
rs217386	G	A	0.036	0.004	1.20E-19	-0.001	0.004	4.99E-01	0.010	0.003	6.35E-03
rs2240327	G	A	0.001	0.004	9.71E-01	0.024	0.003	1.11E-11	-0.002	0.003	8.67E-01
rs2241210	G	A	0.008	0.004	8.55E-02	0.033	0.004	2.49E-20	0.003	0.003	2.47E-01
rs2247056	C	T	0.025	0.004	1.42E-08	0.012	0.004	3.79E-03	0.038	0.004	3.86E-21
rs2255141	A	G	0.030	0.004	1.32E-13	0.034	0.004	2.35E-17	-0.021	0.004	1.70E-09
rs2278236	A	G	0.007	0.004	1.27E-01	0.033	0.004	3.19E-18	-0.014	0.003	1.52E-04
rs2287623	G	A	0.022	0.004	5.40E-08	0.011	0.004	2.05E-03	-0.001	0.003	9.20E-01
rs2288002	G	A	0.029	0.004	1.26E-12	0.007	0.004	1.21E-01	0.009	0.003	1.69E-03
rs2290547	A	G	0.001	0.005	7.93E-01	-0.030	0.005	3.69E-09	0.010	0.004	2.21E-02
rs2293889	T	G	0.015	0.004	2.42E-04	-0.031	0.004	4.27E-17	0.006	0.003	1.51E-01
rs2294261	A	C	0.033	0.004	6.57E-17	-0.009	0.004	2.06E-02	0.002	0.003	5.87E-01
rs2297374	C	T	0.033	0.004	1.26E-15	-0.006	0.004	2.18E-01	0.009	0.003	4.74E-03
rs2303975	G	A	0.001	0.005	9.35E-01	-0.028	0.005	1.59E-07	0.012	0.005	2.68E-02
rs2326077	C	T	0.034	0.004	5.00E-17	0.004	0.004	2.18E-01	0.018	0.003	5.35E-07
rs2328223	C	A	0.030	0.005	5.63E-09	0.000	0.005	8.59E-01	-0.007	0.005	1.15E-01
rs2412710	G	A	0.002	0.015	6.40E-01	0.084	0.014	1.36E-09	-0.099	0.013	1.66E-11
rs2472509	G	T	0.000	0.004	7.08E-01	0.023	0.004	1.21E-09	-0.002	0.004	7.22E-01

rs2587534	A	G	0.039	0.004	8.06E-25	0.009	0.003	3.85E-03	0.004	0.003	2.71E-01
rs2602836	G	A	0.001	0.004	8.31E-01	-0.019	0.003	4.96E-08	0.009	0.003	2.12E-02
rs261342	C	G	0.003	0.007	7.36E-01	-0.107	0.006	1.47E-68	-0.045	0.006	2.53E-12
rs2642438	G	A	0.035	0.004	7.32E-16	0.030	0.004	7.78E-14	-0.017	0.004	5.27E-06
rs2652834	A	G	0.002	0.005	7.32E-01	-0.029	0.004	3.59E-11	0.025	0.004	1.92E-08
rs267733	A	G	0.033	0.005	5.29E-09	-0.016	0.005	3.58E-03	0.003	0.005	6.16E-01
rs2710642	A	G	0.024	0.004	6.09E-09	-0.010	0.004	7.69E-03	0.007	0.003	4.71E-02
rs2737252	G	A	0.031	0.004	7.04E-14	0.013	0.004	3.94E-03	0.009	0.004	1.07E-02
rs2923084	G	A	0.012	0.005	1.84E-02	-0.026	0.005	5.02E-08	0.012	0.004	5.97E-03
rs2925979	C	T	0.003	0.004	6.30E-01	0.035	0.004	1.32E-19	-0.021	0.004	2.14E-07
rs2954022	C	A	0.055	0.004	2.39E-47	-0.040	0.003	2.12E-29	0.078	0.003	2.23E-113
rs2980885	G	A	0.031	0.005	6.26E-11	-0.035	0.004	1.73E-14	0.058	0.004	3.00E-40
rs314253	T	C	0.024	0.004	3.44E-10	-0.003	0.004	3.53E-01	0.009	0.003	2.98E-02
rs3198697	T	C	0.010	0.004	6.86E-03	0.016	0.004	3.28E-05	-0.020	0.003	2.21E-08
rs326214	A	G	0.007	0.005	2.04E-01	-0.061	0.005	2.17E-36	0.024	0.004	3.79E-07
rs355838	T	G	0.018	0.004	3.05E-05	-0.019	0.004	4.10E-07	0.014	0.003	1.21E-04
rs364585	G	A	0.025	0.004	4.28E-10	0.001	0.004	8.22E-01	-0.002	0.003	4.40E-01
rs3741414	C	T	0.016	0.004	3.41E-04	-0.030	0.004	6.10E-14	0.028	0.004	1.44E-13
rs3761445	A	G	0.008	0.004	3.99E-02	-0.016	0.004	3.94E-06	0.023	0.003	8.06E-12
rs3780181	A	G	0.045	0.007	1.76E-09	0.004	0.007	5.42E-01	-0.007	0.007	4.91E-01
rs3817588	T	C	0.026	0.005	4.43E-07	-0.005	0.004	2.30E-01	0.067	0.004	1.30E-55
rs3822072	A	G	0.007	0.004	3.71E-02	-0.025	0.003	4.06E-12	0.018	0.003	5.74E-07
rs38855	A	G	0.001	0.004	9.73E-01	-0.015	0.003	9.05E-05	0.019	0.003	2.11E-08
rs3996352	A	G	0.005	0.004	1.21E-01	-0.030	0.003	3.59E-17	0.018	0.003	5.88E-08
rs4075205	C	T	0.012	0.004	8.21E-04	-0.022	0.004	3.54E-09	0.009	0.003	5.16E-02
rs4148005	G	T	0.015	0.004	1.49E-04	-0.028	0.004	5.74E-14	0.007	0.004	4.37E-02
rs4148218	G	A	0.044	0.005	6.76E-21	-0.003	0.004	4.56E-01	0.004	0.004	2.95E-01
rs4240624	A	G	0.067	0.006	2.62E-23	0.082	0.006	1.32E-45	-0.028	0.006	1.09E-06
rs4332136	C	G	-0.043	0.098	6.60E-01	0.480	0.065	1.00E-13	0.024	0.053	6.50E-01
rs442177	T	G	0.016	0.004	6.09E-05	-0.022	0.003	2.19E-09	0.031	0.003	1.32E-18
rs4465830	G	A	0.009	0.005	5.99E-02	-0.060	0.004	5.18E-40	0.053	0.004	2.98E-34
rs4530754	A	G	0.028	0.004	3.58E-12	0.001	0.003	9.34E-01	0.002	0.003	7.42E-01
rs4587594	G	A	0.049	0.004	1.63E-32	0.015	0.004	1.08E-04	0.069	0.004	3.50E-82
rs4650994	A	G	0.003	0.004	3.38E-01	-0.021	0.003	6.70E-09	0.002	0.003	3.98E-01
rs4660293	G	A	0.011	0.004	1.23E-02	-0.035	0.004	2.86E-18	0.020	0.004	2.87E-07
rs4722551	C	T	0.039	0.005	3.95E-14	0.010	0.005	2.47E-02	-0.027	0.004	1.58E-09
rs4791641	C	T	0.020	0.004	1.31E-07	0.004	0.003	9.51E-02	-0.003	0.003	4.59E-01
rs4846914	G	A	0.004	0.004	2.34E-01	-0.048	0.003	3.51E-41	0.040	0.003	7.20E-31
rs4871137	G	T	0.004	0.004	2.36E-01	0.021	0.004	1.93E-07	0.001	0.004	6.56E-01
rs4917014	G	T	0.005	0.004	2.46E-01	0.022	0.004	1.03E-08	-0.001	0.004	8.87E-01
rs4921914	C	T	0.023	0.004	1.92E-07	0.002	0.004	3.94E-01	0.035	0.004	4.87E-17
rs492571	T	C	0.003	0.010	4.72E-01	0.066	0.009	1.27E-12	-0.080	0.009	6.74E-17
rs492602	G	A	0.029	0.004	9.42E-14	-0.003	0.004	4.27E-01	0.014	0.004	2.48E-04

