

ONLINE SUPPLEMENTARY MATERIALS

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Supplementary method 1. Details of studies and participants

Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC)

The MAGIC represents a collaborative effort to combine data from multiple genome-wide meta analyses (GWAS) to identify additional loci that impact on glycemic and metabolic traits. The MAGIC investigators have initially studied fasting glucose, fasting insulin, 2h glucose and HBA1c, as well as performed meta-analysis of more sophisticated measures of insulin secretion and sensitivity. The MAGIC undertook meta-analyses of GWAS of glycemic traits in non-diabetic individuals in up to 159,940 individuals from 82 cohorts of European, African, East Asian, and South Asian ancestry. Results for fasting glucose are from models adjusted for age and sex, and from up to 133,010 non-diabetic participants from 66 studies. Fasting insulin results are for ln-transformed fasting insulin as the outcome and are adjusted for age, sex and are reported both with and without BMI adjustment, and from up to 108,557 individuals from 56 studies. (PUBMED: 22885924; 22581228)

The Contributors of these works include the members from MAGIC consortium.

Global Lipids Genetics Consortium (GLGC)

The GLGC is a world-wide collaboration of investigators dedicated to understanding the genetic etiology of quantitative lipid traits. The GLGC undertook meta-analyses of GWAS of lipid traits in 188,577 European-ancestry individuals and 7,898 non-European-ancestry individuals. The European ancestry subjects included 94,595 individuals from 23 studies genotyped with GWAS arrays and 93,982 individuals from 37 studies genotyped with the Metabochip array. The Metabochip includes variants representing promising loci from previous GWAS (14,886 SNPs) and from GWAS of other CAD risk factors and related traits (50,459 SNPs), variants from the 1000 Genomes Project and focused resequencing efforts in 64 previously associated loci (28,923 SNPs) and fine-mapping variants in 181 loci associated with other traits (93,308 SNPs). (PMID: 24097068)

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Coronary ARtery Disease Genome-wide Replication And Meta-Analysis Plus Coronary Artery Disease Genetics (CARDIoGRAMplusC4D) 1000 Genomes-based GWAS

CARDIoGRAMplusC4D consortium represents a collaborative effort to combine data from multiple large-scale genetic studies to identify risk loci for coronary artery disease and myocardial infarction. The CARDIoGRAMplusC4D 1000 Genomes-based GWAS is a meta-analysis of GWAS studies from 48 studies of mainly European, South Asian, and East Asian, descent imputed using the 1000 Genomes phase 1 v3 training set with 38 million variants. The study interrogated 9.4 million variants and involved 60,801 CAD cases and 123,504 controls. Case status was defined by an inclusive CAD diagnosis (for example, myocardial infarction, acute coronary syndrome, chronic stable angina or coronary stenosis of >50%). About 70% of the total number of cases reported history of myocardial infarction. The majority (77%) of the participants were of European ancestry; 13% and 6% were of South Asian (India and Pakistan) and East Asian (China and Korea) ancestry, respectively, with smaller samples of Hispanic and African Americans. The present study involved European participants only. (PMID: 26343387)

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Multiancestry Genome-wide Association Study of Stroke (MEGASTROKE)

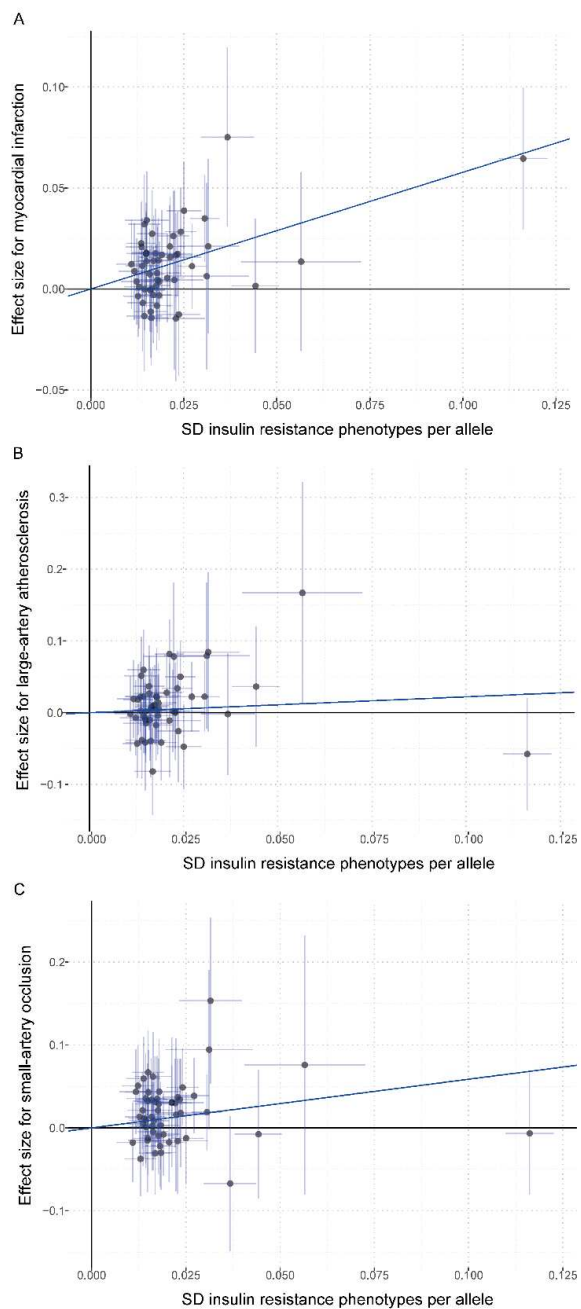
The MEGASTROKE consortium represents a large-scale international collaboration launched by the International Stroke Genetics Consortium, and releases the summary statistics from the 2018 meta-analysis of GWAS data in stroke and stroke subtypes. Participants were drawn from 29 studies with genome-wide genotypes imputed to 1000 Genomes Project (1000G) phase 1v3 or similar. The MEGASTROKE consortium tested ~8 million SNPs and indels with minor-allele frequency ≥ 0.01 in up to 67,162 stroke cases and 454,450 controls for association with stroke. Analyses were performed for any stroke ($n = 67,162$); any ischemic stroke regardless of subtype ($n = 60,341$); and ischemic stroke subtypes (large-artery atherosclerosis, $n = 6,688$; small-artery occlusion, $n = 11,710$; cardioembolism, $n = 9,006$). The MEGASTROKE consortium involved participants of European (40,585 cases; 406,111 controls), East Asian (17,369; 28,195), African (5,541; 15,154), South Asian (2,437; 6,707), mixed Asian (365; 333), and Latin American (865; 692) ancestry. The present study involved European participants only (40,585 cases; 406,111 controls). (PMID: 29531354)

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Supplementary figure 1. Associations of IR phenotypes variants with risk of myocardial infarction (A), large-artery atherosclerosis (B) and small-artery occlusion (C). The blue line indicates the estimate of effect using IVW method. Circles indicate marginal genetic associations with IR phenotypes and risk of outcome for each variant. Error bars indicate 95% confidence intervals. IR, insulin resistance; SD, standard error.

