

## *Supplementary Material*

**Supplementary table 1:** Study details for the GWAS of IHD, stroke and AF

| Study                                   | Phenotype<br>(Phewas<br>code) | Cases           | Non-<br>cases      | Mean<br>age of<br>cases          | Phenotype definition   | Adjusted for (non-<br>genetic)                         |
|---|-------------------------------|-----------------|--------------------|----------------------------------|--|--|
| Cardiogram<br>1000 genomes<br>GWAS [43] | Ischemic<br>heart<br>disease  | 60,801          | 123,504            | n/a,<br>possibly<br>~58<br>years | “Case status was defined by an inclusive CAD diagnosis (e.g. myocardial infarction (MI), acute coronary syndrome, chronic stable angina, or coronary stenosis >50%)” | Study-specific<br>covariates (not age<br>or sex)       |
| UK biobank<br>SAIGE [46]                | CAD (411)<br>Stroke (433)     | 31,355<br>8,742 | 377,103<br>399,017 | n/a                              | Phewas code based on self-report, hospital episodes and death  | Sex, birth year,<br>and principal<br>components 1 to 4 |
| MEGASTROKE<br>[44]                      | All<br>ischemic<br>stroke     | 60,341          | 454,450            | ~69<br>years                     | Several different definitions used   | Minimum of age<br>and sex                              |
| AF [45]                                 | Atrial<br>fibrillation        | 60,620          | 970,216            | ~74<br>years                     | Usually based on ICD-9 427.3 and ICD-10 I48  | Minimum of age<br>(birth year) and<br>sex              |

| Outcome                | Source                                 | Exposure           | Odds ratio | 95% Confidence Interval |
|------------------------|--|--------------------|------------|-------------------------|
| Ischemic heart disease | CARDIoGRA<br>M plusC4D<br>1000 Genomes | SBP                | 2.01       | 1.69 to 2.39            |
|                        |  | DBP                | 1.62       | 1.38 to 1.92            |
|                        |  | Smoking initiation | 2.19       | 1.65 to 2.92            |
|                        |  | BMI                | 1.57       | 1.36 to 1.81            |
|                        | UK Biobank                             | SBP                | 2.17       | 1.85 to 2.56            |
|                        |  | DBP                | 1.57       | 1.33 to 1.85            |
|                        |  | Smoking initiation | 4.13       | 3.08 to 5.55            |
|                        |  | BMI                | 1.38       | 1.18 to 1.61            |
| All ischemic stroke    | MEGASTRO<br>KE                         | SBP                | 1.84       | 1.54 to 2.19            |
|                        |  | DBP                | 1.42       | 1.21 to 1.67            |
|                        |  | Smoking initiation | 2.10       | 1.60 to 2.76            |
|                        |  | BMI                | 1.18       | 1.04 to 1.34            |
| Stroke                 | UK Biobank                             | SBP                | 2.28       | 1.83 to 2.84            |
|                        |  | DBP                | 1.55       | 1.25 to 1.93            |
|                        |  | Smoking initiation | 3.93       | 2.63 to 5.87            |
|                        |  | BMI                | 1.12       | 0.93 to 1.36            |
| AF                     | Nielsen                                | SBP                | 1.55       | 1.35 to 1.77            |
|                        |  | DBP                | 1.16       | 0.97 to 1.39            |
|                        |  | Smoking initiation | 1.56       | 1.24 to 1.96            |
|                        |  | BMI                | 1.46       | 1.34 to 1.59            |

**Supplementary Table 2:** Univariable MR inverse variance weighted estimates for systolic blood pressure (SBP) [50], diastolic blood pressure (DBP) [50], smoking initiation [47] and BMI [42] on IHD using the CARDIoGRAMplusC4D 1000 Genomes based GWAS [43] and the UK Biobank, on all ischemic stroke using MEGASTROKE [44] and the UK Biobank and on AF using a study by Nielsen et al [45]