rs4939883	C	T	0.021	0.005	1.47E-05	0.080	0.005	1.80E-66	0.005	0.004	3.81E-01
rs4942486	T	C	0.024	0.004	2.26E-11	-0.014	0.003	1.16E-04	0.007	0.003	2.38E-02
rs4969178	G	A	0.011	0.004	8.20E-03	0.026	0.004	1.53E-12	-0.018	0.003	5.70E-06
rs4976033	A	G	0.001	0.004	8.75E-01	0.022	0.004	6.42E-08	-0.014	0.004	2.01E-04
rs4983559	G	A	0.003	0.004	5.83E-01	0.020	0.004	9.57E-09	0.000	0.004	9.71E-01
rs499974	A	C	0.001	0.005	8.26E-01	-0.026	0.004	1.12E-08	-0.009	0.004	5.41E-02
rs515135	C	T	0.139	0.005	1.09E-178	-0.011	0.004	9.01E-03	0.019	0.004	1.36E-04
rs5763662	T	C	0.077	0.012	1.19E-08	0.033	0.011	6.37E-03	0.000	0.011	8.88E-01
rs579459	C	T	0.067	0.005	2.42E-44	0.015	0.004	1.68E-03	-0.014	0.004	1.08E-03
rs5880	C	G	0.047	0.010	1.59E-06	-0.307	0.009	1.37E-233	0.048	0.009	4.71E-08
rs6016381	T	C	0.036	0.004	6.85E-20	-0.008	0.004	6.08E-02	0.014	0.003	1.99E-05
rs603446	C	T	0.009	0.004	1.14E-02	-0.002	0.004	8.73E-01	0.050	0.003	3.92E-43
rs6065311	C	T	0.042	0.004	1.66E-30	0.002	0.003	4.37E-01	0.006	0.003	2.27E-02
rs634869	T	C	0.013	0.004	8.37E-04	-0.023	0.003	1.00E-10	0.027	0.003	1.78E-14
rs6450176	A	G	0.010	0.004	1.18E-02	-0.025	0.004	6.88E-10	0.019	0.004	3.61E-07
rs646776	T	C	0.160	0.004	1.63E-272	-0.034	0.004	2.72E-15	0.003	0.004	3.73E-01
rs6489818	A	G	0.028	0.005	4.57E-09	0.000	0.005	9.28E-01	-0.004	0.004	5.40E-01
rs6511720	G	T	0.221	0.006	3.85E-262	-0.025	0.006	6.32E-05	0.008	0.006	1.04E-01
rs653178	T	C	0.023	0.004	3.88E-09	0.026	0.004	1.06E-12	-0.010	0.003	2.88E-02
rs6544713	T	C	0.081	0.004	4.84E-83	-0.003	0.004	3.88E-01	0.013	0.004	9.60E-04
rs6603981	T	C	0.034	0.004	3.10E-13	0.004	0.004	3.81E-01	0.007	0.004	1.74E-01
rs6680658	G	A	0.006	0.005	2.18E-01	-0.023	0.004	7.49E-08	0.017	0.004	1.44E-05
rs6805251	T	C	0.012	0.004	1.86E-03	0.020	0.004	1.33E-08	-0.001	0.003	9.94E-01
rs6831256	G	A	0.019	0.004	9.07E-07	-0.013	0.004	2.97E-03	0.026	0.004	1.60E-12
rs6859	A	G	0.084	0.004	4.65E-88	-0.018	0.004	7.73E-06	0.014	0.004	8.10E-05
rs686030	A	C	0.009	0.005	2.36E-01	0.055	0.005	4.29E-27	0.025	0.005	2.23E-07
rs687339	T	C	0.011	0.005	9.97E-03	-0.032	0.004	7.11E-13	0.029	0.004	2.51E-12
rs688	T	C	0.054	0.004	1.01E-43	-0.011	0.003	1.55E-03	0.004	0.003	2.18E-01
rs6882076	C	T	0.046	0.004	3.31E-31	0.002	0.004	6.85E-01	0.029	0.004	1.51E-15
rs702485	G	A	0.001	0.004	7.87E-01	0.024	0.003	6.45E-12	-0.002	0.003	4.75E-01
rs7033354	C	T	0.019	0.004	1.42E-06	-0.015	0.004	6.54E-05	0.019	0.003	4.44E-07
rs7117842	C	T	0.019	0.004	7.56E-07	0.027	0.004	1.06E-14	-0.002	0.003	5.43E-01
rs7225700	C	T	0.030	0.004	3.56E-13	0.010	0.004	2.35E-02	-0.005	0.004	2.36E-01
rs7254892	G	A	0.485	0.012	0.00E+00	-0.053	0.011	4.17E-05	-0.124	0.011	1.40E-24
rs7264396	C	T	0.025	0.005	4.41E-08	0.005	0.004	6.02E-02	0.011	0.004	2.58E-03
rs731839	A	G	0.002	0.004	5.17E-01	0.022	0.004	3.44E-09	-0.022	0.004	2.65E-09
rs7422339	A	C	0.008	0.004	1.42E-01	-0.027	0.004	8.73E-10	0.000	0.004	8.60E-01
rs749671	G	A	0.015	0.004	1.05E-04	-0.007	0.004	9.57E-02	0.021	0.003	6.11E-10
rs7607980	T	C	0.007	0.006	2.88E-01	-0.045	0.005	1.81E-15	0.036	0.005	2.41E-12
rs7640978	C	T	0.039	0.007	9.84E-09	0.000	0.006	7.22E-01	0.018	0.006	5.54E-03
rs7703051	A	C	0.073	0.004	1.40E-77	0.002	0.004	4.21E-01	0.006	0.003	1.63E-01
rs7832643	T	G	0.034	0.004	2.67E-17	-0.001	0.004	5.95E-01	0.002	0.003	4.72E-01
rs7897379	C	T	0.010	0.004	4.07E-03	0.019	0.003	1.31E-08	-0.027	0.003	1.27E-17

rs799160	T	C	0.005	0.004	2.86E-01	-0.013	0.004	2.94E-04	0.040	0.004	5.46E-30
rs8017377	A	G	0.030	0.004	2.52E-15	-0.004	0.004	4.34E-01	0.006	0.004	1.42E-01
rs8077889	C	A	0.001	0.005	9.15E-01	-0.021	0.004	1.50E-06	0.025	0.004	9.88E-09
rs8176720	T	C	0.033	0.004	1.59E-17	0.001	0.004	9.43E-01	-0.007	0.004	6.09E-02
rs838876	G	A	0.003	0.004	4.42E-01	-0.049	0.004	7.33E-33	0.005	0.004	3.77E-01
rs868943	G	A	0.026	0.004	8.44E-11	0.008	0.004	3.55E-02	0.014	0.003	3.18E-04
rs894210	G	A	0.007	0.004	1.22E-01	-0.069	0.003	1.68E-84	0.067	0.003	2.94E-89
rs903319	C	T	0.027	0.004	5.22E-11	0.010	0.004	1.22E-02	-0.005	0.004	1.38E-01
rs931992	T	G	0.002	0.006	7.03E-01	0.029	0.005	4.20E-07	-0.009	0.005	1.33E-01
rs9491696	G	C	0.006	0.004	2.64E-01	-0.020	0.003	5.21E-10	0.018	0.003	4.87E-07
rs952044	C	T	0.003	0.004	5.79E-01	0.023	0.004	1.19E-08	-0.010	0.004	2.45E-03
rs9686661	T	C	0.018	0.005	5.29E-04	-0.028	0.004	1.37E-08	0.038	0.004	2.54E-16
rs9693857	C	T	0.005	0.004	2.98E-01	0.004	0.004	5.27E-01	-0.020	0.003	1.69E-08
rs970548	C	A	0.016	0.004	6.65E-04	0.026	0.004	1.71E-10	0.003	0.004	4.59E-01
rs9875338	G	A	0.027	0.004	2.21E-11	0.007	0.004	2.10E-02	0.014	0.003	1.62E-05
rs9930333	T	G	0.000	0.004	7.18E-01	0.020	0.004	2.07E-08	-0.021	0.004	3.25E-08
rs998584	A	C	0.001	0.004	9.36E-01	-0.026	0.004	2.27E-11	0.029	0.004	3.42E-15
rs9989419	A	G	0.028	0.004	2.49E-12	-0.147	0.004	0.00E+00	0.024	0.004	1.05E-11

Reference: Global Lipids Genetics Consortium[1]

Supplemental Table II. Association of 185 lipid-associated single nucleotide polymorphisms with ischemic stroke subtypes in the Stroke Genetics Network genome-wide association meta-analysis.

