Causal Effect of Lp(a) [Lipoprotein(a)] Level on Ischemic Stroke and Alzheimer Disease

A Mendelian Randomization Study

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Background and Purpose—Stroke and Alzheimer disease are 2 major causes of neurological disability in aged people and shared overlapping predictors. In recent prospective studies, high Lp(a) [lipoprotein(a)] level is associated with high risk of stroke but low risk of Alzheimer disease. Whether this reflects a causal association remains to be established. The aim of this study is to examine the causal associations of Lp(a) concentrations on ischemic stroke, ischemic stroke subtypes, and Alzheimer disease.

Methods—We used 9 single-nucleotide polymorphisms associated with Lp(a) concentrations as instrumental variables. Summary-level data on ischemic stroke and its subtypes were obtained from the Multiancestry Genome-Wide Association Study of Stroke consortium with European individuals ≤446 696 individuals. Summary-level data on Alzheimer disease were obtained from the International Genomics of Alzheimer Project With European individuals ≤54 162 individuals. Two-sample Mendelian randomization (MR) estimates were calculated with inverse-variance weighted, penalized inverse-variance weighted, simple median, weighted median, and MR Pleiotropy Residual Sum and Outlier approaches, and MR-Egger regression was used to explore pleiotropy.

Results—Genetically predicted 1-SD log-transformed increase in Lp(a) concentrations was associated with a substantial increase in risk of large artery stroke (odds ratio, 1.20; 95% CI, 1.11–1.30; $P<0.001$) and a reduce in risk of small vessel stroke (odds ratio, 0.92; 95% CI, 0.88–0.97; $P=0.001$) and Alzheimer disease (odds ratio, 0.94; 95% CI, 0.91–0.97; $P<0.001$) using inverse-variance weighted method. No significant association was observed for total ischemic stroke or cardioembolic stroke. MR-Egger indicated no evidence of pleiotropic bias. Results were broadly consistent in sensitivity analyses using penalized inverse-variance weighted, simple median, weighted median, and MR Pleiotropy Residual Sum and Outlier approaches accounting for potential genetic pleiotropy or outliers.

Conclusions—This study provides evidence to support that high Lp(a) concentrations was causally associated with an increased risk of large artery stroke but a decreased risk of small vessel stroke and Alzheimer disease. The mechanism underlying the double-edged sword effect of Lp(a) concentrations on neurological system requires further investigation. **(*Stroke*. 2019;50:3532-3539. DOI: 10.1161/STROKEAHA.119.026872.)**

Key Words: humans ■ lipoprotein(a) ■ odds ratio ■ risk ■ stroke

Stroke and Alzheimer disease are 2 major conditions of impaired brain health and major causes of neurological disability in aged people.[1] Globally, ≈1 in 4 adults will develop stroke in their lifetime from the age of 25 years onward.[2] Alzheimer disease is a progressive neurodegenerative disease of the brain without available curative treatment.[3] The prevalence of dementia was increasing in recent years because of increases in population aging and growth, and ≈43.8 million people lived with dementia globally in 2016.[4] Recent studies showed that many vascular risk factors were shared predictors for stroke and dementia.[5]

Lp(a) [lipoprotein(a)] is an LDL (low-density lipoprotein)-like particle containing Apo(a) [apolipoprotein(a)] and apolipoprotein B100 covalently linked by a disulfide bridge.[6] Lp(a) has been shown to have proatherosclerotic effects and is considered as a causal risk factor for incident ischemic vascular diseases.[7,8] Although Lp(a) level has been consistently reported to be associated with incidence of coronary heart diseases,[7,8] the results for incidence of ischemic stroke were less consistent in previous observational studies.[8–12] Most previous studies focused on the risk of total ischemic stroke,[7,8,10–12] whereas the associations of Lp(a) level with stroke subtypes have not been well elucidated. Several,[13–15] but not all,[16,17] previous observational studies have suggested that elevated Lp(a) level was associated with a decreased risk of Alzheimer disease. Furthermore, it is difficult to completely protect

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observational studies from potential unmeasured confounders (such as lifestyle, dietary, and behavior factors) and reverse causation, which may limit the ability of causal inference.[18] Therefore, the causal associations between Lp(a) concentrations and ischemic stroke, ischemic stroke subtypes, and Alzheimer disease are still controversial.

Mendelian randomization (MR) is an epidemiological approach that makes stronger causal inferences between an exposure and risk of diseases.[18] Because the random assortment of alleles occurs at conception, MR analysis can avoid potential unmeasured confounders and reverse causation by using genetic variants as instrumental variables.[18] In this study, we aimed to use MR analysis to comprehensively evaluate the causal association of Lp(a) concentrations with risk of ischemic stroke, ischemic stroke subtypes, and Alzheimer disease.

