SUPPLEMENTAL MATERIAL

SUPPLEMENTAL METHODS

Description of Datasets

GENISIS

The GENISIS study aims to understand the genetic architecture of early neurological change after ischemic stroke onset. It uses a quantitative clinical trait to measure the improvement or deterioration of each participant by calculating the difference between the NIHSS at baseline (within 6 hours after stroke onset) and at 24hours (ΔNIHSS). This endophenotype (ΔNIHSS) accounts for a large proportion of the variance in the 3-month modified ranking scale (personal communication with Dr. Heitsch). Written informed consent was obtained from all participants or their proxy prior to enrollment. This study was reviewed and approved by the Institutional Review Board at Washington University in St. Louis and all participating centers.

To date, 2,317 participants have been included in the GENISIS study (Table 1). It is a multi-ethnic study as it recruits subjects from multiple genetic backgrounds from Europe and the United States (Supplementary Figure I–Panel A for clustering by PCA Principal Component Analysis (PCA) using HapMap as anchor).17 European Ancestry was defined as those clustering in with the Non-Hispanic Whites (NHW) population from HapMap (Supplementary Figure I–Panel B). Although the study includes a subset of African American individuals (N=187), it is mainly composed of European populations (N=2,130), the latter of which includes a Finnish cohort (N=391). The Finnish population has been considered to be a homogeneous isolate with reduced diversity.18 Moreover, it has the greatest fixation indices in Europe, and clusters separately from the other European populations (Supplementary Figure I-Panel B). We defined those cluster as: Finnish Cluster PC1>0.08 and 0.02<PC2<0.08, and Non-Hispanic White cluster PC1>0 and PC2<0.02. Finnish individuals were included or excluded depending on the analyses.

The cohort form Barcelona (Spain) included 1,198 individuals. This population has a median age of 78.0 (75.0-76.5) and with a median baseline NIHSS of 9.0 and delta NIHSS of 2.66 (±5.67). Of these, 46.77% were females and 64.83% were treated with tPA. The cohort from Helsinki (Finland) consisted of 391 individuals with median age of 67.0 (64.5-67.5). Of these, 38.94% were females and 48.85% were treated with tPA. This cohort presented a median baseline NIHSS of 5.0 and mean delta NIHSS of 2.33 (±5.95). The last European population was from Krakow (Poland). Of the 111 individuals, 47.75% were females and 51.35% were treated with tPA. The median age was 69.0 (68.0-73.0). The median baseline NIHSS was 6.0 and the mean delta NIHSS was 2.23 (±4.42). The cohort from Saint Louis (US) was classified by ethnicity (430 European Americans and 187 African Americans). The median age for the individuals of European Ancestry was 70.0 (68.0-70.5), whereas individuals of African Ancestry had a median age of 62.0 (61.0-65.5). The proportion of females was 43.91% in the European American group and 57.67% in the African American group. The proportion of tPA treatment was the same in both populations, a little over 79%. The median baseline NIHSS was also the same (7.0) whereas delta NIHSS was different by half a point (European American 1.93±6.11 and African American 2.43±6.04). In all populations, the most common stroke etiology was Cardioembolic stroke (Table 1). The factors contributing the most to Delta NIHSS and Baseline NIHSS, apart from TOAST, were age and glucose levels at baseline. Blood pressure levels were also associated with Baseline NIHSS.

All the individuals were genotyped using Illumina genotyping arrays and underwent standard quality control. Individuals with less than 98% of the SNPs genotyped were removed from the analyses. Likewise, SNPs with call rate less than 98% were excluded. After quality control, samples were imputed with SHAPTEIT and IMPUTE2 with the 1,000 Genomes Project Phase 3 as the reference panel. All genotypes with dosage levels <0.9 for all possible genotypes or with information scores <0.3 were excluded. Variants

out of Hardy Weinberg Equilibrium (HWE) ($p<1\times10^{-06}$) or with a genotyping rate below 98% were also removed. The different datasets were imputed separately and then combined to perform the analyses.

MEGASTROKE

The MEGASTROKE study examined the genetic architecture of stroke risk, and that of stroke subtypes (All stroke, all ischemic stroke), and underlying stroke etiologies (large artery stroke, cardioembolic stroke and small vessel disease). Statistically, they conducted fixed effects inverse variance weighted meta-analysis with METAL (SR1) in each ethnic group (European, Asian, African, South Asian, Latin and other Asians). Then they performed an ancestry-specific meta-analysis. They also performed a trans-ethnic meta-analysis using MANTRA (SR2) to meta-analyze the results from all the ethnicities taking into account different effects and minor allele frequencies.

References for the Supplemental Methods

SR1. Willer CJ, Li Y, Abecasis GR. Metal: Fast and efficient meta-analysis of genomewide association scans. Bioinformatics. 2010;26:2190-2191

SR2. Morris AP. Transethnic meta-analysis of genomewide association studies. Genetic epidemiology. 2011;35:809-822

SUPPLEMENTAL RESULTS

Single variants

The variant rs8103309 (associated with stroke risk in the Trans-Ethnic analyses), was found to be associated with ΔNIHSS (p=0.031) in the NHFW population. The variant rs880315, associated with stroke risk and HTN (CHARGE) at genome-wide level, was nominally associated with baseline NIHSS (p=0.013) in the NHW population. One more variant, rs13143308, which was associated with stroke risk, was found to be nominally associated with baseline NIHSS in both NHW (p=0.028) and NHFW (p=0.042) populations.

Multiple variants that had genome-wide significance in the T2DM study (Diagram) were found nominally associated with ΔNIHSS (NHW: rs11759026-p=0.026 and rs810517-p=0.016; NHFW: rs11759026-p=0.027) and with baseline NIHSS (NHW: rs4846569-p=0.024, rs2215383-p=0.017; NHFW: rs4846569–p=0.023, rs2215383-p=0.014 and rs810517- p=0.046).