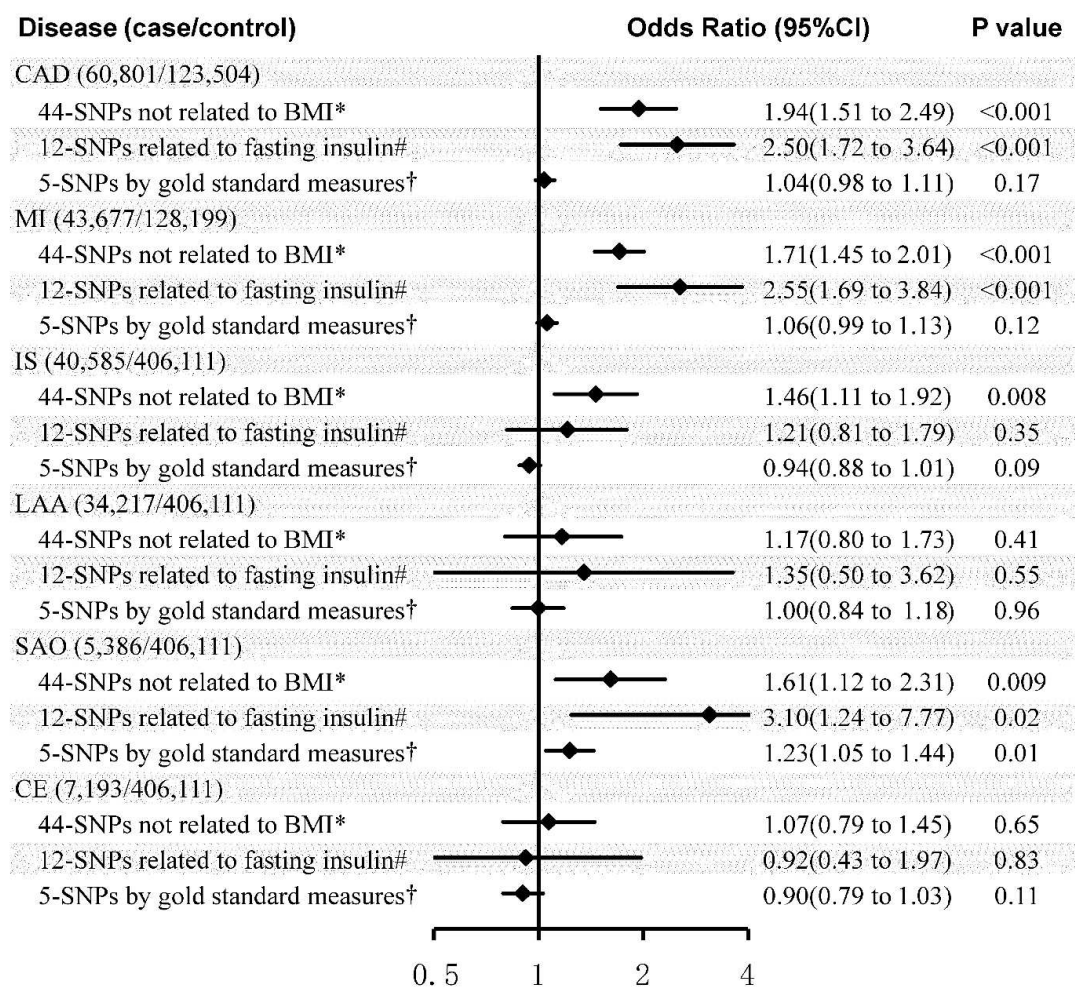


Supplementary figure 2. Estimates of genetically predicted insulin resistance phenotypes on coronary artery disease and ischemic stroke in sensitivity analyses. Estimates are derived from inverse-variance weighted method of Mendelian randomisation analysis and represented odds ratio (95% CI) per 1-SD insulin resistance phenotypes. BMI, body mass index; CAD, coronary artery disease; CE, cardioembolism; CI, confidence interval; IS, ischemic stroke; LAA, large-artery atherosclerosis; MI, myocardial infarction; SAO, small-artery occlusion; SNP, single nucleotide polymorphism.

*: 44 SNPs after exclusion of 9 SNPs individually associated with BMI at $p < 0.001$ using GIANT summary statistics from 53-SNPs instrument identified by Lotta et al. (PMID: 27841877; 29046328; 25673413).

#: 12 SNPs associated with fasting insulin (BMI adjusted) reported by the MAGIC Consortium in up to 108,557 individuals of European ancestry without diabetes (PMID: 22885924).

†: 5 SNPs for gold standard measures of insulin resistance, such as euglycemic clamp or insulin suppression test, identified by the GENESIS Consortium in 2,764 European individuals (PMID: 25798622).



Supplementary table 1. Characteristics of included 53 SNP loci associated with insulin resistance phenotypes