Methods

Study Design and Data Sources

We designed an MR approach to evaluate the causal effect of Lp(a) concentrations on risk of ischemic stroke, stroke subtypes, and Alzheimer disease (Figure 1). MR design uses the principle that the random meiotic assortment of genotypes is independent of confounding factors, thus can control potential confounders and reverse causation and make stronger causal inferences.[18] We selected single-nucleotide polymorphisms (SNPs) that achieved significance ($P<1.0\times10^{-6}$) for the Lp(a) concentrations identified by Clarke et al[19] as instrumental variable in the MR analysis. Data on associations of SNPs with ischemic stroke and its subtypes were obtained from the Multiancestry Genome-Wide Association Study of Stroke consortium.[20] Data on associations of SNPs with Alzheimer disease were obtained from the International Genomics of Alzheimer Project (IGAP).[21] All data in this MR analysis were based on subjects of European ancestry only. The protocol and data collection of the original studies were approved by the ethics committee of participating sites, and informed consents were obtained from all participants. All data generated or analyzed during this study are included in this published article.

Selection of Genetic Variants

We used previous published genetic variants associated with Lp(a) concentrations identified by Clarke et al[19] as the instruments. They evaluated potential SNPs associated with Lp(a) concentrations using a gene chip in 3145 cases with coronary artery disease and 3352 controls. The gene chip contained 48 742 SNPs in ≈2100 candidate genes including 40 SNPs form the *LPA* region. They identified 16 SNPs achieved significance ($P<1.0\times10^{-6}$) for the Lp(a) concentrations. We selected only independent genetic variants, that is, not in linkage disequilibrium with other SNPs for Lp(a) concentrations. When we encountered genetic variants in linkage disequilibrium, we chose the SNP with the lowest *P* for association with Lp(a) concentrations. Among the 16 SNPs, 7 SNPs (rs9355813, rs13202636, rs7765781, rs6923877, rs7765803, rs9365171, and rs1321195) were potentially in linkage disequilibrium with other SNPs (D′ >50). We used the remaining 9-SNP as the instrument in the MR analysis. In sensitivity analysis, we further used only 5 SNPs (rs10455872, rs3798220, rs10945682, rs6919346, and rs3127596) with a stricter criterion of linkage equilibrium (D′ ≤20) as the instrument. Among these variants, 2 SNPs (rs10455872 and rs3798220) in the *LPA* gene, which encode the Apo(a) protein, were in linkage equilibrium and strongly associated with an increased level of Lp(a). The 2 SNPs (rs10455872 and rs3798220) together explained 36% of variation in Lp(a) concentrations.[19]

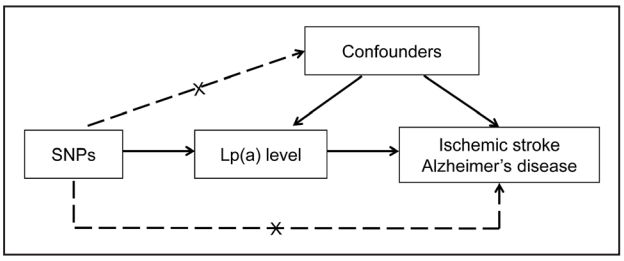

Figure 1. Conceptual framework for the Mendelian randomization analysis of Lp(a) [lipoprotein (a)] and risk of ischemic stroke and Alzheimer disease. The design is under the assumption that the genetic variants are associated with Lp(a) level, but not with confounders, and the genetic variants are not associated with risk of ischemic stroke or Alzheimer disease conditional on Lp(a) level and confounders. SNP indicates single-nucleotide polymorphism.

The MR analysis required that the SNPs in the instruments were in linkage equilibrium. We conducted sensitivity analyses based on 3 instruments with different criteria of linkage equilibrium: (1) 2-SNP instrument only included rs10455872 and rs3798220 (D′=0); (2) 5-SNP instrument in linkage equilibrium (D′ ≤20); (3) 9-SNP instrument potential in linkage equilibrium (D′ ≤50). The associations of the 9 individual SNPs with the Lp(a) concentrations are presented in Table 1. Potential pleiotropic effects of these SNPs were assessed through the MR-Egger regression method, which slope represents pleiotropy-corrected causal estimates and the intercept represents the average pleiotropic effects across all SNPs.[22]

Outcomes

Summary statistics for the associations of each SNP with any ischemic stroke and its 3 main subtypes (large artery stroke [LAS], small vessel stroke [SVS], and cardioembolic stroke [CES]) were obtained from the previously published genome-wide association studies (GWAS) of Multiancestry Genome-Wide Association Study of Stroke consortium.[20] In brief, the Multiancestry Genome-Wide Association Study of Stroke consortium is large-scale international collaboration launched by the International Stroke Genetics consortium and the largest GWAS meta-analysis on stroke and stroke subtypes to date that involved and tested ≈8 million SNPs and indels with minor-allele frequency ≥0.01 in ≤67 162 stroke cases and 454 450 controls for association with stroke, involving 40 585 cases and 406 111 control European participants (Methods in the online-only Data Supplement).

