# SUPPLEMENTAL MATERIAL

*Supplemental Methods*

*A. UK Biobank*

Individual level genetic data was available from 335,464 individuals in UK Biobank, after excluding one related individual of each related pair of individuals, individuals whose genetic sex did not match self-reported sex and extreme outliers. Of these individuals, 43,525 were genotyped using the Affymetrix UK BiLEVE array and 291,939 were genotyped using the Affymetrix UK Biobank Axiom Array. Phasing and imputation were performed centrally, by UK Biobank, using the Haplotype Reference Consortium panel. As recommended by UK Biobank, we excluded any variants with an information measure < 0.3 and any variant not in the Haplotype Reference Consortium panel.

To adjust for the presence of antihypertensive medication, we added 15 mm Hg to systolic blood pressure and 10 mm Hg to diastolic blood pressure of individuals on antihypertensive medication at baseline, as in the International Consortium for Blood Pressure GWAS.[1] Type 2 diabetes and coronary heart disease (CHD) were both ascertained at baseline by self-report, followed by a verbal interview with a trained nurse to confirm the diagnosis. Type 2 diabetes was defined as history of diabetes unspecified or type 2 diabetes during verbal interview with trained nurse or hospitalization for or death due to ICD code E11. CHD was defined as: (1) Myocardial infarction (MI), coronary artery bypass grafting, or coronary artery angioplasty documented in medical history at time of enrollment by a trained nurse or (2) Hospitalization for ICD-10 code for acute myocardial infarction (I21.0, I21.1, I21.2, I21.4, I21.9) or (3) Hospitalization for OPCS-4 coded procedure: coronary artery bypass grafting (K40.1-40.4, K41.1-41.4, K45.1-45.5) or (4) Hospitalization for OPCS-4 coded procedure: coronary angioplasty ± stenting (K49.1-49.2, K49.8-49.9, K50.2, K75.1-75.4, K75.8-75.9). Definitions for all outcomes in UK Biobank are provided in Supplemental Table 3.

To combine cardiometabolic trait data from both genome wide association studies and UK Biobank (for analysis of waist-to-hip ratio adjusted for body mass index (WHRadjBMI) and BMI), we used inverse variance weighted fixed effects meta-analysis to pool estimates from UK Biobank with genome wide association study estimates (estimates from GIANT for WHRadjBMI and BMI). For WHRadjBMI and BMI, estimates were inverse normalized separately by sex, with adjustment for age, to allow for direct comparison to the GIANT consortium.

*B. Summary level data*

An overview of the included genome wide association studies is provided in Supp. Table 2.

For lipids (LDL cholesterol, HDL cholesterol, triglycerides and total cholesterol), we used data from the Global Lipids Genetics Consortium, a meta-analysis of 188 587 individuals of European descent.[2] This GWAS included 37 studies genotyped using the Illumina Metabochip array as well as an additional 23 studies genotyped using a variety of arrays.

For glycaemic traits, we used data from the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC), which included 133 010 individuals of European ancestry without diabetes.[3] This included studies genotyped using the Metabochip as well as studies genotyped using various arrays who were imputed to 2.5 million SNPs using the HapMap reference panel. SNPs included on the Metabochip were then meta-analyzed across studies.

For BMI and WHRadjBMI we used data from the Genetic Investigation of ANthropometric Traits (GIANT) consortium.[4,5] For WHRadjBMI, data from 210,088 individuals of European ancestry were included. For BMI, data for 322,154 individuals of European ancestry were included. Individuals were genotyped using various arrays and imputed with the HapMap reference panel to 2.5 million SNPs.

For estimated glomerular filtration rate (eGFR) and chronic kidney disease, we used data from the Chronic Kidney Disease Genetics consortium (CKDGen), a meta-analysis of 133 413 individuals of European descent from 49 studies.[6] Individuals were genotyped using various arrays and imputed with the HapMap reference panel to 2.5 million SNPs.

For coronary heart disease, we used data from the CARDIoGRAMplusC4D 1000 Genomes imputation, a meta-analysis of 60801 coronary heart disease cases and 123504 controls.[7] Individuals were genotypes using various arrays and imputed to 9.5 million SNPs using the1000 Genomes reference panel.

