

## Polygenic Risk for Depression Increases Risk of Ischemic Stroke

### From the Stroke Genetics Network Study

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**Background and Purpose**—Although depression is a risk factor for stroke in large prospective studies, it is unknown whether these conditions have a shared genetic basis.

**Methods**—We applied a polygenic risk score (PRS) for major depressive disorder derived from European ancestry analyses by the Psychiatric Genomics Consortium to a genome-wide association study of ischemic stroke in the Stroke Genetics Network of National Institute of Neurological Disorders and Stroke. Included in separate analyses were 12 577 stroke cases and 25 643 controls of European ancestry and 1353 cases and 2383 controls of African ancestry. We examined the association between depression PRS and ischemic stroke overall and with pathogenic subtypes using logistic regression analyses.

**Results**—The depression PRS was associated with higher risk of ischemic stroke overall in both European ( $P=0.025$ ) and African ancestry ( $P=0.011$ ) samples from the Stroke Genetics Network. Ischemic stroke risk increased by 3.0% (odds ratio, 1.03; 95% confidence interval, 1.00–1.05) for every 1 SD increase in PRS for those of European ancestry and by 8% (odds ratio, 1.08; 95% confidence interval, 1.04–1.13) for those of African ancestry. Among stroke subtypes, elevated risk of small artery occlusion was observed in both European and African ancestry samples. Depression PRS was also associated with higher risk of cardioembolic stroke in European ancestry and large artery atherosclerosis in African ancestry persons.

**Conclusions**—Higher polygenic risk for major depressive disorder is associated with increased risk of ischemic stroke overall and with small artery occlusion. Additional associations with ischemic stroke subtypes differed by ancestry. (*Stroke*. 2018;49:543-548. DOI: 10.1161/STROKEAHA.117.018857.)

**Key Words:** atherosclerosis ■ depression ■ genetics ■ risk ■ stroke

Major depressive disorder (MDD) is one of the most common psychiatric disorders worldwide, with a lifetime prevalence estimated to be 15%.<sup>1,2</sup> The prevalence of mild, moderate, or severe depressive symptoms was 20% in a national representative sample of US adults, with 7% reporting moderate or severe symptoms.<sup>3</sup> Numerous large-scale epidemiological studies have demonstrated that MDD or depressive symptoms prospectively predict increased risk of stroke in white, Asian, and black populations.<sup>4-8</sup>

Despite the consistency of multiple large cohort studies showing that a history of depression prospectively predicts

incident stroke, the mechanisms underlying this association have not been elucidated. Specifically, little is known about whether depression is a general risk factor for stroke or a more specific risk factor for hemorrhagic or ischemic stroke. Further, depression may be a cause of stroke or a prodromal symptom of an impending stroke may influence behaviors that increase risk of stroke or may relate indirectly to other unknown factors that increase both depression and stroke risk.

Genetic studies offer an important opportunity to evaluate shared pathogenic contributions to depression and stroke. Recent genome-wide association studies (GWAS) have enabled

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the estimation of common variant heritability for complex traits (single nucleotide polymorphism [SNP] heritability or  $h^2_{\text{SNP}}$ ). Significant  $h^2_{\text{SNP}}$  estimates have been reported for both depression ( $\approx 5\%$ – $20\%$ )<sup>9,10</sup> and stroke and its subtypes ( $\approx 20\%$ – $40\%$ ).<sup>11–16</sup> In the present study, we used polygenic risk scores (PRS) derived from genetic analyses of MDD from the Psychiatric Genomics Consortium (PGC)<sup>17</sup> to examine whether genetic risk for depression is associated with ischemic stroke and its subtypes. As an alternative to testing, the effects of individual SNPs, PRS have been commonly used to evaluate whether genetic risk for one condition (eg, depression) is associated with risk for a second condition (eg, stroke). A PRS is the weighted sum of individual SNP effect sizes derived from a GWAS. An association of the PRS with the second trait is typically interpreted as evidence for pleiotropy—that is, a common set of genetic variants that jointly influence risk of both conditions.

PRS for depression have been created for different phenotypic definitions of depression.<sup>18</sup> A PRS for the clinical phenotype of MDD has been constructed by PGC's MDD Working Group<sup>17</sup> where a GWAS was performed on a discovery sample of 11 625 individuals (4984 cases of depression and 6641 controls). In the present report, we applied this PRS to participants in the Stroke Genetics Network (SiGN) to test whether genetic risk for MDD is associated with risk of stroke. SiGN also includes adjudicated cases of stroke subtypes by presumed mechanism, allowing us to examine whether genetic predisposition to depression is associated with pathogenic subtypes of stroke.