| SNP | Locus name | Genomic coordinate | EA/OA | EAF | FIadjBMI† | | TGs‡ | | HDL-C‡ | | Meta-analyzed score§ | |
|--------------|------------------------|--------------------|-------|-------|-----------|--------|--------|--------|---------|--------|----------------------|--------|
| | | | | | Beta | SE | Beta | SE | Beta | SE | Beta | SE |
| rs17386142* | <i>DMRTA2</i> | chr1:50815783 | C/T | 0.927 | 0.0238 | 0.0071 | 0.0218 | 0.0068 | -0.0218 | 0.0069 | 0.0224 | 0.0040 |
| rs11577194* | <i>CSF1</i> | chr1:110500175 | T/C | 0.479 | 0.0105 | 0.0034 | 0.0106 | 0.0034 | -0.0194 | 0.0034 | 0.0135 | 0.0020 |
| rs9425291* | <i>DNM3</i> | chr1:172312769 | A/G | 0.429 | 0.0151 | 0.0036 | 0.0159 | 0.0034 | -0.0138 | 0.0034 | 0.0149 | 0.0020 |
| rs4846565* | <i>RNU5F-1/LYPLAL1</i> | chr1:219722104 | G/A | 0.694 | 0.0221 | 0.0037 | 0.0143 | 0.0035 | -0.0130 | 0.0036 | 0.0163 | 0.0021 |
| rs2249105* | <i>CEP68</i> | chr2:65287896 | A/G | 0.623 | 0.0158 | 0.0036 | 0.0162 | 0.0034 | -0.0158 | 0.0035 | 0.0159 | 0.0020 |
| rs492400** | <i>USP37</i> | chr2:219349752 | T/C | 0.603 | 0.0100 | 0.0034 | 0.0184 | 0.0036 | -0.0108 | 0.0036 | 0.0130 | 0.0020 |
| rs308971* | <i>SYN2/PPARG</i> | chr3:12116620 | G/A | 0.139 | 0.0357 | 0.0053 | 0.0210 | 0.0049 | -0.0155 | 0.0050 | 0.0236 | 0.0029 |
| rs3864041* | <i>COL6A4P1</i> | chr3:15185634 | T/C | 0.623 | 0.0109 | 0.0037 | 0.0094 | 0.0036 | -0.0126 | 0.0037 | 0.0109 | 0.0021 |
| rs9881942** | <i>ADCY5</i> | chr3:123082416 | A/G | 0.435 | 0.0133 | 0.0036 | 0.0099 | 0.0033 | -0.0152 | 0.0034 | 0.0127 | 0.0020 |
| rs6822892* | <i>PDGFC</i> | chr4:157734675 | A/G | 0.646 | 0.0238 | 0.0037 | 0.0124 | 0.0035 | -0.0190 | 0.0036 | 0.0182 | 0.0021 |
| rs4976033* | <i>PIK3R1</i> | chr5:67714246 | G/A | 0.380 | 0.0150 | 0.0039 | 0.0141 | 0.0036 | -0.0215 | 0.0037 | 0.0169 | 0.0022 |
| rs6887914* | <i>MCC</i> | chr5:112711486 | C/T | 0.781 | 0.0128 | 0.0044 | 0.0135 | 0.0041 | -0.0168 | 0.0043 | 0.0144 | 0.0025 |
| rs1045241* | <i>TNFAIP8</i> | chr5:118729286 | C/T | 0.743 | 0.0117 | 0.0039 | 0.0153 | 0.0038 | -0.0139 | 0.0039 | 0.0137 | 0.0022 |
| rs2434612* | <i>EBF1</i> | chr5:158022041 | G/A | 0.207 | 0.0162 | 0.0044 | 0.0148 | 0.0042 | -0.0196 | 0.0043 | 0.0168 | 0.0025 |
| rs966544** | <i>CPEB4</i> | chr5:173350405 | G/A | 0.307 | 0.0122 | 0.0037 | 0.0162 | 0.0036 | -0.0132 | 0.0038 | 0.0139 | 0.0021 |
| rs12525532* | <i>ANKS1A</i> | chr6:35004819 | T/C | 0.396 | 0.0187 | 0.0036 | 0.0108 | 0.0035 | -0.0153 | 0.0035 | 0.0149 | 0.0020 |
| rs9492443* | <i>L3MBTL3</i> | chr6:130398731 | C/T | 0.764 | 0.0138 | 0.0039 | 0.0163 | 0.0038 | -0.0130 | 0.0039 | 0.0144 | 0.0022 |
| rs17169104* | <i>MEOX2</i> | chr7:15883727 | G/C | 0.342 | 0.0204 | 0.0044 | 0.0174 | 0.0042 | -0.0173 | 0.0044 | 0.0183 | 0.0025 |
| rs4738141* | <i>EYAI</i> | chr8:72469742 | G/A | 0.249 | 0.0138 | 0.0043 | 0.0199 | 0.0043 | -0.0186 | 0.0044 | 0.0174 | 0.0025 |
| rs498313* | <i>MIR548H3</i> | chr9:78034169 | A/G | 0.691 | 0.0126 | 0.0037 | 0.0109 | 0.0036 | -0.0135 | 0.0037 | 0.0123 | 0.0021 |
| rs11231693** | <i>MACROD1</i> | chr11:63862612 | A/G | 0.061 | 0.0357 | 0.0073 | 0.0300 | 0.0073 | -0.0289 | 0.0074 | 0.0316 | 0.0042 |
| rs17402950* | <i>ATF7IP</i> | chr12:14571671 | G/A | 0.055 | 0.0272 | 0.0097 | 0.0324 | 0.0101 | -0.0344 | 0.0104 | 0.0312 | 0.0058 |
| rs718314* | <i>ITPR2</i> | chr12:26453283 | G/A | 0.235 | 0.0168 | 0.0041 | 0.0121 | 0.0038 | -0.0196 | 0.0039 | 0.0161 | 0.0023 |