For diabetes, we used data from the DIAbetes Genetics Replication and Meta-analysis (DIAGRAM) Consortium, a meta-analysis of 34 840 diabetes cases and 114 981 controls, overwhelmingly of European descent.[8] This meta-analysis included 12 studies genotyped using a range of arrays and imputed with the HapMap reference panel to 2.5 million SNPs. These studies were meta-analysed with 26 studies genotyped using the Illumina Metabochip array.

For migraine, we used data from the International Headache Genetics Consortium, a meta-analysis of 59674 migraine cases and 316 078 controls.[9] Individuals were genotyped using a range of arrays and imputed to 9.5 million SNPs using 1000 Genomes reference panel.

*Standardization*

While GIANT and GLGC reported effect estimates of variants in units of standard deviations, the MAGIC and CKDGen consortia did not. We wished to standardize betas from these consortia so that the effects of genetically increased nitric oxide signaling on cardiometabolic traits could be uniformly expressed in terms of standard deviations for each trait. Therefore, to standardize betas for HbA1c, fasting glucose and two-hour glucose from the MAGIC consortium, one SD was assumed to correspond to 0.53%, 0.73 mM and 0.56 mM, the pooled standard deviation of studies included in a previous report from the MAGIC consortium.[10] As a pooled SD for log-transformed fasting insulin was not available from the MAGIC consortium, we used an estimate of 0.44 from Framingham.[11] To estimate the effect for estimated glomerular filtration rate, we used data from the National Health and Nutrition

Examination Survey (NHANES) from 2005-2012.[12] We calculated that a one unit increase in log(eGFR) corresponded to a 77 ml/min increase in estimated glomerular filtration rate or a 2.89 standard deviation increase among Caucasian individuals (restricted to Caucasians as CKDGen is predominantly among individuals of European ancestry).

To express increases in lipid levels in absolute terms, which may be easier for clinicians to interpret, we calculated population level SDs in lipid levels using the National Health and Nutrition Examination Survey (NHANES) from 2005-2012.[12] We calculated that one SD in total cholesterol was 1.03 mM, a one SD in LDL cholesterol was 0.90 mM, a one SD in HDL cholesterol was 0.40 mM and a one SD in triglycerides was 0.74 mM.

*C. Rare Variant Sequencing and Analysis*

The Myocardial Infarction Genetics (MIGen) Consortium exome sequencing was performed as previously described.[13,14] Studies included in the MIGen consortium were: 1) the Italian Atherosclerosis Thrombosis and Vascular Biology (ATVB) study (dbGaP Study Accession phs000814.v1.p1); 2) the Exome Sequencing Project Early-Onset Myocardial Infarction (ESP-EOMI) study(9); 3) a nested case-control cohort from the Jackson Heart Study (JHS); 4) the South German Myocardial Infarction study (dbGaP Study Accession phs000916.v1.p1); 5) the Ottawa Heart Study (OHS) (dbGaP Study Accession phs000806.v1.p1); 6) the Precocious Coronary Artery Disease (PROCARDIS) study (dbGaP Study Accession phs000883.v1.p1) ; 7) the Pakistan Risk of Myocardial Infarction Study (PROMIS) (dbGaP Study Accession phs000917.v1.p1); 8) the Registre Gironi del COR (Gerona Heart Registry or REGICOR) study (dbGaP Study Accession phs000902.v1.p1); 9) the Leicester Myocardial Infarction study (dbGaP Study Accession phs001000.v1.p1); 10) the BioImage study (dbGaP Study Accession phs001058.v1.p1); 11) and the North German Myocardial Infarction study (dbGaP Study Accession phs000990.v1.p1).

The Burrows–Wheeler Aligner algorithm was used to align reads from participants to the reference genome (hg19). The GATK HaploTypeCaller was used to jointly call variants. Metrics including Variant Quality Score Recalibration (VQSR), quality over depth, and strand bias were then used to filter variants. We excluded samples which were related to other samples, which had high ratios of heterozygous to non-reference homozygous genotypes, which had high missing genotypes, which had a discordant genetic gender relative to reports gender, and samples which were discordant relative to genotype data.