## Methods

### Population: SiGN

The Stroke Genetics Network of National Institute of Neurological Disorders and Stroke was launched in 2010 to identify genetic loci associated with ischemic stroke and its subtypes. The design, rationale, and primary GWAS findings from SiGN have been described elsewhere.<sup>19–21</sup> The present report is based on 13 930 ischemic stroke cases and 28 026 controls of European and African ancestry for whom a PRS for MDD was generated. Ischemic stroke cases were accrued from 24 genetic research centers across the United States and Europe. Among the 24 individual cohorts, informed consent procedures may have varied, but each had its own institutional review board approval. To remain compliant with institutional review board approvals at some sites, only summary statistics are publicly available at <http://www.cerebrovascularportal.org/>. A subset of the SiGN individual-level data that is institutional review board compliant is available at dbGaP (phs000615.v1.p1). Requests for analysis of the full set of individual-level data can be made through the authors (B.D.M.).

All SiGN GWAS were adjusted for sex and the top 10 principal components,<sup>21</sup> after matching cases and controls within multiple analytic strata based on ancestry and genotyping platform as previously described.<sup>22</sup>

Subtypes for ischemic stroke were standardized using the web-based causative classification of stroke system (CCS) that uses a validated algorithm to assign stroke subtypes according to presumed mechanism based on clinical and ancillary test findings and were developed to maximize interexaminer reliability in stroke classification while using the full diagnostic data set from a typical stroke workup. There are 2 major versions: CCS phenotypic (CCSp) and CCS causative (CCSc). The CCS phenotypic algorithm is a documentation of abnormal test findings and does not require judgments on the part of the adjudicator. CCSc algorithm involves the integration of symptoms, vascular risk factors, diagnostic test results, response to treatment, and prognosis and thus requires a decision-making process. We present CCS phenotypic in this article and but also present the results for CCSc algorithm in the online-only Data Supplement.

Data were entered by trained and certified adjudicators at participating genetic research centers. TOAST (Trial of ORG 10172 in Acute Stroke Treatment) stroke subtype classifications were also available, and the comparison between the CCS and TOAST classifications has been published,<sup>20</sup> indicating that the overall agreement was moderate and varied widely across study sites, ranging from 28% to 90%. Furthermore, the interrater reliability of TOAST is considerably lower than that of CCS, with  $\kappa$  ranging between 0.42 and 0.54, whereas CCS  $\kappa$  range between 0.8 and 0.9.<sup>23–29</sup> Thus, in this article, we use CCS because it is a uniform classification system using algorithms that are applied across many different international cohorts; however, we also present the TOAST results in the online-only Data Supplement.

Genotyping was conducted at the Center for Inherited Diseases Research. Strokes were classified as being caused by large artery atherosclerosis, small artery occlusion (SAO), cardioembolic, other type or mixed type, or cryptogenic undetermined or unknown usually because of insufficient workup or imaging.

### Depression PRS and Its Application to SiGN Participants

The depression PRS was derived from GWAS results from the Major Depressive Disorder Working Group of the PGC.<sup>17</sup> The PGC GWAS analyzed >1.2 million SNPs in 18 759 cases and controls. The full set of PGC GWAS results can be found at <https://www.med.unc.edu/pgc/results-and-downloads>. The PGC association results were generated for 123 025 independent SNPs based on linkage disequilibrium structure. MDD risk alleles were designated as the allele for each SNP associated with higher MDD risk. Alleles were weighted by their  $\beta$  coefficients from the MDD association analysis. In the PGC analysis, multiple  $P$  value thresholds for the association of individual SNPs with MDD were applied for inclusion in the depression PRS (from  $P_i=0.001$ – $0.5$ ). The  $P$  value threshold of 0.5 performed best in the PGC test sample and was highly significant in predicting MDD (with  $P<10^{-6}$ ) but accounted for only a small proportion of the variance with  $R^2$  of 0.6%. The SNP weights generated by the PGC were then used to generate PRS for subjects in the SiGN data set.

We extracted data for the PGC polygenic score SNPs from the SiGN data. For each SNP, we converted the genotype posterior probabilities into single allelic dosages according to Equation 1 below.

$$\text{Allelic Dosage (AD)} = 2 * P(\text{AA}) + 1 * P(\text{AB}) + 0 * P(\text{BB}) \quad (1)$$

where  $P(\text{AA})$ ,  $P(\text{AB})$ , and  $P(\text{BB})$  indicate probabilities of having genotype AA, AB, and BB, with allele A corresponding to the risk allele.