			Ischemic Stroke			Large Artery Atherosclerosis			Small Artery Occlusion			Cardio-embolic		
SNP	A1	A2	beta	se	p	beta	se	p	beta	se	p	beta	se	p
rs10019888	G	A	0.007	0.020	0.735	-0.002	0.044	0.962	0.032	0.038	0.398	-0.003	0.037	0.942
rs10029254	T	C	0.001	0.019	0.972	-0.007	0.040	0.857	-0.015	0.037	0.689	-0.002	0.034	0.950
rs1010167	G	C	0.026	0.016	0.095	0.001	0.034	0.981	-0.026	0.030	0.381	0.024	0.029	0.405
rs10102164	A	G	0.035	0.019	0.069	0.040	0.042	0.343	-0.002	0.037	0.964	0.010	0.036	0.773
rs10282707	C	T	-0.016	0.015	0.294	0.037	0.034	0.268	-0.017	0.030	0.554	-0.033	0.028	0.243
rs103294	T	C	0.023	0.019	0.237	0.010	0.042	0.819	0.026	0.037	0.474	0.036	0.035	0.304
rs1035744	T	C	0.013	0.017	0.417	-0.025	0.037	0.503	0.000	0.032	0.992	0.012	0.031	0.695
rs10401969	T	C	0.013	0.026	0.613	-0.053	0.060	0.376	-0.024	0.050	0.631	0.067	0.052	0.197
rs10493326	A	G	-0.017	0.018	0.348	-0.023	0.038	0.550	-0.056	0.035	0.113	-0.004	0.032	0.899
rs10513688	A	G	0.005	0.024	0.833	0.014	0.053	0.787	-0.008	0.046	0.870	0.091	0.043	0.034
rs10773105	T	C	0.014	0.016	0.372	0.028	0.035	0.423	0.025	0.031	0.409	-0.009	0.029	0.751
rs10790162	A	G	-0.006	0.030	0.836	-0.005	0.066	0.943	0.042	0.056	0.449	0.060	0.054	0.266
rs10832962	T	C	-0.017	0.017	0.323	-0.028	0.037	0.449	-0.008	0.033	0.800	-0.013	0.031	0.673
rs10861661	C	A	0.000	0.017	0.981	0.021	0.039	0.594	0.019	0.033	0.581	0.008	0.033	0.817
rs10903129	G	A	-0.021	0.015	0.160	-0.007	0.033	0.831	-0.019	0.029	0.511	-0.076	0.028	0.006
rs11045163	A	G	0.001	0.015	0.925	0.007	0.034	0.826	-0.005	0.029	0.867	-0.005	0.028	0.854
rs11220462	A	G	-0.038	0.023	0.092	0.050	0.048	0.298	-0.050	0.045	0.264	-0.122	0.043	0.004
rs11246602	C	T	0.040	0.024	0.095	-0.016	0.052	0.762	0.008	0.047	0.861	0.060	0.044	0.172
rs11563251	T	C	0.021	0.023	0.355	0.099	0.050	0.049	-0.035	0.044	0.424	-0.020	0.044	0.645
rs11660468	T	C	0.017	0.016	0.288	0.089	0.033	0.008	0.042	0.030	0.165	-0.036	0.028	0.205
rs1169288	C	A	0.027	0.017	0.103	-0.015	0.036	0.684	0.082	0.032	0.009	0.033	0.030	0.272
rs1186380	C	T	0.011	0.018	0.536	0.019	0.039	0.621	-0.004	0.036	0.922	0.031	0.032	0.335
rs12133576	A	G	-0.028	0.016	0.074	-0.058	0.035	0.094	-0.045	0.030	0.141	-0.009	0.029	0.760
rs12145743	T	G	0.000	0.016	0.994	0.003	0.035	0.925	0.040	0.032	0.213	0.019	0.030	0.529
rs12226802	G	A	0.044	0.024	0.068	-0.008	0.053	0.875	0.031	0.047	0.503	0.050	0.044	0.257
rs1250229	C	T	-0.026	0.018	0.139	-0.020	0.038	0.602	-0.040	0.035	0.257	-0.022	0.032	0.490
rs12525163	T	C	0.008	0.017	0.627	-0.016	0.037	0.666	-0.008	0.032	0.809	-0.013	0.031	0.668
rs1260326	T	C	0.011	0.016	0.484	0.007	0.034	0.826	0.014	0.030	0.647	-0.009	0.028	0.764
rs12670798	C	T	-0.013	0.018	0.458	-0.006	0.039	0.887	-0.002	0.033	0.954	-0.003	0.033	0.934
rs12678919	A	G	-0.014	0.025	0.573	-0.063	0.053	0.233	0.058	0.048	0.227	-0.029	0.045	0.517
rs12801636	A	G	-0.024	0.018	0.182	-0.131	0.040	0.001	-0.003	0.033	0.936	0.010	0.033	0.764
rs13107325	C	T	-0.013	0.030	0.665	-0.016	0.064	0.798	-0.013	0.059	0.819	-0.024	0.053	0.647
rs13326165	G	A	-0.008	0.019	0.657	-0.062	0.041	0.126	-0.007	0.036	0.849	0.007	0.035	0.851
rs1341267	A	C	0.008	0.016	0.639	0.030	0.035	0.381	0.008	0.033	0.806	0.029	0.029	0.321
rs1367117	A	G	-0.007	0.017	0.680	0.022	0.036	0.551	-0.032	0.033	0.330	-0.019	0.031	0.542
rs1482852	A	G	0.008	0.015	0.588	0.021	0.034	0.533	0.022	0.029	0.458	-0.019	0.028	0.513
rs1515110	T	G	0.017	0.016	0.284	0.040	0.034	0.248	0.044	0.030	0.146	0.023	0.029	0.422
rs1532085	A	G	-0.003	0.015	0.852	0.077	0.034	0.021	0.003	0.029	0.919	-0.029	0.028	0.308