After variant calling and quality controls, the Variant Effect Predictor[15] was used to annotate variants which were predicted to lead of loss-of-function: (1) nonsense mutations that resulted in early termination of NOS3/GUCY1A3 (2) frameshift mutations due to insertions or deletions of DNA; or (3) splice-site mutations which result in an incorrectly spliced protein. Predicted loss-of-function variants analysed are provided (Supplemental Tables 5-6).

For analysis of rare, predicted loss-of-function variants, we pooled variants in MIGen, testing for the association of a predicted loss-of-function variant with coronary heart

disease using linear and logistic regression, respectively, after adjustment for age, sex, cohort and five principle components.

To examine the association of predicted loss-of-function variants in Type 2 Diabetes exome sequencing portal with blood pressure, we used the online Genetic Association Interactive Test in the T2D Knowledge portal. Exome sequencing was performed in the T2D Genes/Go T2D as previously described[16] and in the SIGMA Type 2 Diabetes Genetics Consortium as previously described. [17] We restricted the analysis to the specified loss-of-function variants (Supplemental Table 6). We tested for the association of a loss-of-function variant with systolic and diastolic blood pressure using linear regression, adjusted for five principal components of ancestry.

*D. Gene tissue expression levels*

To derive effect estimates of the association between NOS3/GUCY1A3 common variation and gene transcription, we used publicly available data from the GTEx project.[18] In the GTex V6p study, discovery of cis-eQTLs was performed across an expanded collection of 44 tissues in 449 individuals (median 16 tissues per individual, 127 samples per tissue). cis-eQTLs, or associations between local genetic variation and gene expression (≤ 1 Mb from 108 the transcription start site, TSS), were identified using genotype and RNA-seq data generated using the FastQTL linear model for each tissue, including lung and aorta.

*E. Mediation Analysis*

To examine what proportion of the decrease in risk of coronary heart disease was mediated through systolic blood pressure, we first estimated the causal effect of systolic blood pressure on coronary heart disease risk. In a recent genome wide association study, 54 loci were identified as being associated with systolic blood pressure at genome wide significance ($p<5*10^{-8}$).[19] For estimation of the effect of systolic blood pressure on coronary heart disease, we excluded variants from the *GUCY1A3* (rs4691707) and *ATP2B1* loci (rs11105354). We excluded GUCY1A3 as it mediates nitric oxide signaling. We excluded ATP2B1 as the allele of rs11105354 that is associated with lower blood pressure (G) is associated with higher coronary heart disease risk ($p=1.3*10^{-10}$), suggesting ATP2B1 has a pleiotropic effect on coronary heart disease independent of blood pressure.

The effect of a 5 mm Hg higher systolic blood pressure on coronary heart disease was calculated using inverse variance weighted fixed effects meta-analysis of the effect of the remaining 52 loci on coronary heart disease from CARDIOGRAM 1000 Genomes[7]: OR 1.21 CI 1.17, 1.24. This effect was then multiplied by the decrease in systolic blood pressure associated with increased nitric oxide signaling to estimate the decrease in CHD risk mediated through decrease in systolic blood pressure levels. We then subtracted this estimate to derive the remaining proportion of CHD risk unaccounted for by a decrease in systolic blood pressure.

*Supplemental Tables*

Supplemental Table 1. Characteristics of individuals in UK Biobank.

| | |
|---|---|
| N Individuals | 335464 |
| Age ± SD, years | 57.4 ± 8.0 |
| Male, n (%) | 155661 (46.4%) |
| UK BiLEVE Array, n (%) | 43525 (12.9%) |
| Systolic Blood Pressure ± SD, mm Hg* | 143.3 ± 21.7 mm Hg |
| Diastolic Blood Pressure ± SD, mm Hg* | 84.3 ± 11.8 mm Hg |
| Body Mass Index ± SD, kg/m2 | 27.4 ± 4.8 kg/m2 |
| Waist-to-Hip Ratio ± SD | 0.87 ± 0.09 |
| Type 2 Diabetes, n (%) | 15727 (4.7%) |
| Coronary Heart Disease, n (%) | 12445 (3.7%) |

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; SD, standard deviation; BMI, body mass index.
*Adjusted for presence of antihypertensive medication (Supplemental Methods A)

Supplemental Table 2. Characteristics of genome wide association studies included in this study.