To obtain the weighted PRSs, we multiplied allelic dosage by the regression  $\beta$  coefficient and summed this product across all loci in the SNP set (see Equation 2):

$$\text{Polygenic risk score (PRS)} = \sum (\beta_i * \text{AD}_i) \quad (2)$$

where  $\beta_i$  indicates  $\beta$  value for the  $i_{\text{th}}$  SNP from the PGC analysis and  $\text{AD}_i$  indicates allelic dosage for SiGN subjects.

Logistic regression analyses were conducted to relate PRS to stroke and its subtypes, where stroke  $(0,1)=\beta_s$  (PRS), adjusted for analytic strata and sex.

### Statistical Analysis

Logistic regression models were applied to test the association between the 8 PRSs, generated by different inclusion probability criteria for the individual SNPs, with separate models for stroke and its subtypes. Analyses were conducted separately for SiGN subjects of European and African ancestry.

## Results

The analyses included 12 577 stroke cases and 25 643 controls of European ancestry and 1353 stroke cases and 2383 controls

**Table 1. Relationship Between Polygenic Risk for Depression and All Ischemic Stroke Using 8 Polygenic Risk Scores for Different Inclusion Criteria ( $P_T$ ) Into the PRS European Ancestry Adults (N = 12,577 Cases, 25,643 Controls)**

$P_T$	No. of SNPs Included in PRS	Beta <sub>s</sub>	SE	P Values for Beta <sub>s</sub>
0.001	2276	0.0288	0.0085	0.000648
0.01	13281	0.0164	0.0040	4.36E-05
0.05	48557	0.0093	0.0022	1.58E-05
0.1	85810	0.0078	0.0017	4.45E-06
0.2	153274	0.0060	0.0014	8.53E-06
0.3	214667	0.0049	0.0012	4.43E-05
0.4	272322	0.0049	0.0011	1.02E-05
0.5	326088	0.0037	0.0010	0.000347

$P_T$ : p-value threshold for SNP inclusion into the PRS. Beta<sub>s</sub> relates PRS to stroke subtype, per unit of PRS.

of African ancestry. Age of onset of stroke was (mean±SD) 65.5±15; in cases, 53.9% were males, and in controls, 45.2% were males. Tables 1 and 2 show the  $\beta$  coefficients for PRS in European and African ancestry groups, respectively, for different SNP inclusion criteria in the PRS.

The MDD PRS was associated with overall risk of ischemic stroke for  $P_T=0.4$  and  $P_T=0.5$  in both European and African ancestry samples. We present the primary results for  $P_T=0.5$  because this threshold was most closely related to depression in the PGC target sample, but the results for  $P_T<0.4$ , which includes 71 315 SNPs, are also shown in the online-only Data Supplement.

In the SNP set where the SNP inclusion criterion was  $P=0.5$  with 83 890 SNPs used in the SiGN PRS, an additional 358 SNPs (0.42% of SNPs) available in the PGC depression PRS were unavailable in SiGN. Overall, for every 1 SD difference in PRS ( $P_T=0.5$ ) ischemic stroke risk increased by 3.0% (odds ratio, 1.03; 95% confidence interval, 1.00–1.05) in those of European ancestry (Table 3), whereas those of African ancestry had an 8% risk increase (odds ratio, 1.08; 95% confidence interval, 1.04–1.13; Table 4). The corresponding figures for

**Table 2. Relationship Between Polygenic Risk for Depression and All Ischemic Stroke Using 8 Polygenic Risk Scores for Different Inclusion Criteria ( $P_T$ ) Into the PRS African Ancestry Adults (N = 1353 cases, 2383 Controls)**

$P_T$	No. of SNPs Included in PRS	Beta <sub>s</sub>	SE	P Values for Beta <sub>s</sub>
0.001	3449	0.0110	0.0163	0.498
0.01	19350	0.0029	0.0055	0.595
0.05	69689	0.0022	0.0016	0.171
0.1	121552	0.0020	0.0011	0.069
0.2	211852	0.0014	0.0007	0.063
0.3	291400	0.0015	0.0007	0.028
0.4	364434	0.0011	0.0006	0.084
0.5	431838	0.0010	0.0006	0.064

$P_T=0.4$  are similar (Tables I and II in the online-only Data Supplement).