rs1535	A	G	0.022	0.016	0.184	0.102	0.036	0.005	-0.019	0.031	0.550	0.011	0.030	0.706
rs1564348	C	T	-0.013	0.021	0.524	0.084	0.044	0.060	-0.019	0.040	0.638	0.004	0.039	0.921
rs16831243	T	C	-0.024	0.024	0.316	-0.031	0.053	0.554	-0.039	0.045	0.382	-0.053	0.044	0.229
rs1688030	C	T	0.027	0.028	0.341	0.000	0.064	0.998	0.071	0.054	0.186	0.006	0.054	0.916
rs1689797	A	C	-0.013	0.016	0.424	0.020	0.035	0.556	-0.004	0.031	0.885	0.010	0.029	0.727
rs16942887	A	G	-0.012	0.022	0.590	0.065	0.047	0.168	-0.003	0.041	0.946	-0.061	0.041	0.138
rs17145738	T	C	-0.043	0.024	0.074	-0.009	0.052	0.866	-0.001	0.047	0.980	-0.017	0.045	0.711
rs17173637	C	T	-0.001	0.026	0.965	-0.029	0.058	0.617	0.007	0.052	0.887	0.017	0.048	0.715
rs17286602	T	A	0.020	0.015	0.192	0.049	0.033	0.140	0.010	0.029	0.748	0.010	0.028	0.722
rs17345563	A	G	-0.006	0.024	0.804	-0.044	0.052	0.401	-0.019	0.048	0.694	-0.060	0.044	0.174
rs174532	A	G	0.006	0.017	0.732	0.041	0.037	0.261	0.013	0.034	0.700	-0.009	0.031	0.763
rs17508045	T	C	0.045	0.029	0.116	0.070	0.062	0.263	0.050	0.057	0.385	0.074	0.053	0.157
rs17695224	G	A	-0.025	0.017	0.146	-0.056	0.037	0.131	-0.012	0.033	0.707	-0.031	0.031	0.326
rs17788930	A	G	-0.008	0.016	0.639	0.022	0.035	0.527	-0.064	0.031	0.039	-0.017	0.030	0.573
rs17789218	T	C	-0.002	0.019	0.928	-0.062	0.041	0.124	0.005	0.037	0.895	-0.051	0.034	0.134
rs1781930	G	A	-0.015	0.021	0.480	0.009	0.045	0.843	0.004	0.041	0.921	-0.029	0.038	0.452
rs1800562	G	A	0.001	0.035	0.971	0.122	0.077	0.111	0.010	0.071	0.885	-0.117	0.061	0.054
rs1800961	C	T	-0.027	0.046	0.553	0.008	0.101	0.936	0.029	0.089	0.747	-0.151	0.082	0.066
rs181362	C	T	-0.025	0.018	0.165	-0.067	0.040	0.098	-0.038	0.034	0.256	-0.034	0.034	0.314
rs1883025	C	T	0.000	0.017	0.992	-0.021	0.037	0.572	-0.048	0.032	0.133	-0.035	0.031	0.268
rs1998013	C	T	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs2000999	A	G	0.027	0.019	0.156	-0.017	0.042	0.692	-0.031	0.038	0.412	0.029	0.035	0.404
rs2030746	T	C	0.020	0.015	0.194	0.008	0.033	0.811	0.037	0.029	0.208	0.008	0.028	0.787
rs205262	A	G	-0.020	0.016	0.223	-0.072	0.036	0.048	-0.010	0.032	0.755	-0.018	0.030	0.548
rs2068888	G	A	0.027	0.015	0.076	0.038	0.033	0.250	-0.016	0.029	0.572	0.050	0.028	0.076
rs2073547	G	A	0.014	0.019	0.459	0.069	0.041	0.094	0.083	0.035	0.018	-0.045	0.036	0.207
rs217386	G	A	0.023	0.016	0.137	0.062	0.034	0.071	0.052	0.031	0.089	-0.025	0.028	0.381
rs2240327	G	A	-0.011	0.015	0.463	-0.020	0.033	0.545	-0.018	0.029	0.527	0.018	0.028	0.510
rs2241210	G	A	0.010	0.015	0.492	0.035	0.033	0.288	-0.006	0.029	0.845	0.000	0.028	0.998
rs2247056	C	T	0.011	0.018	0.558	0.032	0.039	0.410	-0.004	0.035	0.917	0.014	0.033	0.666
rs2255141	A	G	0.016	0.017	0.341	0.000	0.037	0.999	0.043	0.033	0.188	0.011	0.031	0.730
rs2278236	A	G	-0.004	0.015	0.768	-0.005	0.033	0.890	-0.012	0.029	0.664	0.033	0.027	0.235
rs2287623	G	A	0.017	0.015	0.253	0.039	0.033	0.246	-0.012	0.029	0.671	0.065	0.028	0.021
rs2288002	G	A	0.021	0.015	0.170	0.053	0.033	0.110	-0.005	0.029	0.865	0.022	0.028	0.432
rs2290547	A	G	0.035	0.021	0.095	0.013	0.045	0.782	0.023	0.041	0.573	0.074	0.038	0.049
rs2293889	T	G	-0.018	0.016	0.241	-0.038	0.034	0.268	-0.033	0.031	0.277	-0.008	0.028	0.792
rs2294261	A	C	-0.005	0.015	0.727	-0.012	0.033	0.712	-0.006	0.030	0.835	-0.021	0.028	0.465
rs2297374	C	T	-0.014	0.015	0.354	0.022	0.034	0.507	-0.023	0.029	0.437	-0.012	0.028	0.671
rs2303975	G	A	0.012	0.023	0.598	-0.006	0.051	0.910	0.058	0.045	0.195	-0.023	0.043	0.595
rs2326077	C	T	0.003	0.016	0.830	-0.103	0.035	0.003	0.003	0.031	0.925	-0.010	0.029	0.738
rs2328223	C	A	0.011	0.019	0.551	0.020	0.042	0.638	0.014	0.037	0.701	0.069	0.035	0.046
rs2412710	G	A	-0.006	0.045	0.889	-0.069	0.102	0.496	-0.037	0.083	0.660	-0.018	0.085	0.836
rs2472509	G	T	0.000	0.016	0.979	-0.012	0.036	0.739	0.014	0.031	0.650	0.030	0.030	0.313

rs2587534	A	G	0.006	0.015	0.699	0.003	0.034	0.930	0.004	0.030	0.891	-0.003	0.028	0.925
rs2602836	G	A	0.006	0.015	0.711	-0.057	0.033	0.085	0.061	0.029	0.037	-0.024	0.028	0.386
rs261342	C	G	0.020	0.018	0.258	0.068	0.040	0.093	0.022	0.034	0.509	-0.015	0.033	0.646
rs2642438	G	A	-0.017	0.017	0.331	-0.032	0.037	0.398	-0.050	0.034	0.139	-0.028	0.031	0.371
rs2652834	A	G	0.013	0.018	0.476	0.062	0.040	0.120	0.009	0.035	0.797	0.026	0.034	0.443
rs267733	A	G	0.005	0.022	0.801	-0.085	0.045	0.060	0.100	0.044	0.022	0.025	0.040	0.522
rs2710642	A	G	0.013	0.016	0.432	-0.011	0.035	0.755	0.006	0.031	0.843	0.068	0.030	0.021
rs2737252	G	A	0.019	0.017	0.260	0.047	0.038	0.213	-0.013	0.033	0.705	0.036	0.032	0.255
rs2923084	G	A	0.019	0.019	0.299	0.075	0.041	0.068	0.011	0.035	0.742	0.026	0.035	0.466
rs2925979	C	T	-0.024	0.016	0.136	-0.056	0.036	0.119	-0.019	0.032	0.548	-0.010	0.030	0.741
rs2954022	C	A	0.003	0.015	0.860	0.015	0.033	0.652	-0.003	0.029	0.909	0.008	0.028	0.765
rs2980885	G	A	-0.003	0.018	0.849	0.017	0.040	0.670	-0.016	0.035	0.655	0.002	0.033	0.960
rs314253	T	C	-0.005	0.016	0.778	0.018	0.035	0.616	0.008	0.031	0.807	-0.050	0.030	0.093
rs3198697	T	C	0.001	0.016	0.930	-0.020	0.034	0.563	0.031	0.031	0.318	0.062	0.029	0.030
rs326214	A	G	-0.014	0.016	0.397	0.010	0.036	0.786	-0.029	0.031	0.347	-0.058	0.030	0.054
rs355838	T	G	0.005	0.016	0.779	0.084	0.034	0.013	0.034	0.031	0.270	-0.010	0.029	0.741
rs364585	G	A	-0.008	0.016	0.625	-0.040	0.034	0.243	0.014	0.031	0.642	-0.015	0.029	0.604
rs3741414	C	T	-0.028	0.019	0.138	-0.040	0.041	0.321	0.004	0.039	0.910	-0.039	0.034	0.255
rs3761445	A	G	0.025	0.016	0.112	0.018	0.034	0.591	0.028	0.031	0.368	-0.025	0.028	0.381
rs3780181	A	G	0.041	0.027	0.138	0.061	0.063	0.340	0.039	0.050	0.440	-0.005	0.053	0.928
rs3817588	T	C	-0.010	0.020	0.642	-0.013	0.044	0.761	-0.032	0.040	0.420	0.005	0.037	0.888
rs3822072	A	G	0.027	0.015	0.070	0.110	0.033	0.001	-0.007	0.029	0.813	0.021	0.028	0.453
rs38855	A	G	-0.007	0.015	0.657	-0.034	0.033	0.301	0.002	0.029	0.960	-0.055	0.028	0.051
rs3996352	A	G	-0.009	0.015	0.551	-0.019	0.033	0.571	0.015	0.029	0.609	-0.007	0.028	0.810
rs4075205	C	T	-0.016	0.015	0.298	-0.058	0.033	0.082	-0.024	0.029	0.408	-0.022	0.028	0.432
rs4148005	G	T	0.006	0.016	0.690	0.002	0.035	0.957	-0.019	0.031	0.542	-0.037	0.030	0.216
rs4148218	G	A	0.014	0.019	0.449	-0.013	0.042	0.759	-0.026	0.035	0.456	0.028	0.035	0.432
rs4240624	A	G	-0.073	0.025	0.003	-0.063	0.057	0.269	-0.069	0.046	0.135	-0.101	0.048	0.035
rs4332136	C	G	0.062	0.075	0.404	0.374	0.218	0.087	-0.072	0.106	0.496	0.347	0.212	0.102
rs442177	T	G	-0.018	0.015	0.233	-0.029	0.033	0.384	-0.073	0.029	0.013	0.060	0.028	0.032
rs4465830	G	A	-0.013	0.020	0.506	-0.022	0.043	0.615	0.029	0.039	0.459	-0.009	0.036	0.811
rs4530754	A	G	-0.020	0.015	0.188	-0.044	0.033	0.190	-0.071	0.029	0.016	-0.007	0.028	0.801
rs4587594	G	A	-0.024	0.016	0.130	-0.072	0.034	0.038	-0.034	0.030	0.255	-0.029	0.029	0.328
rs4650994	A	G	-0.019	0.015	0.204	-0.014	0.033	0.663	-0.006	0.029	0.828	-0.040	0.028	0.150
rs4660293	G	A	0.023	0.019	0.224	-0.009	0.040	0.823	0.039	0.038	0.307	0.054	0.033	0.106
rs4722551	C	T	0.056	0.022	0.009	0.039	0.047	0.402	0.081	0.041	0.050	-0.006	0.040	0.880
rs4791641	C	T	-0.003	0.015	0.860	-0.057	0.033	0.089	-0.025	0.030	0.399	-0.016	0.028	0.564
rs4846914	G	A	-0.018	0.016	0.265	0.045	0.034	0.186	-0.031	0.031	0.318	-0.005	0.029	0.874
rs4871137	G	T	0.002	0.016	0.915	-0.020	0.035	0.568	0.039	0.031	0.202	0.016	0.029	0.597
rs4917014	G	T	-0.040	0.016	0.014	-0.023	0.036	0.519	-0.059	0.032	0.064	-0.057	0.030	0.058
rs4921914	C	T	0.013	0.017	0.470	0.019	0.039	0.631	0.029	0.033	0.376	0.013	0.033	0.701
rs492571	T	C	-0.019	0.031	0.548	0.010	0.074	0.893	-0.065	0.058	0.264	-0.006	0.060	0.923
rs492602	G	A	0.004	0.015	0.787	0.032	0.033	0.330	0.003	0.029	0.916	-0.010	0.028	0.733