| Consortium | Outcome/Trait | Sample Size | Genotyping |
|---|---|---|---|
| GLGC[2] | LDL cholesterol<br>HDL cholesterol<br>Total cholesterol<br>Triglycerides | Up to 188 587 individuals | 37 studies using metabochip, 23 studies using various arrays |
| MAGIC[3] | Fasting glucose<br>Fasting insulin<br>Two hour glucose<br>HbA1c | Up to 133 010 individuals | Various arrays, imputation to 2.5 million SNPs using HapMap reference panel |
| GIANT[4,5] | Waist-to-hip ratio<br>Waist circumference<br>Hip circumference<br>Body mass index | Up to 322,154 individuals | Various arrays, imputation to 2.5 million SNPs using HapMap reference panel |
| CKDGen[6] | Serum estimated glomerular filtration rate<br>Chronic kidney disease | Up to 133 413 individuals | Various arrays, imputation to 2.5 million SNPs using HapMap reference panel |
| CARDIoGRAM Consortium[7] | Coronary heart disease | Up to 60801 cases/ 123504 controls | Various arrays, imputation to 9.5 million SNPs using 1000 Genomes reference panel |
| DIAGRAM[8] | Diabetes | Up to 34 840 cases/ 114 981 controls | 37 studies using Metabochip, 23 studies various arrays, imputation to 2.5 million SNPs using HapMap reference panel |
| IHGC[9] | Headache | Up to 59 674 cases / 316 078 controls | Various arrays, imputation to 9.5 million SNPs using 1000 Genomes reference panel |

Abbreviations: CARDIoGRAM, Coronary ARtery DIsease Genome wide Replication and Meta-analysis; DIAGRAM, DIAbetes Genetics Replication And Meta-analysis; GIANT, Genetic Investigation of ANthropometric Traits; GLGC, Global Lipids Genetics Consortium; MAGIC, Meta-Analyses of Glucose and Insulin-related traits Consortium; CKDGen, Chronic Kidney Disease Genetics Consortium; IHGC, International Headache Genetics Consortium; SNPs, single nucleotide polymorphism; LDL cholesterol, low-density lipoprotein cholesterol; HDL cholesterol, high-density lipoprotein cholesterol.

Supplemental Table 3. Definitions of outcomes

| Outcome | Definition (UK Biobank unless otherwise specified) |
|---|---|
| Coronary heart disease | Inverse variance weighted fixed effects meta-analysis of CARDIOGRAM Exome Consortium[20] outcome (coronary heart disease) and UK Biobank outcome:<br>(1) Myocardial infarction (MI), coronary artery bypass grafting, or coronary artery angioplasty documented in medical history at time of enrollment by a trained nurse or<br>(2) Hospitalization for ICD-10 code for acute myocardial infarction (I21.0, I21.1, I21.2, I21.4, I21.9) or<br>(3) Hospitalization for OPCS-4 coded procedure: coronary artery bypass grafting (K40.1-40.4, K41.1-41.4, K45.1-45.5) or<br>(4) Hospitalization for OPCS-4 coded procedure: coronary angioplasty ± stenting (K49.1-49.2, K49.8-49.9, K50.2, K75.1-75.4, K75.8-75.9) |
| Atrial fibrillation/flutter | History of atrial fibrillation or flutter during verbal interview with trained nurse or hospitalization for or death due to ICD code I48 |
| Heart failure | History of heart failure during verbal interview with trained nurse or hospitalization for or death due to ICD code I11.0, I13.0, I13.2, I125.5, I42, I50 |
| Stroke | History of stroke, adjudicated by UK Biobank centrally as report of stroke during verbal interview with trained nurse or hospitalization for or death due to ICD code I60-64 *(http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=462)* |
| Peripheral vascular disease | History of peripheral vascular disease or intermittent claudication during verbal interview with trained nurse or hospitalization for or death due to ICD code I70, I73.8 or I73.9 |
| Venous thromboembolism | History of venous thromboembolism, deep vein thrombosis or pulmonary embolism during verbal interview with trained nurse or hospitalization for death due to I26, I80.1, I80.2, I81, or I82.0 |
| Aortic stenosis | History of aortic stenosis during verbal interview with trained nurse or hospitalization for ICD code I06.0, I06.2 I35.0 or I35.2 |
| Type 2 Diabetes | Inverse variance weighted fixed effects meta-analysis of DIAGRAM Consortium outcome (type 2 diabetes) and UK Biobank (history of diabetes unspecified, type 2 diabetes during verbal interview with trained nurse or hospitalization for or death due to ICD code E11) |
| Chronic kidney disease | Chronic Kidney Disease Genetics Consortium outcome[6] (creatinine estimated glomerular filtration rate <60 ml/min) |
| Inflammatory bowel disease | History of inflammatory bowel disease, Crohn's disease or ulcerative colitis during verbal interview with trained nurse or hospitalization for or death due to ICD code K50 or K51 |
| Gastric reflux | History of gastric reflux during verbal interview with trained nurse or hospitalization for or death due to ICD code K21 |
| Irritable bowel syndrome | History of irritable bowel syndrome during verbal interview with trained nurse or hospitalization for or death due to ICD code K58 |
| Gallstone | History of gallstones during verbal interview with trained nurse or hospitalization for or death due to ICD code K56.3 or K80 |
| Hyperthyroidisim | History of hyperthyroidism during verbal interview with trained nurse or hospitalization for or death due to ICD code E05 |
| Hypothyroidism | History of hypothyroidism during verbal interview with trained nurse or hospitalization for or death due to ICD code E03 |
| Gout | History of gout during verbal interview with trained nurse or hospitalization for or death due to ICD code M10 |
| Enlarged prostate | History of enlarged prostate during verbal interview with trained nurse or |