For analyses of ischemic stroke subtypes, we limited PRS analyses to SNPs included based on  $P_T=0.5$ . In those of European ancestry (Table 3), polygenic risk for MDD was associated with SAO stroke ( $P<0.001$ ) and cardioembolic stroke ( $P<0.042$ ). In those of African ancestry (Table 4), the MDD PRS was associated with large artery atherosclerosis ( $P<0.032$ ) and SAO ( $P\leq 0.029$ ), despite the smaller sample of African ancestry cases. For each SD increase in PRS, the risk of SAO increased by 8% (odds ratio, 1.08; 95% confidence interval, 1.03–1.13) for those of European ancestry and by 9% (odds ratio, 1.09; 95% confidence interval, 1.01–1.19) for those of African ancestry. The results were similar when using the CCS classification (Tables III and IV in the online-only Data Supplement). The TOAST classification also showed a significant increase in risk of SAO of 5% and 10% per 1 SD increase in PRS in European and African samples, respectively ( $P<0.03$ ), but other subtypes generally did not reach statistical significance (Tables V and VI in the online-only Data Supplement).

## Discussion

Large epidemiological studies have demonstrated that depression is associated with increased risk of stroke; however, it has been unclear whether this phenotypic association reflects a shared genetic basis. To our knowledge, this is the first report of an association between genetic risk for depression and ischemic stroke subtypes, providing a potential mechanism underlying the link between these common conditions.

We used a PRS for MDD derived from a large European ancestry sample and applied it to GWAS results from the National Institute of Neurological Disorders and Stroke SiGN study (Stroke Genetics Network). We found that higher PRS for depression is associated with higher risk of ischemic stroke, particularly of the SAO subtype, in both European and African ancestry subsamples of SiGN. As the MDD PRS was derived from GWAS of European ancestry samples, these results suggest a transethnic association between polygenic risk for MDD and stroke. For every 1 SD difference in the PRS for MDD, overall ischemic stroke risk increased by 2.6% and 7.0% for those of European and African ancestry, respectively. Further, in those of European ancestry, the PRS was additionally associated with cardioembolic strokes, whereas in the African ancestry group, it was associated with the large artery atherosclerosis subtype. PRS was significantly associated with SAO in the CCS phenotypic, the CCS classification, and TOAST classification systems.

In contrast to our results, a recent large-scale analysis of genetic correlations among 24 psychiatric and neurological disorders conducted by the Brainstorm consortium, which included 10 307 ischemic stroke cases and 19 326 population-matched controls from Metastroke, found no significant relationship between MDD and ischemic stroke.<sup>30</sup> There is some overlap of data with our SiGN cases and controls: 5247 of the total 16 851 SiGN cases (31%) and 8034 of the 32 473 SiGN controls (25%) were also part of Metastroke. The current report, however, is based on a subset of the larger SiGN samples after excluding those of Hispanic ancestry, resulting in 13 930 cases

**Table 3. Relationship Between PRS Based on 85,810 SNP's With Inclusion Criterion Into PRS of  $P_T < .1$ , by CCSp Stroke Subtype for European Ancestry Adults**

Phenotype (CCSp)	Total No. of Cases	Total No. of Controls	Beta <sub>s</sub>	SE	P Value for Beta <sub>s</sub>	OR (95% CI) for Stroke, per 1 SD of PRS= $e^{\text{Beta}_s \text{SD}}$
All stroke	12577	25643	0.0078	0.0017	4.45E-06	1.05 (1.03–1.08)
LAA	2229	25643	0.0105	0.0033	0.002	1.07 (1.03–1.12)
SAO	2029	25643	0.0125	0.0034	2.41E-04	1.09 (1.04–1.14)
CE	3400	25643	0.0048	0.0028	0.087	1.03 (1.00–1.07)
Other	612	25643	0.0067	0.0062	0.281	1.05 (0.96–1.13)
Crypto	963	25643	0.0051	0.0050	0.310	1.03 (0.97–1.10)

CCSp is the Causative Classification System - phenotypic. Beta<sub>s</sub> relates PRS to stroke subtype, per unit of PRS.

of European or African ancestry and 28026 controls. On the basis of the total SiGN sample, one can assume that less than one third of the cases and controls used in this SiGN study overlap with those in the Brainstorm analysis. With regard to depression data, Brainstorm used a larger and more recent PGC-MDD data set, not available at the time of our analyses.