rs4939883	C	T	-0.016	0.019	0.392	0.018	0.043	0.676	-0.047	0.037	0.198	-0.022	0.036	0.543
rs4942486	T	C	-0.022	0.015	0.130	-0.061	0.033	0.064	-0.010	0.029	0.738	-0.074	0.028	0.007
rs4969178	G	A	-0.012	0.015	0.442	-0.028	0.034	0.400	-0.001	0.030	0.987	0.011	0.028	0.711
rs4976033	A	G	-0.003	0.016	0.840	-0.026	0.034	0.445	0.021	0.030	0.495	0.025	0.029	0.385
rs4983559	G	A	0.008	0.017	0.639	-0.011	0.037	0.770	0.045	0.031	0.151	-0.036	0.031	0.238
rs499974	A	C	0.041	0.019	0.035	0.082	0.042	0.051	0.120	0.036	0.001	-0.026	0.036	0.478
rs515135	C	T	0.041	0.019	0.031	-0.024	0.042	0.573	0.080	0.038	0.036	0.059	0.036	0.100
rs5763662	T	C	-0.034	0.054	0.528	-0.006	0.116	0.961	0.029	0.112	0.796	0.148	0.092	0.107
rs579459	C	T	0.052	0.018	0.004	0.053	0.039	0.183	0.031	0.036	0.390	0.093	0.033	0.005
rs5880	C	G	0.071	0.037	0.054	0.116	0.080	0.147	0.074	0.070	0.293	0.038	0.069	0.579
rs6016381	T	C	-0.025	0.016	0.108	0.039	0.035	0.270	-0.025	0.031	0.424	-0.070	0.029	0.015
rs603446	C	T	-0.021	0.016	0.186	0.028	0.034	0.407	-0.026	0.030	0.384	-0.032	0.028	0.265
rs6065311	C	T	0.031	0.015	0.040	0.087	0.033	0.008	0.023	0.029	0.435	0.005	0.028	0.847
rs634869	T	C	0.015	0.015	0.311	0.086	0.034	0.010	0.018	0.029	0.548	0.007	0.028	0.812
rs6450176	A	G	0.007	0.017	0.684	0.013	0.037	0.730	0.023	0.032	0.486	-0.018	0.032	0.582
rs646776	T	C	0.025	0.018	0.150	0.070	0.039	0.072	0.022	0.034	0.507	0.016	0.033	0.624
rs6489818	A	G	-0.076	0.019	0.000	-0.070	0.044	0.110	-0.115	0.036	0.002	-0.055	0.036	0.124
rs6511720	G	T	0.044	0.024	0.065	0.094	0.053	0.078	0.007	0.045	0.883	0.045	0.044	0.301
rs653178	T	C	-0.104	0.016	0.000	-0.109	0.034	0.001	-0.159	0.031	0.000	-0.062	0.029	0.030
rs6544713	T	C	0.010	0.017	0.560	0.041	0.037	0.271	-0.010	0.034	0.766	-0.033	0.031	0.294
rs6603981	T	C	-0.006	0.019	0.763	0.007	0.041	0.864	0.014	0.038	0.717	-0.018	0.035	0.606
rs6680658	G	A	-0.009	0.018	0.605	0.027	0.040	0.496	-0.003	0.035	0.944	-0.046	0.033	0.155
rs6805251	T	C	-0.016	0.016	0.326	-0.010	0.035	0.777	0.038	0.033	0.251	-0.051	0.029	0.084
rs6831256	G	A	-0.003	0.015	0.840	0.012	0.033	0.715	0.000	0.029	0.999	-0.024	0.028	0.384
rs6859	A	G	0.005	0.015	0.732	0.060	0.034	0.075	0.021	0.030	0.469	-0.021	0.028	0.452
rs686030	A	C	0.018	0.022	0.417	-0.042	0.046	0.359	0.022	0.043	0.607	0.038	0.040	0.333
rs687339	T	C	-0.020	0.018	0.256	-0.068	0.038	0.077	-0.012	0.034	0.734	-0.009	0.033	0.772
rs688	T	C	0.033	0.016	0.034	0.043	0.034	0.201	0.091	0.030	0.002	0.009	0.028	0.759
rs6882076	C	T	0.001	0.016	0.930	0.041	0.034	0.233	0.019	0.030	0.524	-0.002	0.029	0.950
rs702485	G	A	-0.004	0.015	0.790	0.002	0.033	0.959	0.012	0.030	0.685	0.005	0.028	0.868
rs7033354	C	T	0.014	0.016	0.373	-0.003	0.035	0.929	-0.019	0.030	0.530	0.092	0.029	0.001
rs7117842	C	T	0.016	0.016	0.293	0.027	0.034	0.429	0.026	0.030	0.382	-0.001	0.029	0.978
rs7225700	C	T	0.029	0.016	0.060	0.028	0.034	0.420	0.038	0.030	0.209	0.018	0.029	0.526
rs7254892	G	A	0.067	0.038	0.075	0.102	0.090	0.255	0.050	0.073	0.489	-0.029	0.070	0.684
rs7264396	C	T	-0.017	0.017	0.329	0.035	0.039	0.372	-0.013	0.033	0.688	-0.045	0.032	0.162
rs731839	A	G	-0.027	0.016	0.090	-0.092	0.034	0.007	-0.040	0.030	0.184	-0.028	0.029	0.346
rs7422339	A	C	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
rs749671	G	A	0.007	0.016	0.648	0.031	0.035	0.374	-0.032	0.031	0.292	-0.034	0.029	0.246
rs7607980	T	C	-0.020	0.022	0.366	0.017	0.049	0.729	-0.028	0.042	0.499	-0.029	0.040	0.465
rs7640978	C	T	0.018	0.024	0.451	-0.077	0.055	0.159	-0.021	0.045	0.647	0.058	0.047	0.215
rs7703051	A	C	0.016	0.015	0.294	-0.014	0.034	0.686	0.063	0.029	0.031	0.029	0.028	0.307
rs7832643	T	G	0.009	0.015	0.577	0.054	0.034	0.110	-0.023	0.030	0.438	0.018	0.028	0.535
rs7897379	C	T	0.007	0.015	0.657	0.046	0.033	0.162	-0.067	0.029	0.021	0.045	0.027	0.097