| | |
|---|---|
| | hospitalization for or death due to ICD code N40 |
| Uterine fibroids | History of uterine fibroids during verbal interview with trained nurse or hospitalization for or death due to ICD code D25 |
| Migraine | Inverse variance weighted fixed effects meta-analysis of International Headache Genetics Consortium outcome (migraine) and UK Biobank (history of migraine during verbal interview with trained nurse or hospitalization for or death due to ICD code G43) |
| Depression | History of depression during verbal interview with trained nurse or hospitalization for or death due to ICD code F32 |
| Anxiety | History of anxiety/panic attacks during verbal interview with trained nurse or hospitalization for or death due to ICD code F41 |
| Osteoporosis | History of osteoporosis during verbal interview with trained nurse or hospitalization for or death due to ICD code M80 or M81 |
| Osteoarthritis | History of osteoarthritis during verbal interview with trained nurse or hospitalization for or death due to ICD code M15-19 |
| Sciatica | History of sciatica during verbal interview with trained nurse or hospitalization for or death due to ICD code M54.3 |
| Prolapsed disc | History of prolapsed disc/slipped disc during verbal interview with trained nurse or hospitalization for or death due to ICD code M50.2 or M51.2 |
| Asthma | History of asthma during verbal interview with trained nurse or hospitalization for or death due to ICD code J45 or J46 |
| COPD/Emphysema | History of chronic obstructive airways disease, emphysema/chronic bronchitis or emphysema during verbal interview with trained nurse or hospitalization for or death due to ICD code J41-44 |
| Pneumonia | History of pneumonia during verbal interview with trained nurse or hospitalization for or death due to ICD code J12-18 |
| Allergic rhinitis | History of hayfever during verbal interview with trained nurse or hospitalization for or death due to ICD code J30 |
| Breast cancer | History of breast cancer during verbal interview with trained nurse or hospitalization for or death due to ICD code C50 |
| Colorectal cancer | History of large bowel cancer/colorectal cancer, colon cancer/sigmoid cancer or rectal cancer during verbal interview with trained nurse or hospitalization for or death due to ICD code C18 |
| Skin cancer | History of skin cancer, malignant melanoma, non-melanoma skin cnacer, basal cell carcinoma or squamous cell carcinoma during verbal interview with trained nurse or hospitalization for or death due to ICD code C43-44 |
| Prostate cancer | History of prostate cancer during verbal interview with trained nurse or hospitalization for or death due to ICD code C61 |
| Cervical cancer | History of cervical cancer or cin cells at the cervix during verbal interview with trained nurse or hospitalization for or death due to ICD code C53 |
| Other cancer | History of any other cancer than lung cancer, colorectal cancer, skin cancer, prostate cancer or cervical cancer during verbal interview with trained nurse |