In addition, our analyses differ from those done in the Brainstorm consortium in several important aspects. First, we focused on the genetic relationship of MDD to subtypes of stroke that was not examined in the Brainstorm analysis. Second, we examined ischemic stroke subtypes defined by the CCS, a classification algorithm based on all relevant clinical and test information that has demonstrated improved reliability relative to the TOAST classification approach used in the Brainstorm analysis. Third, to examine cross-phenotype relationships, we use PRS, whereas the Brainstorm analysis used linkage disequilibrium score regression. Linkage disequilibrium score regression is used to estimate genetic correlation using only summary statistics and can be less powerful in some contexts compared with methods that use individual-level genotype data. In addition, linkage disequilibrium score regression can estimate the genetic correlation of traits using data across the entire genome; in PRS analyses, the scores examined are subsets of SNPs, typically restricted to those in the upper tails of the distribution of GWAS results (ie, the *P* value thresholds are prespecified for inclusion of SNPs in the PRS). Thus, if the genetic overlap is concentrated in loci that are within the selected *P* value threshold, PRS analyses may be more likely to show significant effects than might be seen with a genome-wide linkage

disequilibrium score regression; this may be relevant to our finding of a genetic relationship between MDD and stroke that was not seen in the Brainstorm analyses.

The underlying mechanism connecting the observed association between genetic predisposition to depression and ischemic stroke risk is unclear. Recent research on the stroke–depression relationship has focused on pathophysiologic mechanisms, including vascular dysfunction and neuroendocrine pathways and genetic predisposition. The vascular depression disconnection hypothesis is that focal ischemic white matter lesions can disrupt neural connections among regions regulating mood and cognition, contributing to the clinical symptomatology of depression.<sup>31,32</sup> Because the disconnection hypothesis depends on the strategic location of such small vessel lesions, it is possible that the strength of the genetic association observed is limited by the randomness of where these small vessel lesions occurred.<sup>33–35</sup> Interestingly, we found a consistent association between polygenic depression risk and the lacunar (small vessel) ischemic stroke mechanism across both ancestry groups.

A second possible mechanistic connection is a common pathway promoting inflammation, although prior evidence is limited. Several candidate gene studies have linked polymorphisms associated with proinflammatory responses in depression. Prior studies linked genetic polymorphisms that promote proinflammatory responses with depression.<sup>36–38</sup> Atherothrombotic (large artery stroke) has also been linked to proinflammatory genes.<sup>39</sup> Third, platelets and endothelial function may play a role in the association between depression and stroke risk. Studies of candidate genes in patients

**Table 4. Relationship Between PRS Based on 121,552 SNPs With Inclusion Criterion Into PRS of  $P_T < .1$ , by CCSp Stroke Subtype for African Ancestry**

Phenotype (CCSp)	Total No. of Cases	Total No. of Controls	Beta <sub>s</sub>	SE	P Value for Beta <sub>s</sub>	OR (95% CI) for Stroke, per 1 SD of PRS= $e^{\text{Beta}_s \text{SD}}$
All stroke	1353	2383	0.0020	0.0011	0.0687	1.07 (1.00–1.14)
LAA	220	2383	0.0054	0.0022	0.0164	1.19 (1.03–1.37)
SAO	390	2383	0.0009	0.0017	0.5771	1.03 (0.93–1.15)
CE	208	2383	0.0004	0.0023	0.8623	1.01 (0.88–1.17)
Other	106	2383	0.0021	0.0032	0.5039	1.07 (0.88–1.31)
Crypto	133	2383	0.0021	0.0028	0.4482	1.07 (0.90–1.27)

CCSp is the Causative Classification System – phenotypic. Beta<sub>s</sub> relates PRS to stroke subtype, per unit of PRS. CCSp is the Causative Classification System – phenotypic.



with depression and coronary disease have implicated platelet dysregulation and inflammation as causal mechanisms. Thus, increased stroke risk with depression may be mediated through excessive platelet activation.<sup>40,41</sup> Endothelial dysfunction may be related as a study of young women with sub-clinical depression found a significant association between depression and abnormal endothelial function assessed by pulse-wave amplitude assessment.<sup>42</sup> We observed evidence of association between MDD and atherothrombotic ischemic stroke only for individuals of European ancestry. The lack of association among those of African ancestry might be because of limited power in that sample or transethnic differences in the genetic pathogenesis of large artery atherosclerosis. Of note, the atherothrombotic type is more common in European ancestry patients.<sup>43</sup> Finally, another possible common mechanism is cerebrovascular dysregulation and hypoperfusion.<sup>31</sup>

An important strength of our study is the large number of strokes in both European and African ancestry individuals, which have been classified by subtype in a uniform manner, although we note several limitations of our study. Power to detect associations with certain subtypes was still limited by sample sizes. Power in African ancestry samples also may have been reduced by transethnic differences in the genetic basis of stroke. A PRS derived from an African ancestry GWAS might contain different SNPs and thus could show a stronger or different relationship to certain subtypes of stroke in African ancestry samples. However, it is noteworthy that a European-derived MDD PRS was also associated with stroke in those of African ancestry. In addition, the relationship of the PRS derived in the PGC to MDD explained only a small proportion of the variance of depression.