SUPPLEMENTAL TABLES

Supplementary Table I. Sentinel Polygenic Risk Score Single Variant Information

Chr	Position	Variant	Gene/Nearest Gene	Effected Allele	Modeling Study				GENISIS				
					TE		NHW		maf			PRS Included	
					P Value	OR	P Value	OR	TE	HNW	NHWE	TE	NHW
Ischemic Stroke Risk (MegaStroke)													
1	10,796,866	rs880315	*CASZ1*	C	5.505×10^{-09}	1.054	ns	-	0.357	0.381	0.369	✓	×
1	156,202,173	rs1052053	*PMF1-BGLAP-SEMA4A*	G	4.479×10^{-11}	0.944	5.257×10^{-09}	0.940	0.410	0.383	0.393	✓	✓
4	111,714,419	rs13143308	*PITX2*	T	1.107×10^{-15}	1.079	4.884×10^{-14}	1.094	0.261	0.262	0.245	✓	✓
4	113,732,090	rs34311906	*ANK2*	T	ns	-	1.07×10^{-08}	0.937	Not Available			×	×
4	155,501,188	rs6825454	*FGA-FGB-FGG*	C	7.431×10^{-10}	1.058	ns	ns	0.239	0.245	0.230	✓	×
5	121,515,195	rs11957829	*LOC100505841*	G	7.514×10^{-09}	0.931	ns	-	0.191	0.192	0.190	✓	×
6	1,356,916	rs4959130	*FOXF2-FOXQ1*	A	2.829×10^{-09}	1.087	1.865×10^{-09}	1.090	0.120	0.128	0.128	✓	✓
7	19,049,388	rs2107595	*HDAC9*	G	9.253×10^{-14}	1.079	2.33×10^{-11}	0.916	Not Available			×	×
7	92,244,422	rs42039	*CDK6*	C	6.554×10^{-09}	1.068	ns	-	0.751	0.736	0.732	✓	×
9	22,102,165	rs7859727	*CDKN2B-AS1*	T	1.047×10^{-09}	1.053	ns	-	0.568	0.538	0.567	✓	×
9	136,155,000	rs635634	*ABO-SURF1*	T	ns	-	9.179×10^{-09}	1.080	0.219	0.231	0.229	×	✓
11	102,770,353	rs2005108	*MMP12-MMP1-MMP3*	T	3.327×10^{-08}	1.083	ns	-	0.131	0.139	0.131	✓	×
12	111,884,608	rs3184504	*Chr12q24*	T	2.172×10^{-14}	1.078	1.229×10^{-14}	1.081	0.453	0.479	0.491	✓	✓
12	115,554,523	rs35436	*TBX3*	T	3.214×10^{-08}	0.952	ns	-	0.371	0.360	0.364	✓	×
13	47,225,745	rs9526212	*LRCH1*	C	9.185×10^{-10}	1.0363	3.557×10^{-08}	1.066	0.778	0.790	0.787	✓	✓
15	91,404,705	rs4932370	*FURIN-FES*	G	2.881×10^{-08}	1.053	ns	-	Not Available			×	×
16	87,575,332	rs12445022	*Chr16q24*	A	1.284×10^{-10}	1.063	ns	-	Not Available			×	×
17	1,571,818	rs11867415	*PRPF8-SCARF1*	A	4.813×10^{-08}	0.916	ns	-	Not Available			×	×
19	10,794,630	rs2229383	*ILF3-SLC44A2*	T	4.721×10^{-08}	1.049	ns	-	0.634	0.627	0.618	✓	×
19	11,174,935	rs8103309	*SMARCA4-LDLR*	T	8.346×10^{-08}	1.053	ns	-	0.625	0.645	0.623	✓	×
Type 2 Diabetes Mellitus (Diagram)													
1	219,771,721	rs4846569	*NOTCH2*	T	-	-	8.80×10^{-09}	2.524	0.264	0.285	0.278	×	✓
2	43,734,847	rs6757251	-	T	-	-	1.90×10^{-10}	2.406	0.107	0.091	0.101	×	✓
2	60,552,476	rs10193447	*THADA*	T	-	-	1.30×10^{-08}	2.926	0.605	0.600	0.593	×	×

2	227,117,778	rs2972156	*BCL11A*	C	-	-	1.20×10^{-09}	2.526	0.348	0.364	0.369	×	✓
3	12,344,730	rs11712037	*IRS1*	C	-	-	8.60×10^{-13}	3.123	0.108	0.119	0.108	×	✓
3	23,455,582	rs35352848	*PPARγ*	T	-	-	1.50×10^{-08}	2.964	0.769	0.774	0.795	×	✓
3	64,710,850	rs7428936	-	T	-	-	1.00×10^{-08}	2.923	0.538	0.564	0.546	×	×
3	123,065,778	rs11708067	*ADAMTS9*	A	-	-	8.80×10^{-13}	3.053	0.828	0.827	0.827	×	✓
3	185,511,687	rs4402960	*IGF2BP2*	T	-	-	2.70×10^{-25}	3.159	0.317	0.299	0.296	×	✓
4	6,299,940	rs3821943	*WFS1*	T	-	-	4.20×10^{-16}	3.020	0.534	0.536	0.539	×	✓
4	185,708,807	rs60780116	*ACSL1*	T	-	-	7.40×10^{-08}	2.987	0.846	0.825	0.825	×	×
5	55,861,464	rs28650790*	*ZBED3*	T	-	-	7.40×10^{-10}	3.020	0.191	0.193	0.200	×	✓
6	20,673,880	rs7451008	*CDKAL1*	T	-	-	3.80×10^{-37}	2.325	0.734	0.726	0.737	×	✓
6	126,792,095	rs11759026	-	A	-	-	5.80×10^{-10}	2.492	0.763	0.754	0.750	×	✓
7	15,062,983	rs2215383	*JAZF1*	T	-	-	1.40×10^{-08}	2.543	0.441	0.452	0.432	×	✓
7	28,189,411	rs1635852	*KLF14*	T	-	-	3.00×10^{-14}	2.993	0.510	0.495	0.489	×	✓
8	118,185,025	rs3802177	*TP53INF1*	A	-	-	1.70×10^{-17}	2.449	0.288	0.312	0.299	×	✓
9	22,133,284	rs10965250	*SLC30A8*	A	-	-	2.70×10^{-17}	2.385	0.179	0.184	0.191	×	✓
9	84,311,800	rs9410573	*CDKN2A/2B*	T	-	-	2.00×10^{-08}	2.932	0.707	0.591	0.608	×	×
9	126,112,812	rs10760280	*CHCHD9*	T	-	-	7.30×10^{-08}	2.916	0.649	0.525	0.525	×	×
10	12,309,269	rs11257659	*CDC123 / CAMK1D*	T	-	-	2.70×10^{-08}	2.958	0.240	0.228	0.221	×	×
10	80,942,620	rs810517	-	T	-	-	1.30×10^{-12}	2.496	0.470	0.472	0.469	×	✓
10	94,444,793	rs10882098	*HHEXADE*	T	-	-	1.40×10^{-26}	2.406	0.366	0.392	0.372	×	✓
10	114,758,349	rs7903146	*TCF7LS*	T	-	-	9.30×10^{-108}	3.805	0.318	0.302	0.327	×	✓
11	2,857,194	rs2237895	*KCNQ1*	A	-	-	1.70×10^{-13}	2.478	0.608	0.592	0.601	×	×
11	17,409,572	rs5219	-	T	-	-	4.30×10^{-08}	2.916	0.372	0.400	0.387	×	✓
11	43,877,934	rs1061810	*KCNJI1*	A	-	-	5.30×10^{-09}	2.954	0.304	0.301	0.291	×	✓
11	72,428,172	rs76550717	*CENTD2*	A	-	-	3.80×10^{-09}	3.006	0.861	0.848	0.867	×	✓
12	4,376,089	rs4238013	-	T	-	-	3.60×10^{-09}	2.474	0.797	0.796	0.803	×	×
12	121,432,117	rs56348580	*MTNR1B*	C	-	-	2.50×10^{-08}	2.533	0.305	0.303	0.314	×	✓
13	80,705,315	rs11616380	-	T	-	-	3.90×10^{-11}	2.494	0.260	0.273	0.271	×	✓
15	62,117,975	rs4774420	*HMGA2*	T	-	-	2.70×10^{-08}	2.529	0.302	0.288	0.291	×	×
15	77,776,498	rs952471	*TSPAN8/LGR5*	C	-	-	4.00×10^{-10}	2.512	0.314	0.307	0.305	×	✓
16	53,803,574	rs1558902	*HNF1A*	A	-	-	4.70×10^{-25}	3.123	0.422	0.434	0.418	×	✓
16	75,252,327	rs8056814	-	A	-	-	3.70×10^{-11}	2.365	0.113	0.095	0.098	×	✓