Abbreviations: COPD, chronic obstructive pulmonary disease; ICD, international classification of disease

Supplemental Table 4. Common variants in NOS3 and GUCY1A3 loci used in the nitric oxide signaling genetic risk score.

| *Variant* | *Gene* | *Effect* | *MAP-Lowering Alelle* | *MAP-Raising Allele* | *MAP-Lowering Allele Frequency (UK Biobank)* | *Effect on MAP levels (mm Hg)* |
|---|---|---|---|---|---|---|
| rs3918226 | NOS3 | Promoter | C | T | 0.92 | 0.68 |
| rs7692387 | GUCY1A3 | Intron | A | G | 0.19 | 0.32 |

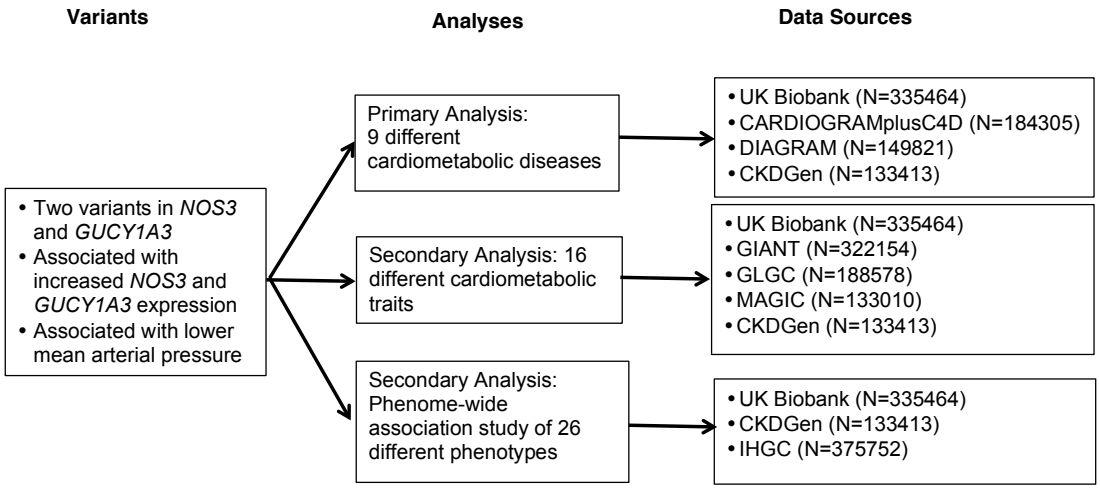
Supplemental Table 5. Rare loss-of-function variants in NOS3 and GUCY1A3 in MIGen.

| CHR:POS_REF/ALT | GENE | Consequence | Amino Acid Change | Cases With Variant | Controls with Variant |
|---|---|---|---|---|---|
| 7:150692313_C/T | NOS3 | Stop gained | Gln61Ter | 1 | 0 |
| 7:150693999_TG/T | NOS3 | Frameshift | | 2 | 0 |
| 7:150695475_C/T | NOS3 | Stop gained | Gln205Ter | 0 | 1 |
| 7:150696043_C/T | NOS3 | Stop gained | Gln276Ter | 0 | 1 |
| 7:150696132_G/GC | NOS3 | Frameshift | | 2 | 0 |
| 7:150696174_G/A | NOS3 | Splice donor | | 1 | 0 |
| 7:150698642_G/A | NOS3 | Stop gained | Trp480Ter | 1 | 0 |
| 7:150704345_G/A | NOS3 | Stop gained | Trp698Ter | 1 | 0 |
| 7:150706357_T/G | NOS3 | Splice donor | | 1 | 1 |
| 7:150708027_G/A | NOS3 | Stop gained | Trp979Ter | 1 | 0 |
| 7:150709455_CT/C | NOS3 | Frameshift | | 1 | 0 |
| 7:150709543_ATGACATTGAGAGCAAAGGTGAG/A | NOS3 | Splice donor | | 1 | 0 |
| 7:150711007_G/C | NOS3 | Splice donor | | 0 | 1 |
| 4:156618221_C/T | GUCY1A3 | Stop gained | Arg68Ter | 1 | 0 |
| 4:156625146_G/A | GUCY1A3 | Splice donor | | 1 | 0 |
| 4:156629431_C/T | GUCY1A3 | Stop gained | Gln121Ter | 1 | 0 |
| 4:156631714_A/T | GUCY1A3 | Stop gained | Lys133Ter | 1 | 0 |
| 4:156631799_A/AT | GUCY1A3 | Frameshift | | 1 | 0 |
| 4:156632362_C/T | GUCY1A3 | Stop gained | Arg349Ter | 1 | 0 |
| 4:156634280_AT/A | GUCY1A3 | Frameshift | | 0 | 1 |
| 4:156638351_T/G | GUCY1A3 | Stop gained | Leu538Ter | 0 | 1 |
| 4:156651181_G/C | GUCY1A3 | Splice acceptor | | 0 | 1 |
| 4:156651352_AT/A | GUCY1A3 | Frameshift | | 1 | 1 |