In the large National Institute of Neurological Disorders and Stroke SiGN study of 13 930 ischemic strokes, we found that higher polygenic risk for MDD depression is associated with higher risk of ischemic stroke overall and with small artery occlusion, both for those of European and African ancestry, supporting a common genetic basis between depression and stroke risk.

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### Disclosures

None.

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## Polygenic Risk for Depression Increases Risk of Ischemic Stroke: From the Stroke Genetics Network Study

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**Polygenic Risk for Depression Increases Risk of Ischemic Stroke: from the Stroke Genetics Network (SiGN) Study  
Supplemental Material**

Supplemental Table 1

**Relationship between PRS based on 71,315 SNP's with inclusion criterion into PRS of  $p < .4$ , by CCSP stroke subtype for European Ancestry Adults**

Phenotype (CCS)	Total N Cases	Total N Controls	Betas	SE	P for Betas	OR (95% CI) for stroke per 1 s.d of PRS* = $e^{\text{beta} \times \text{s.d}}$
<b>All stroke</b>	12577	25643	0.00005	0.000021	0.0157	1.03 (1.01, 1.06)
<b>LAA</b>	2229	25643	0.000036	0.000041	0.3786	1.02 (0.97, 1.07)
<b>SAO</b>	2029	25643	0.00015	0.000042	0.0004	1.09 (1.04, 1.15)
<b>CE</b>	3400	25643	0.00006	0.000034	0.0817	1.04 (1.00, 1.08)
<b>OTHER</b>	612	25643	0.00014	0.000076	0.0665	1.09 (0.99, 1.19)
<b>Crypto</b>	963	25643	0.000056	0.00006	0.3506	1.03 (0.96, 1.11)



## Supplemental Table II

**Relationship between PRS based on 71,315 SNPs with inclusion criterion into PRS of  $p < .4$ , by CCSp stroke subtype for African Ancestry Adults**

Phenotype (CCS)	Total N Cases	Total N Controls	Betas	SE	P for Betas	OR (95% CI) for stroke per 1 s.d of PRS* = $e^{\text{beta} \times \text{s.d}}$
<b>All stroke</b>	1353	2383	0.000132	0.000048	0.0062	1.08 (1.02, 1.15)
<b>LAA</b>	220	2383	0.000233	0.000101	0.0208	1.15 (1.02, 1.20)
<b>SAO</b>	390	2383	0.000207	0.000078	0.0078	1.13 (1.03, 1.24)
<b>CE</b>	208	2383	-0.000020	0.0001	0.8565	0.99 (0.88, 1.11)
<b>OTHER</b>	106	2383	0.000187	0.000142	0.1863	1.12 (0.95, 1.32)
<b>Crypto</b>	133	2383	0.000124	0.000124	0.3145	1.08 (0.93, 1.25)

## Supplemental Table III

**Relationship between PRS based on 83,890 SNPs with inclusion criterion into PRS of  $p < .5$ , by CCSc stroke subtype for European Ancestry Adults**

Phenotype (CCS)	Total N Cases	Total N Controls	Betas	SE	P for Betas	OR (95% CI) for stroke per 1 s.d of PRS* = $e^{\text{beta} \times \text{s.d.}}$
<b>LAA</b>	<b>2207</b>	<b>25643</b>	<b>4.08E-07</b>	<b>0.000038</b>	<b>0.9915</b>	<b>1.00 (0.96, 1.05)</b>
<b>SAO</b>	<b>1881</b>	<b>25643</b>	<b>0.000134</b>	<b>0.000041</b>	<b>0.001</b>	<b>1.08 (1.03, 1.14)</b>
<b>CE</b>	<b>2835</b>	<b>25643</b>	<b>0.000038</b>	<b>0.000034</b>	<b>0.2623</b>	<b>1.02 (0.98, 1.06)</b>
<b>CRYPTO</b>	<b>1027</b>	<b>25643</b>	<b>0.000071</b>	<b>0.000054</b>	<b>0.1884</b>	<b>1.04 (0.98, 1.11)</b>
<b>UNDETERMINED</b>	<b>4031</b>	<b>25643</b>	<b>0.000054</b>	<b>0.000029</b>	<b>0.0645</b>	<b>1.03 (1.00, 1.07)</b>
<b>INCONCLUSIVE</b>	<b>2038</b>	<b>25643</b>	<b>0.000091</b>	<b>0.000039</b>	<b>0.0203</b>	<b>1.06 (1.01, 1.11)</b>

## Supplemental Table IV

Relationship between PRS based on 83,890 SNP's with inclusion criterion into PRS of  $p < .5$ , by CCSc stroke subtype for African Ancestry Adults