16	81,534,790	rs2925979	*ZFAND6*	T	-	-	2.70×10^{-08}	2.935	0.270	0.270	0.263	×	✓
17	9,780,387	rs78761021**	*PRC1*	A	-	-	5.50×10^{-08}	2.541	0.714	0.688	0.688	×	✓
17	36,102,833	rs757209	*FTD*	A	-	-	1.10×10^{-09}	2.510	0.319	0.345	0.345	×	×
19	45,411,941	rs429358		T	-	-	1.40×10^{-10}	3.088	0.904	0.896	0.919	×	×
22	30,599,562	rs2023681	*HNF1B*	A	-	-	3.90×10^{-09}	2.428	0.081	0.081	0.079	×	×
Hypertension (CHARGE)													
1	10,796,866	rs880315	*CASZ9*	C	-	-	6.74×10^{-10}	1.032	0.357	0.381	0.369	×	✓
6	26,107,463	rs198846		A	-	-	5.65×10^{-09}	1.040	0.175	0.174	0.188	×	✓
10	104,652,323	rs11191447		T	-	-	1.42×10^{-08}	1.052	0.102	0.101	0.106	×	✓
12	112,007,756	rs653178		C	-	-	2.76×10^{-08}	1.027	0.455	0.482	0.491	×	✓
12	90,008,959	rs2681472		G	-	-	8.93×10^{-09}	1.038	0.153	0.150	0.168	×	✓

Chr = Chromosome; OR = Odds Ratio; maf = minor allele frequency; PRS = Polygenic Risk Score; TE = Trans-Ethnic; NHW = Non-Hipsanic White; NHFW = Non-Hispanic Non-Finnish White; LD = Linkage Disequilibrium; *Proxy: rs13173241 (LD = 0.91); **Proxy: rs62066051 (LD = 0.92)

Supplementary Table II. Analysis of Variance Results

	Delta NIHSS	
	NHW	**NHFW**
Source	**Variance**	**Variance**
V(G)	2.20	2.83
V(e)	27.06	27.14
Vp	29.26	29.97
V(G)/Vp	7.52%	9.45%
N	2130	1739

SE = Standard Error; V(G) = Genetic Variance; V(e) = Residual Variance; Vp = Proportion of variance explained by all SNPs; V(G)/Vp = Proportion of Phenotypic Variance explained by the Genetic Variance; Pval = P value; N = Sample Size

Supplementary Table III. P values for Sentinel SNPs in the GENISIS Cohorts

Chr	Position	Variant	GENISIS Cohort P Values					
			Delta			Baseline		
			TE*	NHW	NHFW	TE*	NHW	NHFW
Stroke Risk Sentinel SNPs (MegaStroke)								
1	10,796,866	rs880315	-0.471	0.893	0.427	0.912	**0.013**	0.057
1	156,202,173	rs1052053	-0.006	0.508	0.715	-0.520	0.653	0.684
4	111,714,419	rs13143308	-0.410	0.884	0.520	0.823	**0.028**	**0.042**
4	155,501,188	rs6825454	-0.335	0.426	0.219	-0.248	0.203	0.122
5	121,515,195	rs11957829	-0.381	0.860	0.986	-0.641	0.771	0.645
6	1,356,916	rs4959130	-	0.169	0.205	-	0.569	0.758
7	92,244,422	rs42039	-0.549	0.371	0.384	-0.320	0.855	0.567
9	22,102,165	rs7859727	-0.547	0.177	0.189	-0.129	0.231	0.166
9	136,155,000	rs635634	-1.260	0.771	0.574	-0.615	0.243	0.319
11	102,770,353	rs2005108	-0.275	0.676	0.735	-0.554	0.776	0.450
12	111,884,608	rs3184504	-0.401	0.585	0.281	-0.393	0.382	0.386
12	115,554,523	rs35436	-0.405	0.953	0.691	0.041	0.104	0.170
13	47,225,745	rs9526212	-0.828	0.792	0.370	-1.026	0.984	0.669
19	10,794,630	rs2229383	-0.516	0.687	0.867	-0.239	0.366	0.396
19	11,174,935	rs8103309	-0.288	0.080	**0.031**	-0.364	0.775	0.516
Type 2 Diabetes Mellitus (Diagram)								
1	219,771,721	rs4846569	-	0.785	0.579	-	**0.024**	**0.023**
2	43,734,847	rs6757251	-	0.246	0.557	-	0.696	0.452
2	*60,552,476*	*rs10193447*	-	*0.557*	*0.393*	-	*0.897*	*0.787*
2	227,117,778	rs2972156	-	0.093	0.204	-	0.762	0.963
3	12,344,730	rs11712037	-	0.223	0.650	-	0.943	0.568
3	23,455,582	rs35352848	-	0.097	0.137	-	0.110	0.083
3	*64,710,850*	*rs7428936*	-	*0.408*	*0.457*	-	*0.907*	*0.885*
3	123,065,778	rs11708067	-	0.688	0.861	-	0.180	0.145
3	185,511,687	rs4402960	-	0.815	0.867	-	0.179	0.072
4	6,299,940	rs3821943	-	0.902	0.342	-	0.152	0.112
4	*185,708,807*	*rs60780116*	-	*0.917*	*0.917*	-	*0.983*	*0.983*
5	55,861,464	rs28650790	-	0.226	0.354	-	0.766	0.870
6	20,673,880	rs7451008	-	0.084	0.174	-	0.990	0.813