Summary statistics for the associations of each SNP with Alzheimer disease were obtained from the previously published GWAS of the IGAP.[21] In brief, IGAP is a large 2-stage study based on GWAS on individuals of European ancestry.[21] In stage 1, IGAP used genotyped and imputed data on 7 055 881 SNPs to meta-analyze 4 GWAS datasets (The Alzheimer Disease Genetics consortium, The Cohorts for Heart and Aging Research in Genomic Epidemiology consortium, The European Alzheimer Disease Initiative, and The Genetic and Environmental Risk in Alzheimer Disease consortium) with a total of 17 008 Alzheimer disease cases and 37 154 controls. In stage 2, 11 632 SNPs were genotyped and tested for association in an independent set of 8572 Alzheimer disease cases and 11 312 controls. We derived summarized data of the 9 SNPs related to Lp(a) concentrations from the dataset of stage 1 of the IGAP (Methods in the online-only Data Supplement).

Summarized data for the associations of the 9 individual SNPs for Lp(a) concentrations with any ischemic stroke, ischemic stroke subtypes, and Alzheimer disease are presented in Table I in the online-only Data Supplement.

Statistical Analysis

Two-sample MR analyses were performed to compute estimates of Lp(a)-outcome (ischemic stroke, ischemic stroke subtypes, and Alzheimer disease) associations using summarized data of the SNP-Lp(a) level and SNP-outcome associations. We used a conventional inverse-variance weighted (IVW) MR analysis in which the SNP-outcome estimate is regressed on the SNP-Lp(a) estimate with the intercept term set to zero, weighted by the inverse-variance of SNP-outcome estimate.[23] In sensitivity analyses, we also conducted

Table 1. Characteristics of Included 9 SNPs Associated With Lp(a) Level

SNP	Locus Name	Genomic Coordinate	EA/OA	EAF	Association With Increased Lp(a)		
					β	SE	*P* Value
rs10455872*†‡	*LPA*	chr6:161010118	G/A	0.07	1.18	0.04	3.6×10^{-166}
rs3798220*†‡	*LPA*	chr6:160961137	C/T	0.02	1.27	0.08	5.9×10^{-51}
rs11751605‡	*LPA*	chr6:160963230	C/T	0.16	0.50	0.04	5.9×10^{-28}
rs10945682†‡	*LPA*	chr6:161069941	G/A	0.64	0.32	0.04	1.8×10^{-17}
rs6919346†‡	*LPA*	chr6:160960359	C/T	0.83	0.43	0.05	1.6×10^{-16}
rs3127596†‡	*LPA*	chr6:160953035	G/A	0.30	0.30	0.04	1.5×10^{-14}
rs10755578‡	*LPA*	chr6:160969738	G/C	0.48	0.27	0.04	3.4×10^{-13}
rs3798221‡	*LPA*	chr6:160998148	G/T	0.81	0.28	0.05	2.0×10^{-9}
rs6415084‡	*LPA*	chr6:160980330	T/C	0.49	0.22	0.04	2.7×10^{-9}

Genomic coordinates refer to hg19. EA indicates effect allele; EAF, effect allele frequency; hg19, human genome build 37; Lp(a), lipoprotein(a); OA, other allele; and SNP, single-nucleotide polymorphism.

*Two variants previously used in Mendelian randomization investigation (Clarke et al[19]).

†Five variants in linkage equilibrium with D′ ≤0.20.

‡Nine variants in linkage equilibrium with D′ ≤0.50.

penalized IVW, MR-Egger, simple median, weighted median, and MR Pleiotropy Residual Sum and Outlier (MR-PRESSO) methods of MR analyses, which are more robust to potential violations of the standard instrumental variable assumptions because of the inclusion of pleiotropic or invalid instruments. The penalized methods penalize the weights of candidate instruments with pleiotropic effect.[24] The MR-Egger method may assess the robustness of estimates to potential violations of the standard instrumental variable assumptions because of directional pleiotropy (a genetic variant affects the outcome via a different biological pathway from the exposure under investigation).[22] The weighted median method may provide precise causal estimates against invalid instruments by downweighting the contribution to the analysis of genetic variants with heterogeneous ratio estimates.[25] The MR-PRESSO method was used to identify potential outliers in multi-instrument summary-level MR testing and provided robust estimate with outlier correction.[26] Potential pleiotropic effects of these SNPs