	Total N Cases	Total N Controls	Betas	SE	P for Betas	OR (95% CI) for stroke per 1 s.d of PRS* = $e^{\text{beta} \times \text{s.d.}}$
LAA	178	2383	0.000201	0.000098	0.0409	1.13 (1.01, 1.27)
SAO	381	2383	0.000127	0.000069	0.0675	1.08 (1.00, 1.17)
CE	165	2383	-2.3E-07	0.000099	0.9982	1.00 (0.89, 1.12)
CRYPTO	133	2383	0.000118	0.00011	0.1884	1.07 (0.94, 1.22)
UNDETERMINED	543	2383	0.000083	0.000059	0.1601	1.05 (0.98, 1.13)
INCONCLUSIVE	242	2383	0.00007	0.000084	0.4047	1.04 (0.94, 1.15)

Supplemental Table V

Relationship between PRS based on 83,890 SNP's with inclusion criterion into PRS of  $p < .5$ , by TOAST stroke subtype for European Ancestry Adults

	Total N Cases	Total N Controls	Betas	SE	P for Betas	OR (95% CI) for stroke per 1 s.d of PRS* = $e^{\text{beta} \times \text{s.d.}}$
<b>LAA</b>	2193	25643	-0.000003	0.000039	0.399	1.00 (0.95, 1.95)
<b>SAO</b>	2252	25643	0.000084	0.000037	0.025	1.05 (1.01, 1.10)
<b>CE</b>	3138	25643	0.000052	0.000033	0.116	1.03 (0.99, 1.07)
<b>Other</b>	331	25643	0.000129	0.000095	0.171	1.08 (0.97, 1.21)
<b>UNDETERMINED</b>	3080	25643	0.000062	0.000033	0.060	1.04 (1.00, 1.08)



Supplemental Table VI  
**Relationship between PRS based on 83,890 SNP's with inclusion criterion into PRS of  $p < .5$ , by TOAST stroke subtype for African Ancestry Adults**

	Total N Cases	Total N Controls	Betas	SE	P for Betas	OR (95% CI) for stroke per 1 s.d of PRS* = $e^{\text{beta} \times \text{s.d.}}$
<b>LAA</b>	125	2383	0.000315	0.000117	0.007	1.21 (1.05, 1.39)
<b>SAO</b>	379	2383	0.000153	0.000069	0.028	1.10 (1.01, 1.19)
<b>CE</b>	195	2383	-0.000004	0.000091	0.624	0.98 (0.88, 1.09)
<b>Other</b>	42	2383	0.000225	0.000195	0.247	1.14 (0.91, 1.44)
<b>UNDETERMINED</b>	399	2383	0.000041	0.000068	0.550	1.02 (0.95, 1.11)

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**Polygenic Risk for Depression Increases Risk of Ischemic Stroke: from the Stroke Genetics Network (SiGN) Study  
Supplemental Material**

Supplemental Table I

**Relationship between PRS based on 71,315 SNP's with inclusion criterion into PRS of  $p < .4$ , by CCSp stroke subtype for European Ancestry Adults**

Phenotype (CCS)	Total N Cases	Total N Controls	Betas	SE	P for Betas	OR (95% CI) for stroke per 1 s.d of PRS* = $e^{\text{beta} \times \text{s.d}}$
<b>All stroke</b>	12577	25643	0.00005	0.000021	0.0157	1.03 (1.01, 1.06)
<b>LAA</b>	2229	25643	0.000036	0.000041	0.3786	1.02 (0.97, 1.07)
<b>SAO</b>	2029	25643	0.00015	0.000042	0.0004	1.09 (1.04, 1.15)
<b>CE</b>	3400	25643	0.00006	0.000034	0.0817	1.04 (1.00, 1.08)
<b>OTHER</b>	612	25643	0.00014	0.000076	0.0665	1.09 (0.99, 1.19)
<b>Crypto</b>	963	25643	0.000056	0.00006	0.3506	1.03 (0.96, 1.11)

## Supplemental Table II

**Relationship between PRS based on 71,315 SNP's with inclusion criterion into PRS of  $p < .4$ , by CCSp stroke subtype for African Ancestry Adults**

Phenotype (CCS)	Total N Cases	Total N Controls	Betas	SE	P for Betas	OR (95% CI) for stroke per 1 s.d of PRS* = $e^{\text{beta} \times \text{s.d}}$
<b>All stroke</b>	1353	2383	0.000132	0.000048	0.0062	1.08 (1.02, 1.15)
<b>LAA</b>	220	2383	0.000233	0.000101	0.0208	1.15 (1.02, 1.20)
<b>SAO</b>	390	2383	0.000207	0.000078	0.0078	1.13 (1.03, 1.24)
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<b>OTHER</b>	106	2383	0.000187	0.000142	0.1863	1.12 (0.95, 1.32)
<b>Crypto</b>	133	2383	0.000124	0.000124	0.3145	1.08 (0.93, 1.25)