6	126,792,095	rs11759026	-	**0.026**	**0.027**	-	0.065	0.145
7	15,062,983	rs2215383	-	0.170	0.614	-	**0.017**	**0.014**
7	28,189,411	rs1635852	-	0.727	0.760	-	0.997	0.665
8	118,185,025	rs3802177	-	0.405	0.987	-	0.487	0.912
9	22,133,284	rs10965250	-	0.626	0.843	-	0.543	0.180
9	*84,311,800*	*rs9410573*	-	*0.824*	*0.952*	-	*0.894*	*0.664*
9	*126,112,812*	*rs10760280*	-	*0.520*	*0.520*	-	*0.168*	*0.168*
10	*12,309,269*	*rs11257659*	-	*0.122*	*0.260*	-	*0.492*	*0.603*
10	80,942,620	rs810517	-	**0.016**	0.300	-	0.214	**0.046**
10	94,444,793	rs10882098	-	0.987	0.524	-	0.962	0.239
10	114,758,349	rs7903146	-	0.602	0.982	-	0.732	0.381
11	*2,857,194*	*rs2237895*	-	*0.537*	*0.574*	-	*0.396*	*0.599*
11	17,409,572	rs5219	-	0.733	0.415	-	0.514	0.674
11	43,877,934	rs1061810	-	0.466	0.537	-	0.977	0.829
11	72,428,172	rs76550717	-	0.691	0.154	-	0.352	0.348
12	*4,376,089*	*rs4238013*	-	*0.409*	*0.916*	-	*0.299*	*0.816*
12	121,432,117	rs56348580	-	0.217	0.330	-	0.986	0.841
13	80,705,315	rs11616380	-	0.325	0.152	-	0.191	0.237
15	*62,117,975*	*rs4774420*	-	*0.716*	*0.624*	-	*0.181*	*0.523*
15	77,776,498	rs952471	-	0.097	0.332	-	0.095	0.085
16	53,803,574	rs1558902	-	0.649	0.776	-	0.240	0.570
16	75,252,327	rs8056814	-	0.790	0.827	-	0.923	0.738
16	81,534,790	rs2925979	-	0.474	0.278	-	0.599	0.524
17	9,780,387	rs78761021	-	0.091	0.091	-	0.259	0.259
17	*36,102,833*	*rs757209*	-	*0.287*	*0.287*	-	*0.273*	*0.273*
19	*45,411,941*	*rs429358*	-	*0.204*	*0.393*	-	*0.576*	*0.200*
22	*30,599,562*	*rs2023681*	-	*0.776*	*0.849*	-	*0.125*	*0.101*
				Hypertension Sentinel SNPs (CHARGE)				
1	10,796,866	rs880315	-	0.893	0.427	-	**0.013**	0.057
6	26,107,463	rs198846	-	0.085	0.176	-	0.978	0.857
10	104,652,323	rs11191447	-	0.828	0.945	-	0.450	0.770
12	112,007,756	rs653178	-	0.475	0.249	-	0.366	0.365
12	90,008,959	rs2681472	-	0.909	0.874	-	0.536	0.353

Chr = Chromosome; PRS = Polygenic Risk Score; TE = Trans-Ethnic; NHW = Non-Hispanic Whites; NHFW = Non-Hispanic Non-Finnish Whites; Nominally significant p values are in bold; Variants not included in the sentinel PRS are in italics; *Bayesian Factor; **Proxy included in the sentinel PRS instead of the variant (See table 2 for proxy rs number)

Supplementary Table IV. P-values for the association of the in-house PRS for ischemic stroke with ΔNIHSS and baseline NIHSS

	Stroke Risk Sentinel SNPs (MegaStroke)		
	Trans-ethnic	**Non-Hispanic White**	**Non-Hispanic Non-Finnish White**
ΔNIHSS	**0.174**	**0.411**	**0.062**
Baseline NIHSS	**0.496**	**0.060**	**0.085**
	Type 2 Diabetes Mellitus Sentinel SNPs (Diagram)		
ΔNIHSS	**-**	**0.817**	**0.803**
Baseline NIHSS	**-**	**0.735**	**0.192**
	Hypertension Sentinel SNPs (CHARGE)		
ΔNIHSS	**-**	**0.313**	**0.125**
Baseline NIHSS	**-**	**0.349**	**0.842**

Nominally significant p values are in bold ; Diagram and CHARGE meta-analyses only included individuals with European Ancestry, in consequence the genetic architecture was not compared to the genetic architecture of trans-ethnic stroke risk

Supplementary Table V. PRSice results for each phenotype, population and p value threshold

Base File	Target File		PRSice Results			
	Population	Phenotype	P value Threshold	P value	Variance	SNPs
Stroke Risk MegaStroke	TE	Delta NIHSS	5.00E-08	9.39E-01	2.23E-06	19
			5.00E-06	6.06E-01	1.01E-04	49
			1.00E-05	3.90E-01	2.80E-04	71
			1.00E-03	3.86E-01	2.84E-04	1257
			1.00E-02	1.54E-01	7.71E-04	7907
			5.00E-02	1.71E-01	7.08E-04	27378
			2.00E-01	4.41E-01	2.25E-04	77153
			5.00E-01	3.09E-01	3.91E-04	141954
			1.00E+00	2.49E-01	5.04E-04	203061
		Baseline NIHSS	5.00E-08	7.13E-01	5.48E-05	19
			5.00E-06	5.98E-01	1.12E-04	49
			1.00E-05	3.91E-01	2.97E-04	71
			1.00E-03	8.98E-01	6.65E-06	1257
			1.00E-02	4.95E-01	1.88E-04	7907
			5.00E-02	2.38E-01	5.62E-04	27378
			2.00E-01	5.70E-01	1.30E-04	77153
			5.00E-01	5.05E-01	1.80E-04	141954
			1.00E+00	5.04E-01	1.81E-04	203061
	NHW	Delta NIHSS	5.00E-08	7.81E-01	3.21E-05	13
			5.00E-06	4.04E-01	2.89E-04	39
			1.00E-05	2.84E-01	4.76E-04	55
			1.00E-03	5.51E-02	1.53E-03	1003
			1.00E-02	4.27E-01	2.62E-04	6627
			5.00E-02	5.95E-01	1.17E-04	24202
			2.00E-01	9.30E-01	3.16E-06	71116
			5.00E-01	9.22E-01	4.02E-06	136023