rs799160	T	C	0.023	0.015	0.126	0.033	0.033	0.317	0.002	0.029	0.952	0.053	0.028	0.058
rs8017377	A	G	-0.007	0.015	0.635	0.011	0.033	0.731	0.024	0.030	0.421	-0.063	0.028	0.024
rs8077889	C	A	-0.013	0.018	0.488	0.033	0.040	0.402	0.021	0.035	0.544	0.011	0.033	0.733
rs8176720	T	C	0.018	0.016	0.258	-0.019	0.034	0.574	-0.009	0.030	0.752	0.084	0.029	0.004
rs838876	G	A	0.002	0.016	0.881	-0.020	0.035	0.577	0.001	0.031	0.987	0.031	0.030	0.297
rs868943	G	A	0.007	0.015	0.654	-0.030	0.033	0.361	0.007	0.029	0.811	-0.006	0.028	0.836
rs894210	G	A	-0.007	0.016	0.639	-0.010	0.034	0.762	0.000	0.030	0.993	-0.020	0.028	0.473
rs903319	C	T	-0.043	0.018	0.015	-0.005	0.038	0.901	0.003	0.035	0.934	-0.079	0.033	0.017
rs931992	T	G	-0.023	0.016	0.144	-0.030	0.035	0.386	-0.031	0.031	0.317	-0.030	0.029	0.295
rs9491696	G	C	0.015	0.015	0.312	0.061	0.033	0.062	-0.031	0.029	0.278	0.035	0.027	0.203
rs952044	C	T	-0.023	0.016	0.140	-0.032	0.035	0.355	-0.059	0.030	0.049	-0.008	0.029	0.785
rs9686661	T	C	0.030	0.019	0.114	0.013	0.042	0.765	-0.001	0.036	0.986	0.036	0.035	0.309
rs9693857	C	T	0.002	0.015	0.897	-0.003	0.033	0.936	0.033	0.029	0.260	-0.025	0.028	0.371
rs970548	C	A	0.002	0.017	0.904	0.018	0.038	0.633	-0.052	0.034	0.119	0.044	0.032	0.169
rs9875338	G	A	0.001	0.015	0.951	0.007	0.034	0.826	-0.003	0.029	0.910	-0.004	0.028	0.874
rs9930333	T	G	-0.011	0.015	0.464	-0.056	0.033	0.091	0.017	0.029	0.559	-0.007	0.028	0.805
rs998584	A	C	0.014	0.016	0.372	0.011	0.035	0.747	0.074	0.032	0.021	-0.005	0.029	0.874
rs9989419	A	G	0.002	0.016	0.892	0.004	0.035	0.912	0.034	0.031	0.277	0.019	0.029	0.506

Reference: NINDS Stroke Genetics Network[2]

Supplemental Table III. Odds ratios thresholds of ischemic stroke and subtypes at 80% power.

Instrument	N SNPs	Variance explained	Odds Ratio at 80% Power							
			IS		LAA		SAO		CE	
			positive	negative	positive	negative	positive	negative	positive	negative
LDL cholesterol										
GWAS threshold*	75	6.4	1.109	0.902	1.236	0.809	1.210	0.826	1.203	0.831
Steiger filter 1†	67	5.9	1.114	0.898	1.246	0.803	1.217	0.822	1.210	0.826
Steiger filter 2‡	61	5.6	1.117	0.895	1.253	0.798	1.225	0.816	1.216	0.822
GWAS restricted§	56	3.6	1.148	0.871	1.316	0.760	1.280	0.781	1.270	0.787
HDL cholesterol										
GWAS threshold	85	5.9	1.114	0.898	1.246	0.803	1.217	0.822	1.210	0.826
Steiger filter 1	77	5.0	1.124	0.890	1.268	0.789	1.237	0.808	1.230	0.813
Steiger filter 2	50	4.2	1.136	0.880	1.292	0.774	1.258	0.795	1.250	0.800
GWAS restricted	50	1.9	1.205	0.830	1.440	0.694	1.390	0.719	1.375	0.727
Triglycerides										
GWAS threshold	51	4.6	1.129	0.886	1.279	0.782	1.248	0.801	1.240	0.806
Steiger filter 1	39	4.0	1.139	0.878	1.300	0.769	1.265	0.791	1.255	0.797
Steiger filter 2	21	3.2	1.156	0.865	1.338	0.747	1.298	0.770	1.290	0.775
GWAS restricted	16	1.2	1.262	0.792	1.555	0.643	1.490	0.671	1.475	0.678

* Includes all SNPs that associates with a trait and have a $p < 5 \times 10^{-8}$

† Includes all SNPs with r^2 values with their traits higher than the other 2 traits

‡ Includes all SNPs with r^2 values with their traits higher and the difference is significant ($p<0.05$) compared to each of the other 2 traits

§Includes that associates with a trait and have a $p < 5 \times 10^{-8}$ and don't associate with any of the other 2 traits $p > 5 \times 10^{-8}$

GWAS, Genome-Wide Association Study; IS, Ischemic Stroke; SAO, Small Artery Occlusion Stroke; CE, Cardio-Embolic Stroke

Supplemental Table IV. Sensitivity Mendelian Randomization Analyses of LDL cholesterol with Ischemic Stroke and Subtypes

						95% CI			
Trait	Instrument	N	Variance	Method	OR	lower limit	upper limit	p	p-intercept
IS	GWAS threshold*	75	6.4	Conventional MR	1.122	1.015	1.240	0.0245	
				MR-Egger	1.224	1.050	1.427	0.0098	0.143
	GWAS threshold (MRPRESSO)	73	6.4	Conventional MR	1.143	1.056	1.237	0.0009	
				MR-Egger	1.179	1.043	1.333	0.0085	0.519
	Steiger filter 1†	67	5.9	Conventional MR	1.164	1.067	1.269	0.0006	
				MR-Egger	1.207	1.059	1.376	0.0048	0.466
	Steiger filter 1 (MRPRESSO)	66	5.9	Conventional MR	1.173	1.084	1.270	0.0001	
				MR-Egger	1.195	1.060	1.347	0.0036	0.693
	Steiger filter 2‡	61	5.6	Conventional MR	1.158	1.061	1.265	0.0010	
				MR-Egger	1.206	1.058	1.375	0.0050	0.412
	Steiger filter 2 (MRPRESSO)	60	5.6	Conventional MR	1.168	1.079	1.264	0.0001	
				MR-Egger	1.193	1.059	1.343	0.0036	0.638
	GWAS restricted§	56	3.6	Conventional MR	1.186	1.053	1.337	0.0050	
				MR-Egger	1.363	1.098	1.693	0.0051	0.134
	GWAS restricted (MRPRESSO)	55	3.6	Conventional MR	1.204	1.081	1.340	0.0007	
				MR-Egger	1.335	1.097	1.625	0.0039	0.218
LAA	GWAS threshold	75	6.4	Conventional MR	1.277	1.068	1.527	0.0070	
				MR-Egger	1.405	1.060	1.862	0.0180	0.393
	Steiger filter 1	67	5.9	Conventional MR	1.360	1.134	1.631	0.0010	
				MR-Egger	1.452	1.098	1.920	0.009	0.544
	Steiger filter 2	61	5.6	Conventional MR	1.324	1.101	1.591	0.003	
				MR-Egger	1.462	1.105	1.933	0.008	0.355