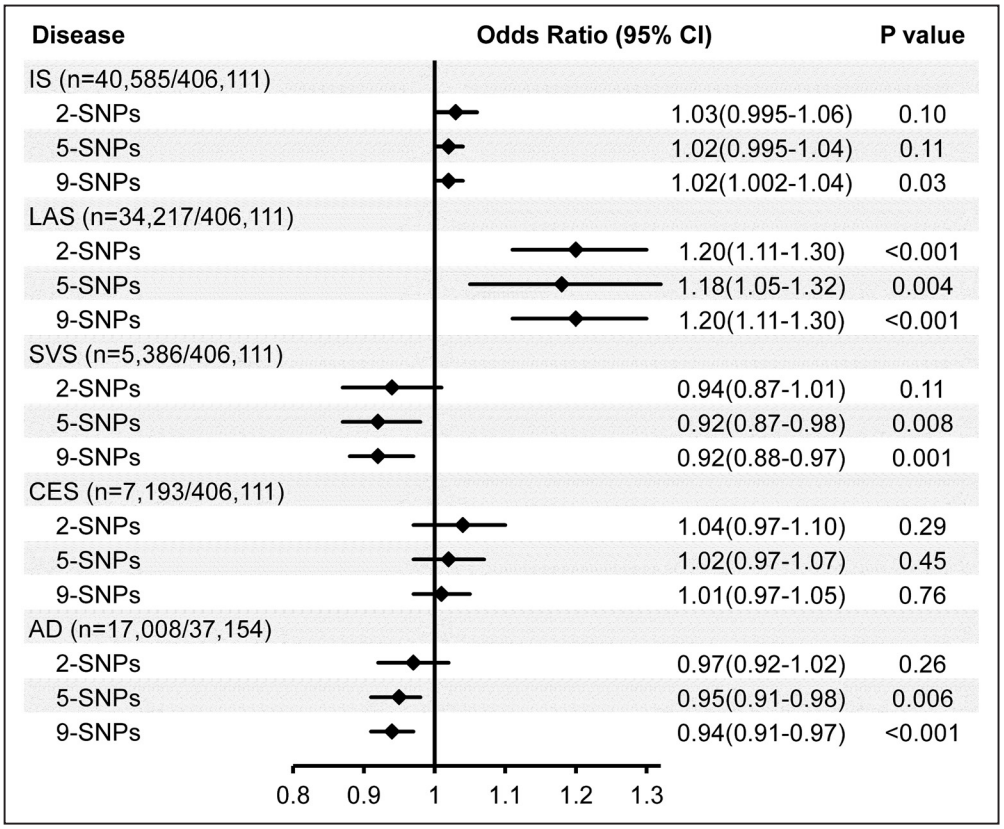

Figure 2. Causal effect estimates of genetically predicted Lp(a) [lipoprotein (a)] level on ischemic stroke (IS) and Alzheimer disease (AD). Estimates are derived from inverse-variance weighted (IVW) method of Mendelian randomization analysis and represented odds ratio (95% CI) per SD elevated Lp(a) level. Random-effect IVW models were used for large artery stroke (LAS) using 5–single-nucleotide polymorphism (SNP) and 9-SNP instruments because of heterogeneity (Q=14.14, *P*=0.01 and Q=20.10, *P*=0.01) and fixed-effect IVW models for others. CES indicates cardioembolic stroke; and SVS, small vessel stroke.