Base File	Target File		PRSice Results			
	Population	**Phenotype**	**P value Threshold**	**P value**	**Variance**	**SNPs**
			1.00E+00	7.87E-01	3.03E-05	200385
		Baseline NIHSS	5.00E-08	8.36E-01	1.89E-05	13
			5.00E-06	2.50E-01	5.78E-04	39
			1.00E-05	1.83E-01	7.74E-04	55
			1.00E-03	9.32E-01	3.16E-06	1003
			1.00E-02	5.66E-02	1.59E-03	6627
			5.00E-02	**3.60E-02**	1.92E-03	24202
			2.00E-01	**1.89E-02**	2.41E-03	71116
			5.00E-01	**5.89E-03**	3.31E-03	136023
			1.00E+00	**7.72E-03**	3.10E-03	200385
	NHFW	**Delta NIHSS**	5.00E-08	2.07E-01	8.42E-04	13
			5.00E-06	9.02E-02	1.52E-03	39
			1.00E-05	9.31E-02	1.49E-03	55
			1.00E-03	**1.38E-02**	3.20E-03	1003
			1.00E-02	3.75E-01	4.16E-04	6627
			5.00E-02	5.89E-01	1.54E-04	24202
			2.00E-01	9.81E-01	3.02E-07	71116
			5.00E-01	9.80E-01	3.34E-07	136023
			1.00E+00	8.30E-01	2.43E-05	200385
		Baseline NIHSS	5.00E-08	9.94E-01	3.36E-08	13
			5.00E-06	4.61E-01	2.96E-04	39
			1.00E-05	3.51E-01	4.73E-04	55
			1.00E-03	8.62E-01	1.65E-05	1003
			1.00E-02	5.78E-02	1.96E-03	6627
			5.00E-02	1.45E-01	1.16E-03	24202
			2.00E-01	9.20E-02	1.54E-03	71116
			5.00E-01	**2.95E-02**	2.57E-03	136023
			1.00E+00	**3.12E-02**	2.52E-03	200385

Base File	Target File		PRSice Results			
	Population	Phenotype	P value Threshold	P value	Variance	SNPs
T2DM Diagram	NHW	Delta NIHSS	5.00E-08	4.83E-01	2.04E-04	80
			5.00E-06	3.64E-01	3.43E-04	217
			1.00E-05	6.44E-01	8.84E-05	268
			1.00E-03	**7.19E-03**	2.99E-03	4618
			1.00E-02	6.81E-01	7.00E-05	30908
			5.00E-02	4.41E-01	2.46E-04	123087
			2.00E-01	2.37E-01	5.80E-04	387302
			5.00E-01	1.80E-01	7.46E-04	773778
			1.00E+00	2.33E-01	5.91E-04	1E+06
		Baseline NIHSS	5.00E-08	9.40E-01	2.49E-06	80
			5.00E-06	4.57E-01	2.42E-04	217
			1.00E-05	4.47E-01	2.53E-04	268
			1.00E-03	7.00E-01	6.48E-05	4618
			1.00E-02	7.15E-01	5.85E-05	30908
			5.00E-02	5.15E-01	1.85E-04	123087
			2.00E-01	9.50E-01	1.71E-06	387302
			5.00E-01	8.22E-01	2.22E-05	773778
			1.00E+00	7.19E-01	5.67E-05	1E+06
	NHFW	Delta NIHSS	5.00E-08	3.13E-01	5.37E-04	80
			5.00E-06	6.29E-02	1.83E-03	217
			1.00E-05	1.71E-01	9.90E-04	268
			1.00E-03	**2.43E-02**	2.68E-03	4618
			1.00E-02	9.41E-01	2.91E-06	30908
			5.00E-02	9.28E-01	4.32E-06	123087
			2.00E-01	6.83E-01	8.81E-05	387302
			5.00E-01	6.10E-01	1.38E-04	773778
			1.00E+00	6.55E-01	1.06E-04	1E+06
			5.00E-08	9.63E-01	1.20E-06	80

Base File	Target File		PRSice Results			
	Population	Phenotype	P value Threshold	P value	Variance	SNPs
			5.00E-06	6.34E-01	1.23E-04	217
			1.00E-05	5.30E-01	2.14E-04	268
			1.00E-03	6.04E-01	1.46E-04	4618
		Baseline NIHSS	1.00E-02	7.17E-01	7.15E-05	30908
			5.00E-02	7.24E-01	6.80E-05	123087
			2.00E-01	8.85E-01	1.14E-05	387302
			5.00E-01	6.11E-01	1.41E-04	773778
			1.00E+00	6.11E-01	1.41E-04	1E+06
HTN CHARGE	**NHW**	**Delta NIHSS**	5.00E-08	9.36E-02	1.17E-03	6
			5.00E-06	7.44E-01	4.42E-05	17
			1.00E-05	8.97E-01	6.89E-06	20
			1.00E-03	1.40E-01	9.01E-04	205
			1.00E-02	6.57E-02	1.40E-03	1257
			5.00E-02	6.57E-02	1.40E-03	1257
			2.00E-01	6.57E-02	1.40E-03	1257
			5.00E-01	6.57E-02	1.40E-03	1257
			1.00E+00	6.57E-02	1.40E-03	1257
		Baseline NIHSS	5.00E-08	**2.65E-02**	2.15E-03	6
			5.00E-06	6.61E-02	1.48E-03	17
			1.00E-05	3.09E-01	4.52E-04	20
			1.00E-03	1.27E-01	1.02E-03	205
			1.00E-02	4.45E-01	2.56E-04	1257
			5.00E-02	4.45E-01	2.56E-04	1257
			2.00E-01	4.45E-01	2.56E-04	1257
			5.00E-01	4.45E-01	2.56E-04	1257
			1.00E+00	4.45E-01	2.56E-04	1257
	NHFW	**Delta NIHSS**	5.00E-08	1.79E-01	9.53E-04	6
			5.00E-06	9.22E-01	5.10E-06	17