	GWAS restricted	56	3.6	Conventional MR	1.350	1.067	1.709	0.012	
				MR-Egger	1.558	1.005	2.416	0.047	0.447
SAO	GWAS threshold	75	6.4	Conventional MR	1.090	0.925	1.284	0.303	
				MR-Egger	1.211	0.940	1.559	0.138	0.285
	GWAS threshold(MRPRESSO)	74	6.4	Conventional MR	1.109	0.960	1.281	0.161	
				MR-Egger	1.164	0.930	1.456	0.185	0.581
	Steiger filter 1	67	5.9	Conventional MR	1.136	0.978	1.319	0.096	
				MR-Egger	1.203	0.960	1.506	0.108	0.502
	Steiger filter 2	61	5.6	Conventional MR	1.149	0.987	1.337	0.074	
				MR-Egger	1.194	0.951	1.498	0.126	0.653
	GWAS restricted	56	3.6	Conventional MR	1.216	0.992	1.490	0.060	
				MR-Egger	1.438	0.991	2.087	0.056	0.291
	GWAS restricted (MRPRESSO)	55	3.6	Conventional MR	1.243	1.030	1.502	0.024	
				MR-Egger	1.393	0.985	1.969	0.061	0.443
CE	GWAS threshold	75	6.4	Conventional MR	0.986	0.838	1.161	0.866	
				MR-Egger	1.160	0.904	1.490	0.244	0.095
	Steiger filter1	67	5.9	Conventional MR	1.001	0.842	1.190	0.995	
				MR-Egger	1.122	0.865	1.456	0.384	0.247
	Steiger filter 2	61	5.6	Conventional MR	1.000	0.837	1.195	0.999	
				MR-Egger	1.135	0.871	1.478	0.349	0.208
	GWAS restricted	56	3.6	Conventional MR	1.020	0.802	1.296	0.874	
				MR-Egger	1.437	0.931	2.217	0.101	0.065

* Includes all SNPs that associates with a trait and have a $p < 5 \times 10^{-8}$
† Includes all SNPs with r^2 values with their traits higher than the other 2 traits
‡ Includes all SNPs with r^2 values with their traits higher and the difference is significant ($p<0.05$) compared to each of the other 2 traits
§Includes that associates with a trait and have a $p < 5 \times 10^{-8}$ and don’t associate with any of the other 2 traits $p > 5 \times 10^{-8}$
GWAS, Genome-Wide Association Study; IS, Ischemic Stroke; SAO, Small Artery Occlusion Stroke; CE, Cardio-Embolic Stroke

Supplemental Table V. Sensitivity Mendelian randomization analyses of HDL cholesterol with ischemic stroke and subtypes.

						95% CI			
Trait	Instrument	N	Variance	Method	OR	lower limit	upper limit	p	p-intercept
IS	GWAS threshold*	85	5.9	Conventional MR	0.915	0.831	1.007	0.0706	
				MR-Egger	1.013	0.869	1.181	0.8672	0.096
	GWAS threshold (MRPRESSO)	84	5.9	Conventional MR	0.930	0.857	1.008	0.0776	
				MR-Egger	0.994	0.874	1.132	0.9334	0.192
	Steiger filter 1†	77	5.0	Conventional MR	0.896	0.807	0.994	0.0388	
				MR-Egger	0.993	0.844	1.169	0.9325	0.110
	Steiger filter 1 (MRPRESSO)	76	4.9	Conventional MR	0.913	0.838	0.995	0.0372	
				MR-Egger	0.976	0.853	1.117	0.7217	0.210
	Steiger filter 2‡	50	4.2	Conventional MR	0.905	0.822	0.998	0.0447	
				MR-Egger	0.954	0.822	1.108	0.5389	0.365
	GWAS restricted§	50	1.9	Conventional MR	0.931	0.812	1.067	0.3053	
				MR-Egger	1.182	0.917	1.522	0.1962	0.031
LAA	GWAS threshold	85	5.9	Conventional MR	0.925	0.745	1.148	0.480	
				MR-Egger	1.240	0.878	1.751	0.221	0.035
	Steiger filter 1	77	5.0	Conventional MR	0.865	0.688	1.089	0.218	
				MR-Egger	1.217	0.850	1.741	0.283	0.017
	Steiger filter 2	50	4.2	Conventional MR	0.967	0.783	1.196	0.760	
				MR-Egger	1.063	0.762	1.482	0.720	0.471
	GWAS restricted	50	1.9	Conventional MR	0.988	0.690	1.413	0.947	
				MR-Egger	2.060	0.991	4.283	0.053	0.026
	GWAS restricted (MRPRESSO)	48	1.9	Conventional MR	1.090	0.799	1.487	0.586	
				MR-Egger	1.830	0.965	3.473	0.064	0.072

SAO	GWAS threshold	85	5.9	Conventional MR	0.788	0.670	0.927	0.004	
				MR-Egger	0.868	0.674	1.119	0.276	0.330
	GWAS threshold (MRPRESSO)	84	5.9	Conventional MR	0.806	0.698	0.931	0.003	
				MR-Egger	0.847	0.675	1.061	0.149	0.577
	Steiger filter 1	77	5.0	Conventional MR	0.803	0.678	0.952	0.011	
				MR-Egger	0.876	0.676	1.136	0.320	0.385
	Steiger filter 1 (MRPRESSO)	76	4.9	Conventional MR	0.824	0.707	0.961	0.014	
				MR-Egger	0.856	0.677	1.082	0.193	0.679
	Steiger filter 2	50	4.2	Conventional MR	0.807	0.685	0.951	0.010	
				MR-Egger	0.869	0.680	1.111	0.263	0.422
	GWAS restricted	50	1.9	Conventional MR	0.824	0.652	1.043	0.107	
				MR-Egger	0.939	0.630	1.400	0.759	0.427
CE	GWAS threshold	85	5.9	Conventional MR	0.901	0.782	1.038	0.150	
				MR-Egger	0.945	0.749	1.194	0.637	0.612
	Steiger filter 1	77	5.0	Conventional MR	0.901	0.772	1.052	0.186	
				MR-Egger	0.875	0.681	1.123	0.294	0.766
	Steiger filter 2	50	4.2	Conventional MR	0.892	0.749	1.062	0.201	
				MR-Egger	0.852	0.645	1.125	0.258	0.672
	GWAS restricted	50	1.9	Conventional MR	0.991	0.772	1.273	0.946	
				MR-Egger	1.267	0.727	2.208	0.403	0.332

* Includes all SNPs that associates with a trait and have a $p < 5 \times 10^{-8}$

† Includes all SNPs with r^2 values with their traits higher than the other 2 traits

‡ Includes all SNPs with r^2 values with their traits higher and the difference is significant ($p<0.05$) compared to each of the other 2 traits

§Includes that associates with a trait and have a $p < 5 \times 10^{-8}$ and don't associate with any of the other 2 traits $p > 5 \times 10^{-8}$

GWAS, Genome-Wide Association Study; IS, Ischemic Stroke; SAO, Small Artery Occlusion Stroke; CE, Cardio-Embolic Stroke

Supplemental Table VI. Sensitivity Mendelian randomization analyses of triglycerides with ischemic stroke and subtypes.