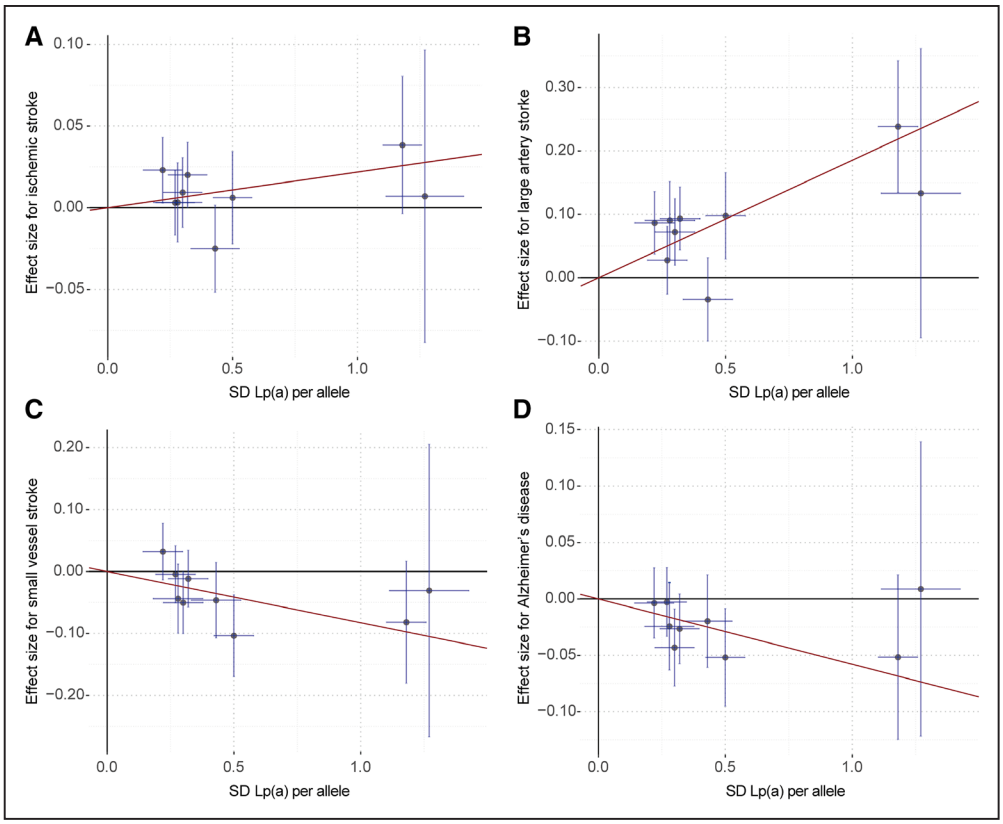

Figure 3. Associations of Lp(a) [lipoprotein (a)] variants with risk of ischemic stroke and Alzheimer disease. **A**, Ischemic stroke, (**B**) large artery stroke, (**C**) small vessel stroke, and (**D**) Alzheimer disease. The red line indicates the estimate of effect using IVW method. Circles indicate marginal genetic associations with Lp(a) level and risk of outcome for each variant. Error bars indicate 95% CIs. IVW indicates inverse-variance weighted.

were assessed through the MR-Egger regression method, which slope represents pleiotropy-corrected causal estimates and the intercept represents the average pleiotropic effects across all SNPs.[22] Heterogeneity between SNPs was estimated by Cochran Q statistic.[25] Random-effects IVW models were used if heterogeneity existed and otherwise using fixed-effects IVW model. To investigate the influence of outlying or pleiotropic genetic variants, we performed a leave-one-out analysis in which we omitted 1 SNP in turn.[27]

Results were presented as odds ratios (ORs) with their 95% CIs of the outcomes (ischemic stroke, ischemic stroke subtypes, and Alzheimer disease) per 1-SD log-transformed genetically predicted increase in Lp(a) concentrations. The association of each genetic variant with Lp(a) concentration was further plotted against its effect for the outcomes.

In our analyses, an observed 2-sided $P<0.05$ was considered as nominally significant evidence for a potential, but yet to be confirmed, causal association. An observed 2-sided $P<0.01$ (Bonferroni-corrected significance threshold calculated as 0.05 divided by 5 [for 5 outcomes]) was considered as statistically significant evidence for a causal association. All analyses were conducted with R 3.5.3 (R Development Core Team).

Results

Causal Association of Lp(a) With Ischemic Stroke and Its Subtypes

The MR analyses showed no significant association of genetic higher Lp(a) concentrations with any ischemic stroke, except that a nominally significant association was observed using 9-SNP instrument (OR, 1.02; 95% CI, 1.002–1.04; $P=0.03$; Figure 2). The IVW method showed that 1-SD increase in Lp(a) concentrations was causally associated with a substantial increase in risk of LAS using all instruments (random-effects model: OR, 1.20; 95% CI, 1.11–1.30; $P<0.001$; fixed-effects model: OR, 1.20; 95% CI, 1.14–1.27; $P<0.001$ using 9-SNP instrument) and a reduce in risk of SVS using 5-SNP and 9-SNP instruments (OR, 0.92; 95% CI, 0.88–0.97; $P=0.001$ using 9-SNP instrument; Figure 2). No significant association was observed using 2-SNP instrument for the risk of SVS. No significant association was observed for CES regardless of the instruments. Associations between each variant with Lp(a) concentrations and risk of ischemic stroke and its subtypes are displayed in Figure 3.

In sensitivity analyses, nominally significant associations were observed for the risk of ischemic stroke using the weighted median methods with the 5-SNP and 9-SNP instruments ($P=0.04$ and 0.03; Table 2). Substantially significant associations were observed for the risk of the LAS using the penalized IVW, simple median, weighted median, and MR-PRESSO methods with the 5-SNP and 9-SNP instruments (all $P<0.01$). Substantially significant associations were observed for the risk of the SVS using penalized IVW method with the 5-SNP and 9-SNP instruments ($P=0.008$ and 0.004), and nominally significant associations were observed using simple median method with the 9-SNP instrument ($P=0.049$), weighted median, MR-PRESSO methods with the 5-SNP and 9-SNP instruments ($P=0.04$ and 0.02; $P=0.02$ and 0.02).