| | | | | | | | | | | | | |
|-------------|-----------------------|-----------------|-----|-------|--------|--------|--------|--------|---------|--------|--------|--------|
| rs7323406* | <i>ANKRD10</i> | chr13:111628195 | A/G | 0.278 | 0.0153 | 0.0051 | 0.0141 | 0.0053 | -0.0157 | 0.0054 | 0.0150 | 0.0030 |
| rs7176058* | <i>C15orf54</i> | chr15:39464167 | A/G | 0.836 | 0.0133 | 0.0046 | 0.0164 | 0.0045 | -0.0149 | 0.0046 | 0.0149 | 0.0026 |
| rs8032586* | <i>LOC100287559</i> | chr15:73081067 | C/T | 0.881 | 0.0187 | 0.0068 | 0.0252 | 0.0078 | -0.0208 | 0.0079 | 0.0213 | 0.0043 |
| rs754814* | <i>ZMYND15</i> | chr17:4657034 | T/C | 0.731 | 0.0112 | 0.0039 | 0.0113 | 0.0037 | -0.0127 | 0.0038 | 0.0117 | 0.0022 |
| rs6066149* | <i>EYA2</i> | chr20:45602638 | G/A | 0.761 | 0.0126 | 0.0041 | 0.0183 | 0.0038 | -0.0102 | 0.0039 | 0.0138 | 0.0023 |
| rs683135 | <i>MACF1</i> | chr1:39895460 | A/G | 0.268 | 0.0139 | 0.0037 | 0.0168 | 0.0037 | -0.0268 | 0.0038 | 0.0191 | 0.0022 |
| rs10195252# | <i>COBLL1/GRB14</i> | chr2:165513091 | T/C | 0.582 | 0.0289 | 0.0036 | 0.0276 | 0.0035 | -0.0250 | 0.0036 | 0.0272 | 0.0021 |
| rs2943645# | <i>IRS1</i> | chr2:227099180 | T/C | 0.623 | 0.0323 | 0.0036 | 0.0279 | 0.0034 | -0.0318 | 0.0035 | 0.0306 | 0.0020 |
| rs295449 | <i>KLHL18</i> | chr3:47375955 | A/G | 0.595 | 0.0114 | 0.0037 | 0.0144 | 0.0040 | -0.0185 | 0.0043 | 0.0144 | 0.0023 |
| rs11130329 | <i>TMEM110-MUSTN1</i> | chr3:52896855 | A/C | 0.864 | 0.0238 | 0.0068 | 0.0204 | 0.0069 | -0.0244 | 0.0071 | 0.0228 | 0.0040 |
| rs645040# | <i>MSL2</i> | chr3:135926622 | T/G | 0.769 | 0.0139 | 0.0043 | 0.0293 | 0.0040 | -0.0312 | 0.0042 | 0.0250 | 0.0024 |
| rs2699429 | <i>DOK7</i> | chr4:3480136 | C/T | 0.406 | 0.0107 | 0.0037 | 0.0252 | 0.0035 | -0.0126 | 0.0036 | 0.0165 | 0.0021 |
| rs3822072 | <i>FAM13A</i> | chr4:89741269 | A/G | 0.488 | 0.0204 | 0.0036 | 0.0182 | 0.0034 | -0.0251 | 0.0034 | 0.0213 | 0.0020 |
| rs4865796# | <i>ARL15/FST</i> | chr5:53272664 | A/G | 0.707 | 0.0255 | 0.0037 | 0.0095 | 0.0036 | -0.0131 | 0.0037 | 0.0158 | 0.0021 |
| rs459193 | <i>ANKRD55</i> | chr5:55806751 | G/A | 0.715 | 0.0255 | 0.0039 | 0.0178 | 0.0038 | -0.0235 | 0.0039 | 0.0222 | 0.0022 |
| rs6937438 | <i>LOC100132354</i> | chr6:43815364 | A/G | 0.708 | 0.0126 | 0.0039 | 0.0135 | 0.0037 | -0.0188 | 0.0038 | 0.0150 | 0.0022 |
| rs2745353 | <i>RSPO3</i> | chr6:127452935 | T/C | 0.479 | 0.0187 | 0.0036 | 0.0169 | 0.0033 | -0.0197 | 0.0034 | 0.0184 | 0.0020 |
| rs3861397 | <i>LOC645434</i> | chr6:139828916 | G/A | 0.342 | 0.0139 | 0.0036 | 0.0237 | 0.0035 | -0.0240 | 0.0036 | 0.0206 | 0.0021 |
| rs972283 | <i>KLF14</i> | chr7:130466854 | G/A | 0.544 | 0.0221 | 0.0046 | 0.0174 | 0.0034 | -0.0287 | 0.0034 | 0.0228 | 0.0021 |
| rs2126259 | <i>PPP1R3B</i> | chr8:9185146 | T/C | 0.091 | 0.0408 | 0.0056 | 0.0165 | 0.0054 | -0.0752 | 0.0054 | 0.0443 | 0.0032 |
| rs1011685 | <i>LPL</i> | chr8:19830769 | C/T | 0.877 | 0.0187 | 0.0058 | 0.1676 | 0.0055 | -0.1557 | 0.0057 | 0.1162 | 0.0033 |
| rs7005992 | <i>TRIB1</i> | chr8:126528955 | C/G | 0.136 | 0.0165 | 0.0051 | 0.0213 | 0.0048 | -0.0156 | 0.0050 | 0.0179 | 0.0029 |
| rs10995441 | <i>NRBF2</i> | chr10:64869239 | G/T | 0.236 | 0.0143 | 0.0043 | 0.0168 | 0.0041 | -0.0176 | 0.0041 | 0.0163 | 0.0024 |
| rs7973683# | <i>CCDC92/DNAH10</i> | chr12:124449223 | C/A | 0.639 | 0.0187 | 0.0036 | 0.0252 | 0.0035 | -0.0286 | 0.0036 | 0.0242 | 0.0021 |
| rs7227237 | <i>LIPG</i> | chr18:47174679 | C/T | 0.768 | 0.0168 | 0.0053 | 0.0171 | 0.0057 | -0.0197 | 0.0058 | 0.0178 | 0.0032 |
| rs8101064 | <i>INSR</i> | chr19:7293119 | T/C | 0.044 | 0.0425 | 0.0122 | 0.0692 | 0.0156 | -0.0664 | 0.0154 | 0.0565 | 0.0082 |
| rs4804833 | <i>MAP2K7</i> | chr19:7970635 | A/G | 0.410 | 0.0163 | 0.0036 | 0.0151 | 0.0037 | -0.0221 | 0.0038 | 0.0177 | 0.0021 |

| | | | | | | | | | | | | |
|-----------|---------------|----------------|-----|-------|--------|--------|--------|--------|---------|--------|--------|--------|
| rs4804311 | <i>MYO1F</i> | chr19:8615589 | A/G | 0.891 | 0.0187 | 0.0065 | 0.0392 | 0.0060 | -0.0507 | 0.0062 | 0.0367 | 0.0036 |
| rs731839 | <i>PEPD</i> | chr19:33899065 | G/A | 0.342 | 0.0255 | 0.0036 | 0.0224 | 0.0036 | -0.0220 | 0.0037 | 0.0233 | 0.0021 |
| rs132985 | <i>PLA2G6</i> | chr22:38563471 | C/T | 0.565 | 0.0156 | 0.0034 | 0.0218 | 0.0033 | -0.0151 | 0.0034 | 0.0176 | 0.0019 |

Genomic coordinates refer to human genome build 37 (hg19). Beta coefficients are in standardized units, fasting insulin beta coefficients were standardized using the standard deviation in 8,917 participants of the Fenland study. The gene column reports the nearest gene and/or additional candidate effector genes at the locus. EA, effect allele; EAF, effect allele frequency; FIadjBMI, fasting insulin adjusted for body mass index; HDL-C, high-density lipoprotein cholesterol; OA, other allele; SE, standard error; SNP, single nucleotide polymorphism; TGs, Triglycerides.

*: 28 SNPs previously not associated with TGs or HDL-C at genome-wide significance reported by the Global Lipids Genetics Consortium (PMID: 24097068).

#: 9 SNPs previously associated with BMI at $p < 0.001$ reported by the Genetic Investigation of ANthropometric Traits (GIANT) consortium (PMID: 25673413).

†: From up to 108,557 participants of the MAGIC consortium (PMID: 22885924, 22581228)

‡: From up to 188,577 participants of the GLGC Consortium (PMID: 24097068)

§: The meta-analysis was performed by Wang et al (29046328), and score represents the association of individual SNPs with exposure phenotype (insulin resistance), which was the meta-analyzed result of the absolute values of the SNP associations with fasting insulin (adjusted for BMI), TGs and HDL-C via fixed effect inverse-variance method. The unit of beta coefficients is 1- standard deviation insulin resistance phenotypes (reflecting 55% higher fasting insulin adjusted for BMI, 0.46 mmol/L lower HDL-C and 0.89 mmol/L higher TGs) per allele.