						95% CI			
Trait	Instrument	N	Variance	Method	OR	lower limit	upper limit	p	p-intercept
IS	GWAS threshold*	51	4.6	Conventional MR	0.978	0.887	1.079	0.659	
				MR-Egger	0.972	0.824	1.146	0.733	0.921
	Steiger filter 1†	39	4.0	Conventional MR	1.039	0.940	1.149	0.452	
				MR-Egger	0.967	0.824	1.134	0.676	0.253
	Steiger filter 2‡	21	3.2	Conventional MR	0.995	0.888	1.114	0.926	
				MR-Egger	1.028	0.853	1.238	0.775	0.666
	GWAS restricted§	16	1.2	Conventional MR	1.054	0.875	1.270	0.580	
				MR-Egger	1.016	0.732	1.411	0.923	0.792
LAA	GWAS threshold	51	4.6	Conventional MR	0.991	0.782	1.254	0.938	
				MR-Egger	0.693	0.475	1.011	0.057	0.021
	Steiger filter 1	39	4.0	Conventional MR	0.996	0.800	1.240	0.971	
				MR-Egger	0.789	0.557	1.119	0.184	0.094
	Steiger filter 2	21	3.2	Conventional MR	0.916	0.716	1.172	0.486	
				MR-Egger	0.978	0.651	1.468	0.914	0.693
	GWAS restricted	16	1.2	Conventional MR	1.239	0.826	1.857	0.300	
				MR-Egger	0.974	0.479	1.983	0.943	0.420
SAO	GWAS threshold	51	4.6	Conventional MR	1.024	0.856	1.224	0.794	
				MR-Egger	1.134	0.842	1.526	0.408	0.401
	Steiger filter 1	39	4.0	Conventional MR	1.052	0.869	1.275	0.602	
				MR-Egger	1.137	0.838	1.543	0.411	0.525
	Steiger filter 2	21	3.2	Conventional MR	1.019	0.807	1.288	0.872	
				MR-Egger	1.268	0.871	1.845	0.215	0.151

	GWAS restricted	16	1.2	Conventional MR	0.900	0.627	1.291	0.566	
				MR-Egger	1.194	0.633	2.250	0.585	0.288
CE	GWAS threshold	51	4.6	Conventional MR	1.017	0.857	1.207	0.846	
				MR-Egger	1.128	0.848	1.501	0.408	0.374
	Steiger filter 1	39	4.0	Conventional MR	1.062	0.857	1.315	0.584	
				MR-Egger	1.053	0.746	1.487	0.769	0.953
	Steiger filter 2	21	3.2	Conventional MR	1.032	0.838	1.269	0.769	
				MR-Egger	1.016	0.723	1.428	0.925	0.915
	GWAS restricted	16	1.2	Conventional MR	0.904	0.605	1.350	0.622	
				MR-Egger	1.141	0.558	2.330	0.718	0.438

* Includes all SNPs that associates with a trait and have a $p < 5 \times 10^{-8}$

† Includes all SNPs with r^2 values with their traits higher than the other 2 traits

‡ Includes all SNPs with r^2 values with their traits higher and the difference is significant ($p<0.05$) compared to each of the other 2 traits

§Includes that associates with a trait and have a $p < 5 \times 10^{-8}$ and don't associate with any of the other 2 traits $p > 5 \times 10^{-8}$

GWAS, Genome-Wide Association Study; IS, Ischemic Stroke; SAO, Small Artery Occlusion Stroke; CE, Cardio-Embolic Stroke

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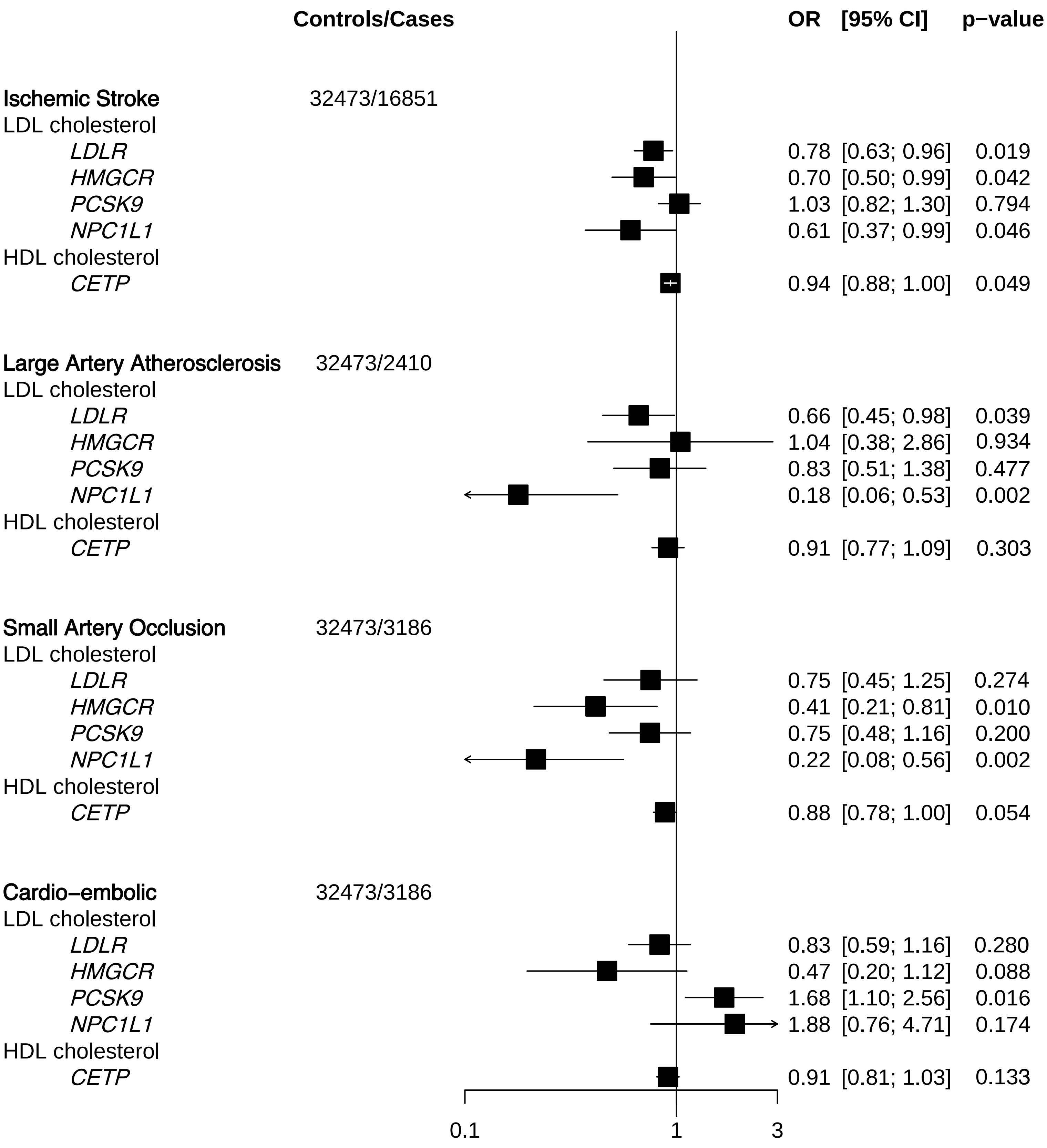
Controls/Cases
OR [95% CI] p−value
Ischemic Stroke 32473/16851
LDL cholesterol
LDLR 0.78 [0.63; 0.96] 0.019
HMGCR 0.70 [0.50; 0.99] 0.042
PCSK9 1.03 [0.82; 1.30] 0.794
NPC1L1 0.61 [0.37; 0.99] 0.046
HDL cholesterol
CETP 0.94 [0.88; 1.00] 0.049
Large Artery Atherosclerosis 32473/2410
LDL cholesterol
LDLR 0.66 [0.45; 0.98] 0.039
HMGCR 1.04 [0.38; 2.86] 0.934
PCSK9 0.83 [0.51; 1.38] 0.477
NPC1L1 0.18 [0.06; 0.53] 0.002
HDL cholesterol
CETP 0.91 [0.77; 1.09] 0.303
Small Artery Occlusion 32473/3186
LDL cholesterol
LDLR 0.75 [0.45; 1.25] 0.274
HMGCR 0.41 [0.21; 0.81] 0.010
PCSK9 0.75 [0.48; 1.16] 0.200
NPC1L1 0.22 [0.08; 0.56] 0.002
HDL cholesterol
CETP 0.88 [0.78; 1.00] 0.054
Cardio−embolic 32473/3186
LDL cholesterol
LDLR 0.83 [0.59; 1.16] 0.280
HMGCR 0.47 [0.20; 1.12] 0.088
PCSK9 1.68 [1.10; 2.56] 0.016
NPC1L1 1.88 [0.76; 4.71] 0.174
HDL cholesterol
CETP 0.91 [0.81; 1.03] 0.133
0.1
1
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