MR-Egger regression showed no evidence of directional pleiotropy for the associations of Lp(a)

Table 2. MR Statistical Sensitivity Analyses

Outcome	Parameter	5-SNP Instrument OR (95% CI)	*P* Value	9-SNP Instrument OR (95% CI)	*P* Value
IS (n=40 585/406 111)*					
Penalized IVW	OR	1.03 (1.00–1.06)	0.07	1.02 (1.00–1.05)	0.09
MR-Egger	OR	1.02 (0.94–1.10)	0.63	1.01 (0.96–1.06)	0.73
	Odds (intercept)	1.00 (0.96–1.04)	0.99	1.01 (0.99–1.03)	0.59
Simple median	OR	1.03 (0.99–1.07)	0.10	1.01 (0.98–1.04)	0.42
Weighted median	OR	1.03 (1.00–1.06)	0.04	1.03 (1.00–1.06)	0.03
MR-PRESSO	OR	1.02 (0.98–1.06)	0.34	1.02 (1.00–1.05)	0.12
LAS (n=34 217/406 111)*					
Penalized IVW	OR	1.23 (1.15–1.32)	<0.001	1.24 (1.18–1.31)	<0.001
MR-Egger	OR	1.16 (0.91–1.49)	0.23	1.14 (0.96–1.34)	0.13
	Odds (intercept)	1.01 (0.89–1.14)	0.89	1.03 (0.96–1.10)	0.43
Simple median	OR	1.22 (1.12–1.34)	<0.001	1.22 (1.14–1.32)	<0.001
Weighted median	OR	1.22 (1.13–1.32)	<0.001	1.22 (1.14–1.31)	<0.001
MR-PRESSO	OR	1.23 (1.16–1.31)	0.006	1.24 (1.18–1.31)	<0.001
SVS (n=5386/406 111)*					
Penalized IVW	OR	0.92 (0.87–0.98)	0.008	0.92 (0.87–0.97)	0.004
MR-Egger	OR	0.95 (0.85–1.06)	0.39	0.90 (0.80–1.01)	0.07
	Odds (intercept)	0.98 (0.93–1.04)	0.54	1.01 (0.96–1.06)	0.62
Simple median	OR	0.93 (0.86–1.01)	0.07	0.93 (0.87–1.00)	0.049
Weighted median	OR	0.93 (0.87–1.00)	0.04	0.93 (0.87–0.99)	0.02
MR-PRESSO	OR	0.93 (0.89–0.96)	0.02	0.92 (0.87–0.97)	0.02
CES (n=7193/406 111)*					
Penalized IVW	OR	1.02 (0.97–1.07)	0.45	1.01 (0.97–1.05)	0.76
MR-Egger	OR	1.05 (0.96–1.16)	0.26	1.07 (0.99–1.17)	0.08
	Odds (intercept)	0.98 (0.94–1.03)	0.40	0.97 (0.94–1.00)	0.07
Simple median	OR	1.03 (0.97–1.10)	0.35	1.00 (0.95–1.06)	0.89
Weighted median	OR	1.03 (0.98–1.10)	0.25	1.03 (0.98–1.09)	0.20
MR-PRESSO	OR	1.02 (0.99–1.05)	0.23	1.01 (0.97–1.04)	0.71
AD (n=17 008/37 154)*					
Penalized IVW	OR	0.95 (0.91–0.99)	0.007	0.94 (0.91–0.97)	<0.001
MR-Egger	OR	1.00 (0.93–1.08)	0.99	0.96 (0.90–1.03)	0.29
	Odds (intercept)	0.97 (0.93–1.01)	0.10	0.99 (0.96–1.02)	0.47
Simple median	OR	0.96 (0.91–1.01)	0.09	0.96 (0.91–1.00)	0.053
Weighted median	OR	0.96 (0.91–1.00)	0.07	0.96 (0.92–1.00)	0.04
MR-PRESSO	OR	0.95 (0.91–0.99)	0.055	0.94 (0.92–0.97)	0.004

AD indicates Alzheimer disease; CES, cardioembolic stroke; IS, ischemic stroke; IVW, inverse-variance weighted; LAS, large artery stroke; MR, mendelian randomization; MR-PRESSO, mendelian randomization Pleiotropy Residual Sum and Outlier; OR, odds ratio; SNP, single-nucleotide polymorphism; and SVS, small vessel stroke.

*Sensitivity analyses were not performed for 2-SNP instruments since these methods require >2 variants.

concentrations with any ischemic stroke (odds [intercept], 1.01; *P*=0.59), LAS (odds [intercept], 1.03; *P*=0.43), SVS (odds [intercept], 1.01; *P*=0.62), and CES (odds [intercept], 0.97; *P*=0.07; Table 2). No obvious heterogeneity was observed for ischemic stroke (Q=12.10, *P*=0.15), SVS (Q=11.22, *P*=0.19), and CES (Q=5.27, *P*=0.73) but for LAS (Q=20.10, *P*=0.01). The results of leave-one-out sensitivity analyses showed that the association between Lp(a) concentrations and ischemic stroke or its subtypes was not substantially driven by any individual SNP (Figures I through IV in the online-only Data Supplement).