## Supplemental Table III

**Relationship between PRS based on 83,890 SNPs with inclusion criterion into PRS of  $p < .5$ , by CCSc stroke subtype for European Ancestry Adults**

Phenotype (CCS)	Total N Cases	Total N Controls	Betas	SE	P for Betas	OR (95% CI) for stroke per 1 s.d of PRS* = $e^{\text{beta} \times \text{s.d.}}$
<b>LAA</b>	<b>2207</b>	<b>25643</b>	<b>4.08E-07</b>	<b>0.000038</b>	<b>0.9915</b>	<b>1.00 (0.96, 1.05)</b>
<b>SAO</b>	<b>1881</b>	<b>25643</b>	<b>0.000134</b>	<b>0.000041</b>	<b>0.001</b>	<b>1.08 (1.03, 1.14)</b>
<b>CE</b>	<b>2835</b>	<b>25643</b>	<b>0.000038</b>	<b>0.000034</b>	<b>0.2623</b>	<b>1.02 (0.98, 1.06)</b>
<b>CRYPTO</b>	<b>1027</b>	<b>25643</b>	<b>0.000071</b>	<b>0.000054</b>	<b>0.1884</b>	<b>1.04 (0.98, 1.11)</b>
<b>UNDETERMINED</b>	<b>4031</b>	<b>25643</b>	<b>0.000054</b>	<b>0.000029</b>	<b>0.0645</b>	<b>1.03 (1.00, 1.07)</b>
<b>INCONCLUSIVE</b>	<b>2038</b>	<b>25643</b>	<b>0.000091</b>	<b>0.000039</b>	<b>0.0203</b>	<b>1.06 (1.01, 1.11)</b>

## Supplemental Table IV

Relationship between PRS based on 83,890 SNP's with inclusion criterion into PRS of  $p < .5$ , by CCSc stroke subtype for African Ancestry Adults

	Total N Cases	Total N Controls	Betas	SE	P for Betas	OR (95% CI) for stroke per 1 s.d of PRS* = $e^{\text{beta} \times \text{s.d.}}$
LAA	178	2383	0.000201	0.000098	0.0409	1.13 (1.01, 1.27)
SAO	381	2383	0.000127	0.000069	0.0675	1.08 (1.00, 1.17)
CE	165	2383	-2.3E-07	0.000099	0.9982	1.00 (0.89, 1.12)
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UNDETERMINED	543	2383	0.000083	0.000059	0.1601	1.05 (0.98, 1.13)
INCONCLUSIVE	242	2383	0.00007	0.000084	0.4047	1.04 (0.94, 1.15)

Supplemental Table V

Relationship between PRS based on 83,890 SNP's with inclusion criterion into PRS of  $p < .5$ , by TOAST stroke subtype for European Ancestry Adults

	Total N Cases	Total N Controls	Betas	SE	P for Betas	OR (95% CI) for stroke per 1 s.d of PRS* = $e^{\text{beta} \times \text{s.d.}}$
<b>LAA</b>	2193	25643	-0.000003	0.000039	0.399	1.00 (0.95, 1.95)
<b>SAO</b>	2252	25643	0.000084	0.000037	0.025	1.05 (1.01, 1.10)
<b>CE</b>	3138	25643	0.000052	0.000033	0.116	1.03 (0.99, 1.07)
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Supplemental Table VI  
**Relationship between PRS based on 83,890 SNP's with inclusion criterion into PRS of  $p < .5$ , by TOAST stroke subtype for African Ancestry Adults**

	Total N Cases	Total N Controls	Betas	SE	P for Betas	OR (95% CI) for stroke per 1 s.d of PRS* = $e^{\text{beta} \times \text{s.d.}}$
<b>LAA</b>	125	2383	0.000315	0.000117	0.007	1.21 (1.05, 1.39)
<b>SAO</b>	379	2383	0.000153	0.000069	0.028	1.10 (1.01, 1.19)
<b>CE</b>	195	2383	-0.000004	0.000091	0.624	0.98 (0.88, 1.09)
<b>Other</b>	42	2383	0.000225	0.000195	0.247	1.14 (0.91, 1.44)
<b>UNDETERMINED</b>	399	2383	0.000041	0.000068	0.550	1.02 (0.95, 1.11)