Base File	Target File		PRSice Results			
	Population	**Phenotype**	**P value Threshold**	**P value**	**Variance**	**SNPs**
			1.00E-05	6.93E-01	8.24E-05	20
			1.00E-03	5.68E-02	1.92E-03	205
			1.00E-02	7.65E-02	1.66E-03	1257
			5.00E-02	7.65E-02	1.66E-03	1257
			2.00E-01	7.65E-02	1.66E-03	1257
			5.00E-01	7.65E-02	1.66E-03	1257
			1.00E+00	7.65E-02	1.66E-03	1257
		Baseline NIHSS	5.00E-08	1.06E-01	1.42E-03	6
			5.00E-06	1.86E-01	9.52E-04	17
			1.00E-05	6.84E-01	9.02E-05	20
			1.00E-03	1.03E-01	1.44E-03	205
			1.00E-02	9.25E-01	4.80E-06	1257
			5.00E-02	9.25E-01	4.80E-06	1257
			2.00E-01	9.25E-01	4.80E-06	1257
			5.00E-01	9.25E-01	4.80E-06	1257
			1.00E+00	9.25E-01	4.80E-06	1257

TE = Trans-Ethnic Population; NHW = Non-Hispanic White Population; NHFW = Non-Hispanic Non-Finnish Population; Nominally significant p values are in bold

Supplementary Table VI. GNOVA results for each phenotype and European population

	All Ischemic Stroke Risk - MegaStroke			
	Non-Hispanic White		Non-Hispanic Non-Finnish White	
	P Value	Correlation	P Value	Correlation
ΔNIHSS	0.078	0.399	0.073	0.350
Baseline NIHSS	0.850	NA	0.260	0.312
	Type 2 Diabetes Mellitus - Diagram			
ΔNIHSS	0.061	-0.360	0.165	-0.243
Baseline NIHSS	0.151	NA	0.014	0.450

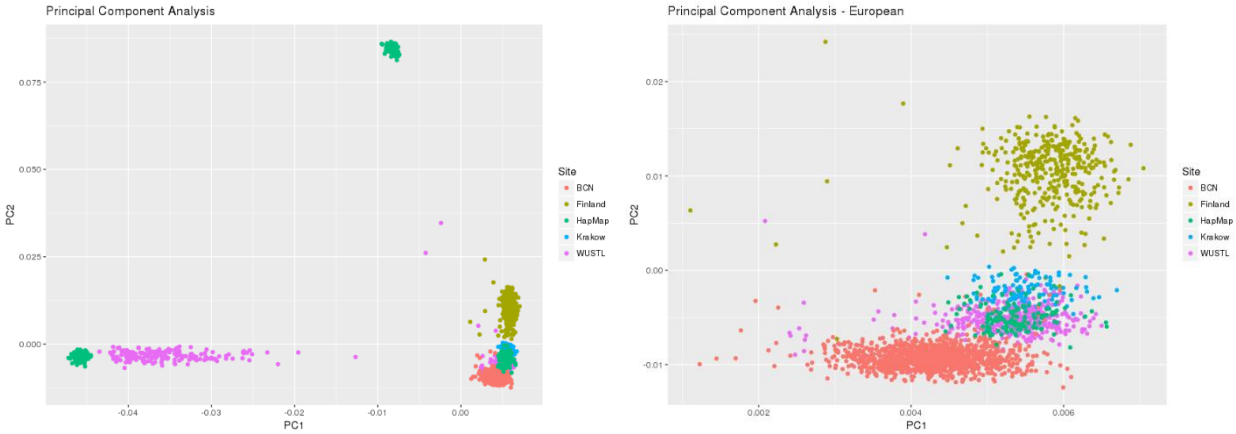
HTN was not included in the GNOVA analysis due to the small number of SNPS available in the summary statistics

P values and correlation values are corrected for sample overlap

Correlation values on NA indicate that the heritability estimates were negative

SUPPLEMENTAL FIGURES

Supplementary Figure I. Ethnic clustering by Principal Component Analyses (PCA) using HapMap as an anchor

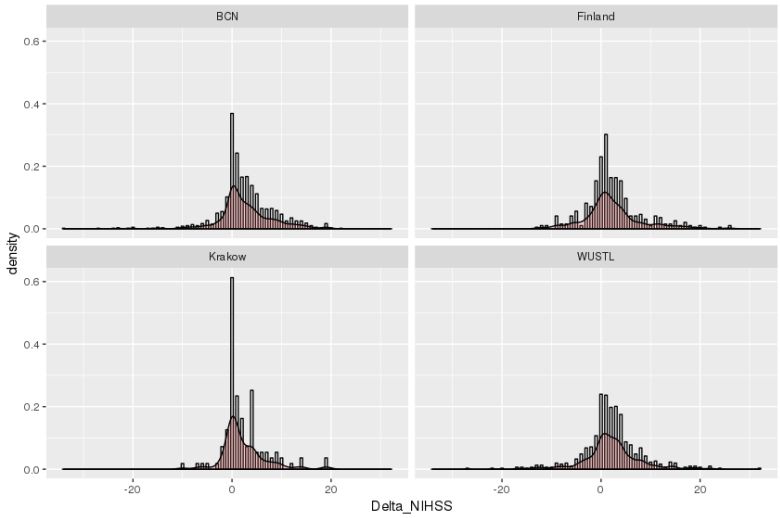


A – Clustering of the multiethnic GENISIS populations by PC1 and PC2

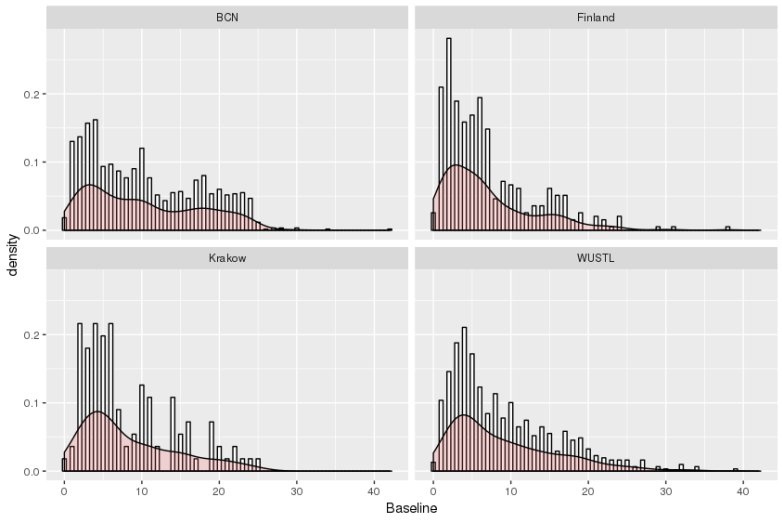
B – Enlargement of the European ancestry GENISIS population as defined by PC1 and PC2