Supplementary table 2. Genetic association of insulin resistance phenotypes related 53 genetic variants with coronary artery disease and myocardial infarction in the CARDIoGRAMplusC4D consortium

| SNPs | EA/OA | Coronary artery disease | | | Myocardial infarction | | |
|------------|-------|-------------------------|--------|---------|-----------------------|--------|---------|
| | | Beta | SE | P value | Beta | SE | P value |
| rs17386142 | C/T | 0.0111 | 0.0206 | 0.589 | 0.0045 | 0.0227 | 0.845 |
| rs11577194 | T/C | 0.0216 | 0.0094 | 0.021 | 0.0226 | 0.0104 | 0.030 |
| rs9425291 | A/G | 0.0163 | 0.0096 | 0.091 | 0.0180 | 0.0107 | 0.091 |
| rs4846565 | G/A | 0.0084 | 0.0099 | 0.398 | 0.0001 | 0.0111 | 0.991 |
| rs2249105 | A/G | -0.0033 | 0.0097 | 0.736 | -0.0006 | 0.0105 | 0.951 |
| rs492400 | T/C | 0.0092 | 0.0098 | 0.350 | 0.0010 | 0.0107 | 0.922 |
| rs308971 | G/A | -0.0032 | 0.0138 | 0.816 | -0.0126 | 0.0156 | 0.420 |
| rs3864041 | T/C | 0.0085 | 0.0099 | 0.393 | 0.0123 | 0.0111 | 0.268 |
| rs9881942 | A/G | -0.0001 | 0.0092 | 0.988 | -0.0036 | 0.0102 | 0.727 |
| rs6822892 | A/G | 0.0090 | 0.0097 | 0.354 | 0.0142 | 0.0107 | 0.185 |
| rs4976033 | G/A | 0.0187 | 0.0103 | 0.070 | 0.0140 | 0.0114 | 0.219 |
| rs6887914 | C/T | -0.0102 | 0.0126 | 0.420 | -0.0134 | 0.0139 | 0.337 |
| rs1045241 | C/T | 0.0096 | 0.0105 | 0.360 | 0.0208 | 0.0117 | 0.075 |
| rs2434612 | G/A | 0.0036 | 0.0107 | 0.738 | -0.0030 | 0.0120 | 0.800 |
| rs966544 | G/A | -0.0099 | 0.0109 | 0.360 | -0.0069 | 0.0122 | 0.571 |
| rs12525532 | T/C | 0.0148 | 0.0095 | 0.119 | 0.0174 | 0.0105 | 0.099 |
| rs9492443 | C/T | 0.0196 | 0.0113 | 0.082 | 0.0320 | 0.0125 | 0.010 |
| rs17169104 | G/C | -0.0007 | 0.0101 | 0.943 | -0.0032 | 0.0113 | 0.781 |
| rs4738141 | G/A | 0.0114 | 0.0102 | 0.264 | 0.0176 | 0.0113 | 0.118 |
| rs498313 | A/G | 0.0098 | 0.0098 | 0.317 | 0.0037 | 0.0109 | 0.734 |
| rs11231693 | A/G | 0.0221 | 0.0190 | 0.243 | 0.0211 | 0.0221 | 0.340 |
| rs17402950 | G/A | -0.0045 | 0.0214 | 0.834 | 0.0063 | 0.0236 | 0.790 |
| rs718314 | G/A | -0.0066 | 0.0105 | 0.530 | -0.0113 | 0.0117 | 0.336 |
| rs7323406 | A/G | 0.0230 | 0.0111 | 0.039 | 0.0340 | 0.0123 | 0.006 |
| rs7176058 | A/G | 0.0146 | 0.0115 | 0.203 | 0.0175 | 0.0129 | 0.174 |
| rs8032586 | C/T | 0.0169 | 0.0134 | 0.208 | 0.0157 | 0.0153 | 0.302 |
| rs754814 | T/C | 0.0025 | 0.0109 | 0.822 | 0.0087 | 0.0122 | 0.476 |
| rs6066149 | G/A | 0.0168 | 0.0110 | 0.129 | 0.0115 | 0.0120 | 0.341 |
| rs683135 | A/G | 0.0214 | 0.0101 | 0.035 | 0.0169 | 0.0113 | 0.133 |
| rs10195252 | T/C | 0.0234 | 0.0100 | 0.020 | 0.0113 | 0.0108 | 0.293 |
| rs2943645 | T/C | 0.0349 | 0.0102 | 0.001 | 0.0349 | 0.0110 | 0.001 |

| | | | | | | | |
|------------|-----|---------|--------|-------|---------|--------|-------|
| rs295449 | A/G | -0.0009 | 0.0094 | 0.922 | -0.0001 | 0.0105 | 0.991 |
| rs11130329 | A/C | -0.0228 | 0.0143 | 0.111 | -0.0146 | 0.0158 | 0.355 |
| rs645040 | T/G | 0.0386 | 0.0112 | 0.001 | 0.0388 | 0.0125 | 0.002 |
| rs2699429 | C/T | 0.0294 | 0.0099 | 0.003 | 0.0273 | 0.0109 | 0.013 |
| rs3822072 | A/G | 0.0190 | 0.0094 | 0.042 | 0.0210 | 0.0105 | 0.044 |
| rs4865796 | A/G | 0.0117 | 0.0104 | 0.263 | 0.0073 | 0.0115 | 0.523 |
| rs459193 | G/A | 0.0264 | 0.0102 | 0.009 | 0.0263 | 0.0113 | 0.019 |
| rs6937438 | A/G | 0.0106 | 0.0106 | 0.313 | 0.0137 | 0.0117 | 0.241 |
| rs2745353 | T/C | 0.0123 | 0.0092 | 0.180 | 0.0038 | 0.0101 | 0.709 |
| rs3861397 | G/A | 0.0072 | 0.0100 | 0.470 | 0.0054 | 0.0113 | 0.631 |
| rs972283 | G/A | 0.0208 | 0.0095 | 0.028 | 0.0167 | 0.0106 | 0.115 |
| rs2126259 | T/C | -0.0109 | 0.0154 | 0.478 | 0.0015 | 0.0170 | 0.929 |
| rs1011685 | C/T | 0.0520 | 0.0161 | 0.001 | 0.0646 | 0.0180 | 0.000 |
| rs7005992 | C/G | 0.0134 | 0.0118 | 0.257 | 0.0044 | 0.0131 | 0.734 |
| rs10995441 | G/T | -0.0263 | 0.0108 | 0.015 | -0.0143 | 0.0120 | 0.231 |
| rs7973683 | C/A | 0.0238 | 0.0101 | 0.019 | 0.0283 | 0.0113 | 0.012 |
| rs7227237 | C/T | 0.0115 | 0.0111 | 0.298 | 0.0079 | 0.0122 | 0.521 |
| rs8101064 | T/C | 0.0337 | 0.0204 | 0.098 | 0.0136 | 0.0225 | 0.547 |
| rs4804833 | A/G | -0.0047 | 0.0101 | 0.643 | -0.0082 | 0.0113 | 0.465 |
| rs4804311 | A/G | 0.0625 | 0.0205 | 0.002 | 0.0752 | 0.0226 | 0.001 |
| rs731839 | G/A | 0.0276 | 0.0097 | 0.004 | 0.0173 | 0.0107 | 0.106 |
| rs132985 | C/T | -0.0004 | 0.0092 | 0.966 | 0.0017 | 0.0103 | 0.869 |