Causal Association of Lp(a) With Alzheimer Disease

Inverse causal associations of genetic higher Lp(a) concentrations with risk of Alzheimer disease were observed using both 5-SNP instrument and 9-SNP instrument (Figure 2). The IVW method showed that 1-SD increase in Lp(a) concentrations was causally associated with a reduce in risk of Alzheimer disease using 5-SNP and 9-SNP instruments (OR, 0.94; 95% CI, 0.91–0.97; $P<0.001$ using 9-SNP instrument; Figure 2). Associations between each variant with Lp(a) concentrations and risk of Alzheimer disease are displayed in Figure 3.

In sensitivity analyses, substantially significant associations were observed for the risk of the Alzheimer disease using penalized IVW method with the 5-SNP and 9-SNP instruments ($P=0.007$ and <0.001) and MR-PRESSO method with the 9-SNP instrument ($P=0.004$; Table 2). Nominally significant association was observed using weighted median method with the 9-SNP instrument ($P=0.04$). Marginal reverse associations were observed using simple median method with the 9-SNP instrument ($P=0.053$) and MR-PRESSO method with the 5-SNP instrument ($P=0.055$).

MR-Egger regression showed no evidence of directional pleiotropy for the association of Lp(a) concentrations with Alzheimer disease (odds [intercept], 0.99; $P=0.47$; Table 2). No obvious heterogeneity was observed ($Q=6.47$, $P=0.60$). The results of leave-one-out sensitivity analysis showed that the inverse association between Lp(a) concentrations and Alzheimer disease was not substantially driven by any individual SNP (Figure V in the online-only Data Supplement).

Discussion

Using 2-sample MR analysis based on data from large-scale GWAS study, our study demonstrated that a higher Lp(a) concentration may lead to an increased risk of LAS. In this study, genetically predicted elevated Lp(a) concentrations was potential, yet to be confirmed, causally associated with a decreased risk of SVS and Alzheimer disease. However, no significant association was observed between Lp(a) concentrations and risk of the CES. The findings were robust in sensitivity analyses with different instruments and statistical models.

The association of increased Lp(a) concentrations with risk of coronary heart disease was well established,[7,19,28,29] but the links with stroke are less consistent in previous observational studies.[8,12] Elevated Lp(a) level was found to be an independent risk factor for ischemic stroke in a recent meta-analysis with 90 904 subjects and 5029 stroke events.[12] A recent MR study indicated 1-SD genetically lowered Lp(a) level was associated with a 13% lower risk of stroke.[30] However, sex disparity was observed in Cardiovascular Health Study[11] and ARIC study (Atherosclerosis Risk in Communities),[10] and race disparity existed in the ARIC study,[8] MESA study (Multi-Ethnic Study of Atherosclerosis),[31] and REGARDS study (Reasons for Geographic and Racial Differences in Stroke).[9] The reason for the discrepancy among our study and previous studies may attribute to many reasons, including differences in study design, participant characteristics, and sample size. Additionally, the heterogeneity of ischemic stroke could be a non-negligible cause. Most previous studies included all subtypes of ischemic stroke.[7–9,30] In contrast, study of the association between Lp(a) concentrations and risk of specific etiological subtype of ischemic stroke is limited. Previous study showed that Lp(a) promoted atherothrombotic stroke rather than lacunar stroke.[32] Previous genetic study showed that *LPA* variants (rs10455872 and rs3798220) were only associated with LAS.[33] Using MR analysis, the present study adds the evidence of causal effect of genetic predicted Lp(a) concentrations on risk of ischemic stroke and its subtypes. Elevated Lp(a) concentrations may lead to an increased risk of LAS but a decreased risk of SVS. This may also help to explain the variable results found in previous studies. The distinct relationship of Lp(a) with LAS (positive association) and SVS (inverse association) may cause variable results when all subtypes of ischemic stroke were investigated together in previous studies.

Compared with studies on association of Lp(a) concentrations with risk of cardiovascular diseases,[7,28,29] the association between Lp(a) concentrations and risk of Alzheimer disease has less been investigated. Slightly better cognitive performance was observed in subjects with elevated Lp(a) levels in a previous cross-sectional study.[34] Several previous case-control studies[13,14] showed a lower Lp(a) concentration, some[16] showed a higher Lp(a) concentration, and others[17,35] had no significant difference in patients with Alzheimer disease compared with healthy control. Other case-control studies found a higher level of Lp(a) in patients with vascular dementia but a lower or no different level of Lp(a) in patients with Alzheimer disease compared with healthy control.[14,36] However, the small sample size (40–371 cases with Alzheimer disease) and nature of case-control design limited the generalizability of these studies. In a recent prospective cohort of 2532 subjects with 228 new cases of dementia in 24.9 years of follow-up, Lp(a) level was shown to be protective of future dementia risk in a middle-aged Finnish male population.[15] Results from the ARIC study also showed that higher Lp(a) was associated with slower cognitive decline.[37] These studies were consistent with our findings but still cannot control the influence of unmeasured confounders because of the nature of observational study. The present study adds the evidence of causal protective effect of Lp(a) concentrations on risk of Alzheimer disease using genetic data via an MR approach, which method may control unmeasured confounders and reverse causation, and its potential to ascertain causal relationship.[18]