BCN = Barcelona; WUSTL = Washington University in Saint Louis; PC=Principal Components

Supplementary Figure II. Distribution of Delta NIHSS in each GENISIS population



Supplementary Figure III. Distribution of Baseline NIHSS in each GENISIS population

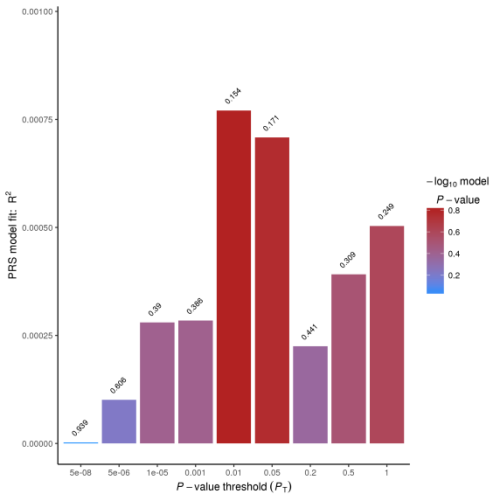

BCN
Finland
Krakow
WUSTL
density
0.0
0.1
0.2
0
10
20
30
40
Baseline

Supplementary Figure VI. PRSice Bar Plots for the Ischemic Stroke PRS with the three GENISIS phenotypes (Delta and Baseline)

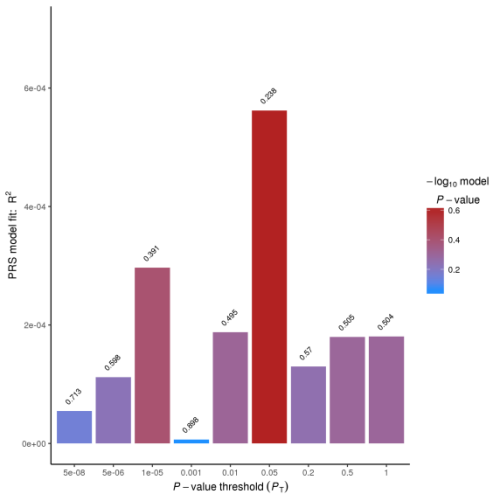
Stroke Risk (MegaStroke)