EA, effect allele; OA, other allele; SE, standard error; SNP, single nucleotide polymorphism. The unit of beta coefficients is log-odds per allele.

Supplementary table 3. Genetic association of insulin resistance phenotypes related 53 genetic variants with ischemic stroke and its subtypes in the MEGASTROKE consortium

| SNPs | EA/OA | Ischemic stroke | | | LAA | | | SAO | | | CE | | |
|------------|-------|-----------------|--------|---------|---------|--------|---------|---------|--------|---------|---------|--------|---------|
| | | Beta | SE | P value | Beta | SE | P value | Beta | SE | P value | Beta | SE | P value |
| rs17386142 | C/T | 0.0005 | 0.0214 | 0.980 | 0.0781 | 0.0526 | 0.137 | 0.0158 | 0.0472 | 0.738 | -0.0283 | 0.0398 | 0.477 |
| rs11577194 | T/C | 0.0116 | 0.0102 | 0.255 | 0.0220 | 0.0248 | 0.376 | 0.0212 | 0.0237 | 0.371 | 0.0241 | 0.0194 | 0.214 |
| rs9425291 | A/G | -0.0034 | 0.0100 | 0.736 | -0.0106 | 0.0246 | 0.666 | -0.0126 | 0.0228 | 0.580 | 0.0370 | 0.0190 | 0.052 |
| rs4846565 | G/A | -0.0242 | 0.0106 | 0.022 | -0.0394 | 0.0258 | 0.127 | -0.0046 | 0.0241 | 0.848 | -0.0316 | 0.0202 | 0.117 |
| rs2249105 | A/G | 0.0230 | 0.0103 | 0.026 | 0.0268 | 0.0262 | 0.308 | 0.0131 | 0.0239 | 0.585 | 0.0231 | 0.0198 | 0.243 |
| rs492400 | T/C | -0.0062 | 0.0103 | 0.543 | 0.0182 | 0.0252 | 0.469 | -0.0375 | 0.0231 | 0.105 | -0.0066 | 0.0194 | 0.732 |
| rs308971 | G/A | -0.0039 | 0.0146 | 0.791 | -0.0257 | 0.0360 | 0.476 | 0.0179 | 0.0333 | 0.592 | -0.0358 | 0.0286 | 0.211 |
| rs3864041 | T/C | 0.0010 | 0.0106 | 0.923 | -0.0014 | 0.0266 | 0.958 | -0.0177 | 0.0244 | 0.468 | 0.0483 | 0.0203 | 0.017 |
| rs9881942 | A/G | -0.0138 | 0.0098 | 0.160 | -0.0432 | 0.0245 | 0.078 | 0.0134 | 0.0227 | 0.557 | -0.0218 | 0.0189 | 0.248 |
| rs6822892 | A/G | 0.0116 | 0.0107 | 0.278 | -0.0041 | 0.0277 | 0.882 | -0.0221 | 0.0248 | 0.373 | 0.0045 | 0.0204 | 0.826 |
| rs4976033 | G/A | -0.0137 | 0.0109 | 0.208 | 0.0093 | 0.0272 | 0.733 | -0.0307 | 0.0249 | 0.218 | -0.0007 | 0.0208 | 0.972 |
| rs6887914 | C/T | 0.0129 | 0.0122 | 0.293 | 0.0224 | 0.0302 | 0.459 | 0.0355 | 0.0280 | 0.205 | 0.0574 | 0.0237 | 0.015 |
| rs1045241 | C/T | 0.0019 | 0.0112 | 0.866 | 0.0026 | 0.0277 | 0.926 | 0.0047 | 0.0260 | 0.856 | -0.0063 | 0.0216 | 0.770 |
| rs2434612 | G/A | 0.0126 | 0.0121 | 0.299 | -0.0818 | 0.0310 | 0.008 | 0.0312 | 0.0281 | 0.266 | -0.0028 | 0.0237 | 0.904 |
| rs966544 | G/A | -0.0154 | 0.0106 | 0.149 | -0.0382 | 0.0268 | 0.154 | 0.0115 | 0.0248 | 0.643 | -0.0487 | 0.0208 | 0.019 |
| rs12525532 | T/C | 0.0151 | 0.0102 | 0.140 | -0.0073 | 0.0250 | 0.770 | 0.0322 | 0.0232 | 0.164 | 0.0233 | 0.0194 | 0.231 |
| rs9492443 | C/T | 0.0201 | 0.0115 | 0.079 | 0.0597 | 0.0285 | 0.036 | 0.0091 | 0.0263 | 0.731 | -0.0258 | 0.0219 | 0.239 |
| rs17169104 | G/C | 0.0197 | 0.0113 | 0.082 | 0.0137 | 0.0278 | 0.622 | 0.0030 | 0.0265 | 0.909 | -0.0059 | 0.0217 | 0.784 |
| rs4738141 | G/A | 0.0139 | 0.0115 | 0.225 | 0.0111 | 0.0282 | 0.695 | 0.0348 | 0.0265 | 0.189 | 0.0179 | 0.0222 | 0.420 |
| rs498313 | A/G | 0.0086 | 0.0108 | 0.423 | -0.0073 | 0.0268 | 0.785 | 0.0508 | 0.0250 | 0.042 | -0.0002 | 0.0207 | 0.993 |
| rs11231693 | A/G | 0.0497 | 0.0228 | 0.029 | 0.0843 | 0.0567 | 0.137 | 0.1533 | 0.0511 | 0.003 | 0.0351 | 0.0462 | 0.448 |