Lp(a) consists of an LDL-like core lipoprotein and glycoprotein Apo(a) and has been attributed to atherogenic, thrombogenic, vascular inflammatory, and antifibrinolytic potential.[6,12] Because of its similarity with LDL and the structural homology with plasminogen, Lp(a) promotes atherosclerotic stenosis and subsequent ischemic vascular events.[6] Previous study also showed that Lp(a) level increased gradually with the extent of intracranial large artery stenoses,[38] and higher level of Lp(a) has greater risk of carotid plaque burden and progression.[31] It is validated in our study that genetic predicted elevated Lp(a) was only associated with an increased risk of LAS. Compared with the proatherosclerotic effects of Lp(a), the mechanism whereby high Lp(a) level suppresses the Alzheimer pathological process is much unclear. There are several potential explanations. First, previous study observed that increasing LDL cholesterol tended to be associated with a decreased frequency and severity of magnetic resonance imaging markers of cerebral small vessel disease.[39] Cerebral small vessel disease is the most common cause of cognitive impairment and dementia and contributes

to the occurrence of Alzheimer disease.[40] We also observed inverse associations of Lp(a) level with both SVS and Alzheimer disease. Second, Lp(a) in cerebrospinal fluid was found to be correlated strongly with plasma levels, indicating that Lp(a) can cross a dysfunctional blood-cerebrospinal fluid barrier.[41] Lipoproteins, like Apo-A1 (apolipoprotein A-1), may regulate cholesterol levels in cerebrospinal fluid, moderate the deposition of amyloid-β, and influence neurodegeneration.[42] It is possible that Lp(a) may also play a role in lipoprotein metabolism in the central nervous system and neuronal maintenance.[15] Third, Apo(a) in Lp(a) primarily determines the plasma Lp(a) level.[6] It has been speculated that the protective effect of Lp(a) on dementia could be due to the Apo(a), which may modify ApoE (apolipoprotein E) isoform metabolism and function against the development of Alzheimer disease.[14] Further studies are still needed to elucidate the exact mechanisms underlying the inverse associations of Lp(a) concentrations with risk of SVS and Alzheimer disease.

The strength of the study is the design of MR analysis based on multiple Lp(a) concentration–related SNPs and effects of SNP outcomes from large-scale GWAS studies. MR analysis is a technique for using genetic variants to estimate the causal effect of an exposure for a disease. The potential bias is greatly reduced because genetic variation is not associated with other confounding factors, such as lifestyle, dietary, and behavior factors, which may influence observational studies.[18] MR analysis can also avoid reverse causation since genetic variation is allocated at conception. The nature of the MR analysis design is less prone to potential unmeasured confounding and reverse causation and can strengthen the evidence for causal inference.[23] In addition, by using the 2-sample MR approach, we were able to test the effect of Lp(a) based on a large-scale cohort (40 585 stroke cases and 406 111 controls; 17 008 Alzheimer disease cases and 37 154 controls). Our analysis also distinguishes itself from previous MR study[30] by performing causal inferences with comprehensive evaluation for the association of Lp(a) concentrations with stroke subtypes and Alzheimer disease. Comprehensive evaluation of stroke subtypes and Alzheimer disease may help better understanding of the clinical consequences of Lp(a) concentrations on the brain. This study suggests a causal deteriorating effect on LAS but protective effect on SVS and Alzheimer disease. Given the causal double-edged sword effect of Lp(a) concentrations on neurological system, this study provides a rationale to investigate the comprehensive effects and optimum maintenance concentrations of Lp(a) in clinical practice.

Our study suffers from several limitations. First, the MR analysis may be biased by potential violations of standard instrumental variable assumptions. It is difficult to completely exclude the potential influence of directional pleiotropy, which may lead to biased causal effect estimates.[22] However, pleiotropic effects were not observed in MR-Egger regression analysis and sensitivity analyses with other instruments, and other robust models showed mostly similar results. Second, our population was limited to individuals of European ancestry, which may limit the generalizability of our findings. Lp(a) concentrations were shown to vary with ethnicity.[9] However, the uniformity of the included subjects ensures minimal risk of confounding by population admixture. Third, the intrinsic limitation of the 2-sample MR analysis may be non-negligible as the data of associations of SNP-exposure, SNP-stroke, and SNP-Alzheimer disease from different populations.

Conclusions

Our MR analysis provides genetic evidences of causal associations between high Lp(a) concentrations and an increased risk of LAS but a decreased risk of SVS and Alzheimer disease. This suggests high Lp(a) concentrations had a causal deteriorating effect on LAS but protective effect on SVS and Alzheimer disease. The mechanism underlying the double-edged sword effect of Lp(a) concentrations on neurological system requires further investigation.

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Disclosures

None.

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