Trans-ethnic Population

A. Delta NIHSS

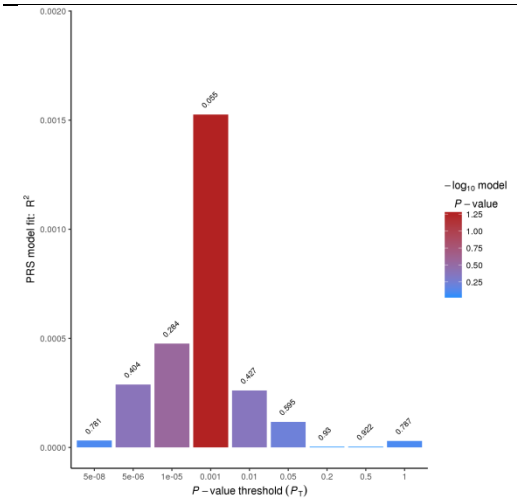


B. Baseline NIHSS

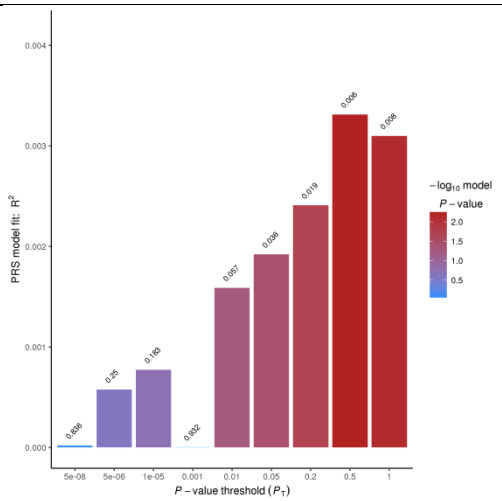


Non-Hispanic White

C. Delta NIHSS

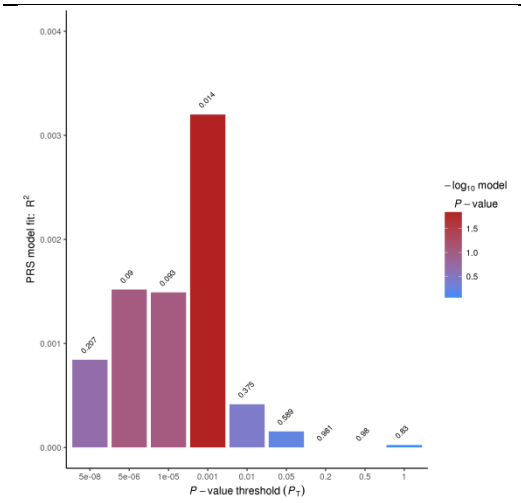


D. Baseline NIHSS

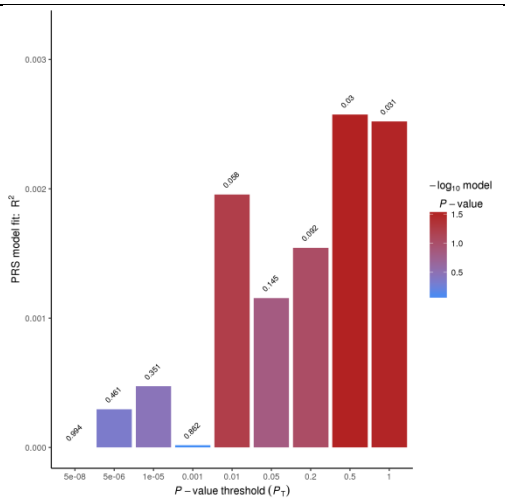


Non-Hispanic Non-Finnish White

E. Delta NIHSS



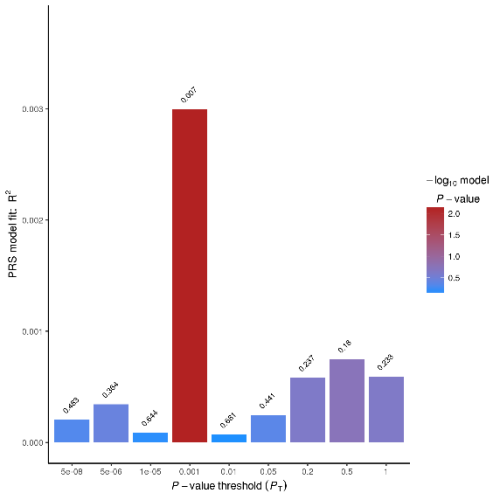
F. Baseline NIHSS



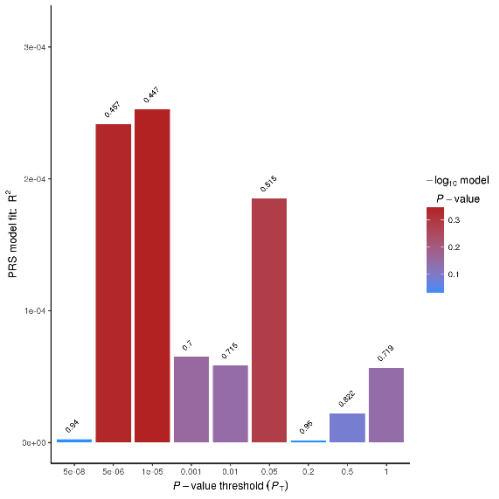
Type 2 Diabetes Mellitus (Diagram)

Non-Hispanic White

G. Delta NIHSS

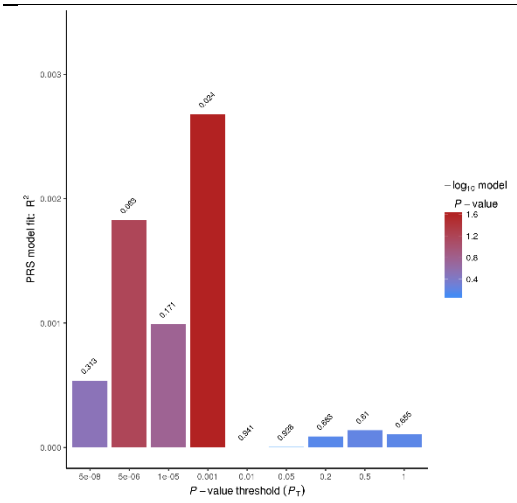


H. Baseline NIHSS

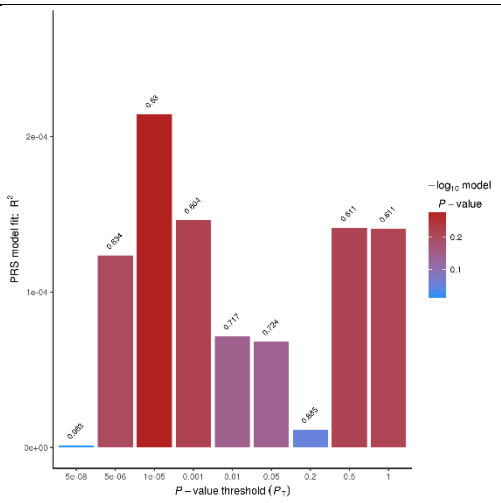


Non-Hispanic Non-Finnish White

I. Delta NIHSS



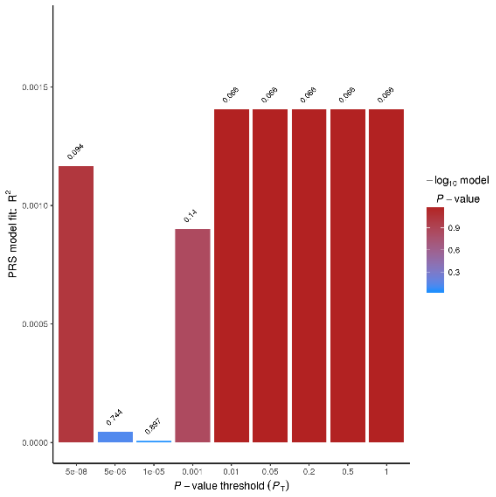
J. Baseline NIHSS



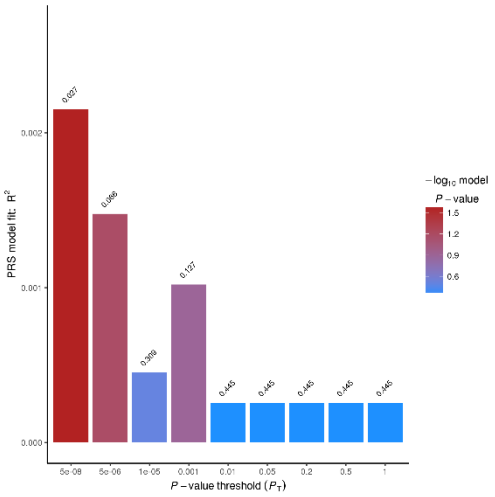
Hypertension (CHARGE)

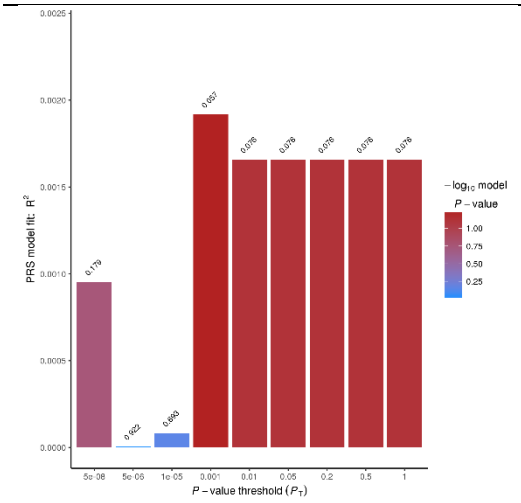
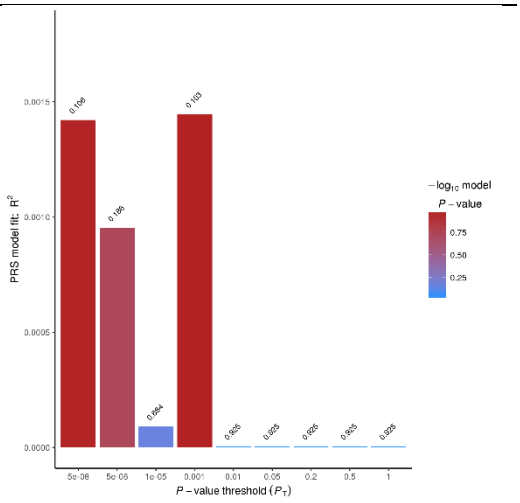
Non-Hispanic White

K. Delta NIHSS



L. Baseline NIHSS



Non-Hispanic Non-Finnish White	
M. Delta NIHSS	**N**. Baseline NIHSS
	

STUDY GROUP

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