| | | | | | | | | | | | | | |
|------------|-----|---------|--------|-------|---------|--------|-------|---------|--------|-------|---------|--------|-------|
| rs17402950 | G/A | -0.0081 | 0.0212 | 0.702 | 0.0792 | 0.0521 | 0.128 | 0.0943 | 0.0491 | 0.055 | 0.0628 | 0.0408 | 0.123 |
| rs718314 | G/A | -0.0003 | 0.0117 | 0.977 | -0.0101 | 0.0290 | 0.728 | 0.0020 | 0.0272 | 0.942 | -0.0123 | 0.0226 | 0.585 |
| rs7323406 | A/G | 0.0036 | 0.0114 | 0.750 | -0.0148 | 0.0276 | 0.592 | 0.0430 | 0.0259 | 0.097 | 0.0141 | 0.0215 | 0.512 |
| rs7176058 | A/G | -0.0315 | 0.0137 | 0.021 | -0.0416 | 0.0340 | 0.222 | -0.0152 | 0.0318 | 0.633 | -0.0409 | 0.0266 | 0.125 |
| rs8032586 | C/T | 0.0200 | 0.0168 | 0.234 | -0.0108 | 0.0405 | 0.791 | 0.0305 | 0.0400 | 0.445 | 0.0104 | 0.0322 | 0.746 |
| rs754814 | T/C | 0.0102 | 0.0112 | 0.365 | 0.0191 | 0.0278 | 0.492 | 0.0435 | 0.0260 | 0.095 | 0.0193 | 0.0218 | 0.376 |
| rs6066149 | G/A | 0.0199 | 0.0112 | 0.077 | 0.0514 | 0.0278 | 0.065 | 0.0594 | 0.0259 | 0.022 | -0.0145 | 0.0225 | 0.520 |
| rs683135 | A/G | -0.0017 | 0.0110 | 0.875 | -0.0415 | 0.0271 | 0.126 | -0.0079 | 0.0253 | 0.756 | 0.0021 | 0.0201 | 0.915 |
| rs10195252 | T/C | 0.0094 | 0.0101 | 0.353 | 0.0222 | 0.0250 | 0.375 | 0.0386 | 0.0232 | 0.096 | -0.0191 | 0.0194 | 0.327 |
| rs2943645 | T/C | -0.0026 | 0.0102 | 0.801 | 0.0223 | 0.0252 | 0.376 | 0.0188 | 0.0234 | 0.421 | -0.0169 | 0.0194 | 0.384 |
| rs295449 | A/G | -0.0140 | 0.0107 | 0.190 | -0.0050 | 0.0264 | 0.849 | 0.0010 | 0.0251 | 0.969 | -0.0024 | 0.0201 | 0.906 |
| rs11130329 | A/C | -0.0015 | 0.0141 | 0.913 | 0.0016 | 0.0346 | 0.964 | -0.0158 | 0.0328 | 0.631 | -0.0366 | 0.0274 | 0.182 |
| rs645040 | T/G | 0.0036 | 0.0123 | 0.769 | -0.0472 | 0.0302 | 0.119 | -0.0126 | 0.0283 | 0.657 | -0.0117 | 0.0233 | 0.616 |
| rs2699429 | C/T | 0.0166 | 0.0103 | 0.107 | 0.0079 | 0.0253 | 0.755 | 0.0086 | 0.0235 | 0.715 | 0.0048 | 0.0197 | 0.806 |
| rs3822072 | A/G | 0.0099 | 0.0097 | 0.306 | 0.0818 | 0.0246 | 0.001 | 0.0306 | 0.0227 | 0.177 | 0.0028 | 0.0191 | 0.885 |
| rs4865796 | A/G | 0.0048 | 0.0106 | 0.652 | 0.0368 | 0.0288 | 0.202 | 0.0338 | 0.0247 | 0.172 | -0.0195 | 0.0207 | 0.346 |
| rs459193 | G/A | 0.0159 | 0.0117 | 0.174 | 0.0021 | 0.0293 | 0.943 | 0.0299 | 0.0272 | 0.272 | -0.0036 | 0.0228 | 0.876 |
| rs6937438 | A/G | 0.0140 | 0.0111 | 0.207 | 0.0016 | 0.0277 | 0.955 | 0.0669 | 0.0256 | 0.009 | -0.0195 | 0.0215 | 0.364 |
| rs2745353 | T/C | 0.0114 | 0.0097 | 0.243 | 0.0053 | 0.0247 | 0.829 | -0.0300 | 0.0229 | 0.189 | 0.0275 | 0.0190 | 0.148 |
| rs3861397 | G/A | 0.0053 | 0.0105 | 0.616 | 0.0278 | 0.0260 | 0.286 | -0.0174 | 0.0243 | 0.475 | 0.0138 | 0.0202 | 0.495 |
| rs972283 | G/A | 0.0214 | 0.0107 | 0.046 | 0.0001 | 0.0257 | 0.998 | 0.0368 | 0.0238 | 0.122 | 0.0267 | 0.0197 | 0.175 |
| rs2126259 | T/C | 0.0145 | 0.0172 | 0.398 | 0.0364 | 0.0428 | 0.395 | -0.0078 | 0.0397 | 0.844 | 0.0114 | 0.0339 | 0.736 |
| rs1011685 | C/T | -0.0156 | 0.0166 | 0.346 | -0.0575 | 0.0400 | 0.151 | -0.0067 | 0.0379 | 0.859 | -0.0380 | 0.0323 | 0.240 |
| rs7005992 | C/G | -0.0139 | 0.0141 | 0.325 | 0.0215 | 0.0349 | 0.537 | 0.0438 | 0.0323 | 0.175 | -0.0168 | 0.0277 | 0.545 |
| rs10995441 | G/T | 0.0278 | 0.0119 | 0.020 | 0.0046 | 0.0296 | 0.876 | 0.0619 | 0.0272 | 0.023 | 0.0196 | 0.0229 | 0.393 |
| rs7973683 | C/A | 0.0159 | 0.0104 | 0.127 | 0.0501 | 0.0256 | 0.051 | 0.0488 | 0.0236 | 0.039 | 0.0204 | 0.0197 | 0.301 |

| | | | | | | | | | | | | | |
|-----------|-----|---------|--------|-------|---------|--------|-------|---------|--------|-------|---------|--------|-------|
| rs7227237 | C/T | 0.0053 | 0.0120 | 0.657 | 0.0231 | 0.0300 | 0.442 | 0.0288 | 0.0277 | 0.298 | -0.0400 | 0.0230 | 0.082 |
| rs8101064 | T/C | 0.0186 | 0.0318 | 0.559 | 0.1669 | 0.0789 | 0.034 | 0.0759 | 0.0797 | 0.341 | -0.0499 | 0.0672 | 0.458 |
| rs4804833 | A/G | 0.0031 | 0.0102 | 0.760 | -0.0173 | 0.0252 | 0.491 | -0.0094 | 0.0235 | 0.689 | -0.0032 | 0.0196 | 0.870 |
| rs4804311 | A/G | -0.0182 | 0.0179 | 0.309 | -0.0019 | 0.0433 | 0.965 | -0.0671 | 0.0416 | 0.106 | 0.0049 | 0.0343 | 0.887 |
| rs731839 | G/A | 0.0099 | 0.0108 | 0.357 | 0.0340 | 0.0268 | 0.204 | 0.0344 | 0.0250 | 0.170 | 0.0300 | 0.0207 | 0.148 |
| rs132985 | C/T | 0.0156 | 0.0101 | 0.124 | 0.0040 | 0.0247 | 0.872 | 0.0210 | 0.0232 | 0.364 | 0.0045 | 0.0192 | 0.816 |

CE, cardioembolism; EA, effect allele; LAA, large-artery atherosclerosis; OA, other allele; SAO, small-artery occlusion; SE, standard error; SNP, single nucleotide polymorphism. The unit of beta coefficients is log-odds per allele.

Supplementary table 4. Association of 12-SNPs instrument related to fasting insulin and 5-SNPs instrument for gold standard measures of insulin resistance with cardiovascular events

| Instrument | SNPs | EA/OA | IR phenotype | | Coronary artery disease | | Myocardial infarction | | Ischemic stroke | | LAA | | SAO | | CE | |
|------------|-------------|-------|--------------|-------|-------------------------|-------|-----------------------|-------|-----------------|-------|--------|-------|--------|-------|--------|-------|
| | | | Beta | SE | Beta | SE | Beta | SE | Beta | SE | Beta | SE | Beta | SE | Beta | SE |
| 12-SNPs* | rs2943645 | T/C | 0.019 | 0.002 | 0.035 | 0.010 | 0.035 | 0.011 | -0.003 | 0.010 | 0.022 | 0.025 | 0.019 | 0.023 | -0.017 | 0.019 |
| 12-SNPs* | rs10195252 | T/C | 0.017 | 0.002 | 0.023 | 0.010 | 0.011 | 0.011 | 0.009 | 0.010 | 0.022 | 0.025 | 0.039 | 0.023 | -0.019 | 0.019 |
| 12-SNPs* | rs2126259 | T/C | 0.024 | 0.003 | -0.011 | 0.015 | 0.002 | 0.017 | 0.015 | 0.017 | 0.036 | 0.043 | -0.008 | 0.040 | 0.011 | 0.034 |
| 12-SNPs* | rs4865796 | A/G | 0.015 | 0.002 | 0.012 | 0.010 | 0.007 | 0.011 | 0.005 | 0.011 | 0.037 | 0.029 | 0.034 | 0.025 | -0.020 | 0.021 |
| 12-SNPs* | rs17036328 | T/C | 0.021 | 0.003 | -0.001 | 0.014 | 0.030 | 0.015 | 0.005 | 0.014 | -0.065 | 0.036 | 0.033 | 0.034 | 0.053 | 0.029 |
| 12-SNPs* | rs731839 | G/A | 0.015 | 0.002 | 0.028 | 0.010 | 0.017 | 0.011 | 0.010 | 0.011 | 0.034 | 0.027 | 0.034 | 0.025 | 0.030 | 0.021 |
| 12-SNPs* | rs974801 | G/A | 0.014 | 0.002 | 0.016 | 0.010 | 0.025 | 0.011 | -0.001 | 0.010 | -0.012 | 0.025 | -0.012 | 0.024 | -0.002 | 0.020 |
| 12-SNPs* | rs459193 | G/A | 0.015 | 0.002 | 0.026 | 0.010 | 0.026 | 0.011 | 0.016 | 0.012 | 0.002 | 0.029 | 0.030 | 0.027 | -0.004 | 0.023 |
| 12-SNPs* | rs6822892 | A/G | 0.014 | 0.002 | 0.009 | 0.010 | 0.014 | 0.011 | 0.012 | 0.011 | -0.004 | 0.028 | -0.022 | 0.025 | 0.005 | 0.020 |
| 12-SNPs* | rs4846565 | G/A | 0.013 | 0.002 | 0.008 | 0.010 | 0.000 | 0.011 | -0.024 | 0.011 | -0.039 | 0.026 | -0.005 | 0.024 | -0.032 | 0.020 |
| 12-SNPs* | rs3822072 | A/G | 0.012 | 0.002 | 0.019 | 0.009 | 0.021 | 0.010 | 0.010 | 0.010 | 0.082 | 0.025 | 0.031 | 0.023 | 0.003 | 0.019 |
| 12-SNPs* | rs6912327 | T/C | 0.016 | 0.003 | -0.008 | 0.011 | -0.017 | 0.012 | -0.013 | 0.012 | -0.071 | 0.029 | 0.037 | 0.029 | 0.008 | 0.023 |
| 5-SNPs# | rs9877159 | G/A | 0.90 | 0.21 | 0.001 | 0.013 | -0.004 | 0.015 | 0.004 | 0.017 | -0.023 | 0.043 | 0.060 | 0.042 | -0.053 | 0.034 |
| 5-SNPs# | rs117421960 | T/G | 0.96 | 0.4 | 0.000 | 0.029 | 0.027 | 0.033 | -0.046 | 0.028 | -0.007 | 0.073 | 0.004 | 0.067 | -0.040 | 0.057 |
| 5-SNPs# | rs1801280 | T/C | 0.55 | 0.13 | 0.013 | 0.010 | 0.017 | 0.011 | -0.009 | 0.010 | 0.008 | 0.024 | 0.050 | 0.023 | -0.004 | 0.019 |
| 5-SNPs# | rs1208 | A/G | 0.57 | 0.13 | 0.016 | 0.010 | 0.023 | 0.011 | -0.009 | 0.010 | 0.016 | 0.026 | 0.041 | 0.024 | -0.003 | 0.020 |
| 5-SNPs# | rs1775921 | T/C | 0.91 | 0.23 | 0.004 | 0.017 | -0.007 | 0.019 | -0.009 | 0.017 | -0.018 | 0.042 | 0.020 | 0.039 | -0.033 | 0.033 |

CE, cardioembolism; EA, effect allele; LAA, large-artery atherosclerosis; OA, other allele; SAO, small-artery occlusion; SE, standard error; SNP, single nucleotide polymorphism. The unit of beta coefficients is log-odds per allele.

*: 12 SNPs associated with fasting insulin (BMI adjusted) reported by the MAGIC Consortium in up to 108,557 individuals of European ancestry without diabetes (PMID: 22885924).

#: 5 SNPs for gold standard measures of insulin resistance, such as euglycemic clamp or insulin suppression test, identified by the GENESIS Consortium in 2,764 European individuals (PMID: 25798622).