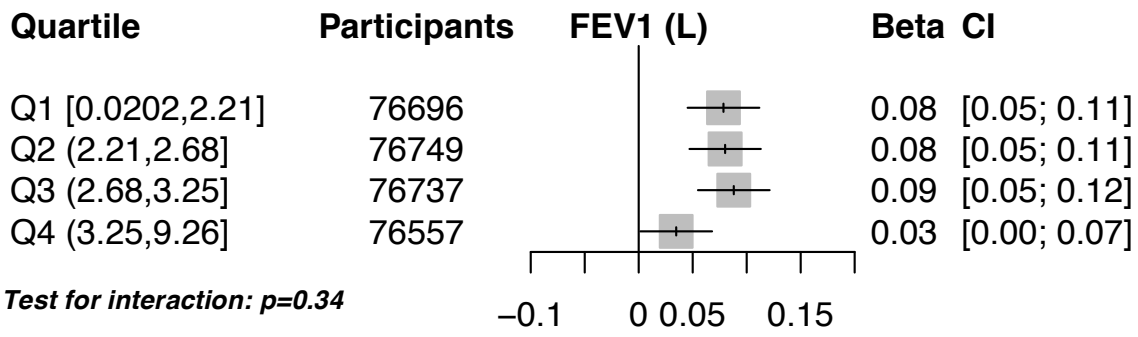
Supplemental Table 6. Rare loss-of-function variants in NOS3 and GUCY1A3 used in T2D GENES.

| CHR:POS_REF/ALT | GENE | Consequence | Amino Acid Change | Participants with Variant |
|---|---|---|---|---|
| 7:150695676_C/T | NOS3 | Stop gained | Arg242Ter | 2 |
| 7:150695722_AG/A | NOS3 | Frameshift | | 1 |
| 7:150697628_TCC/T | NOS3 | Frameshift | | 1 |
| 7:150698396_CA/C | NOS3 | Frameshift | | 2 |
| 7:150703523_AG/TGA | NOS3 | Frameshift | | 2 |
| 7:150703584_T/C | NOS3 | Splice donor | | 1 |
| 7:150704338_C/T | NOS3 | Stop gained | Arg696Ter | 3 |
| 7:150706066_C/T | NOS3 | Stop gained | Arg721Ter | 1 |
| 7:150707816_C/A | NOS3 | Stop gained | Tyr939Ter | 1 |
| 7:150710317_A/G | NOS3 | Splice acceptor | | 1 |
| 7:150710928_GC/G | NOS3 | Frameshift | | 1 |
| 4:156629400_AAG/A | GUCY1A3 | Frameshift | | 2 |
| 4:156632156_C/A | GUCY1A3 | Stop gained | Ser280Ter | 1 |
| 4:156632405_T/C | GUCY1A3 | Splice donor | | 1 |
| 4:156634315_AC/A | GUCY1A3 | Frameshift | | 1 |
| 4:156634415_C/T | GUCY1A3 | Stop gained | Gln418Ter | 1 |
| 4:156634421_C/T | GUCY1A3 | Stop gained | Arg420Ter | 2 |
| 4:156634427_C/T | GUCY1A3 | Stop gained | Gln422Ter | 1 |
| 4:156651181_G/C | GUCY1A3 | Splice acceptor | | 1 |
| 4:156651352_AT/A | GUCY1A3 | Frameshift | | 1 |

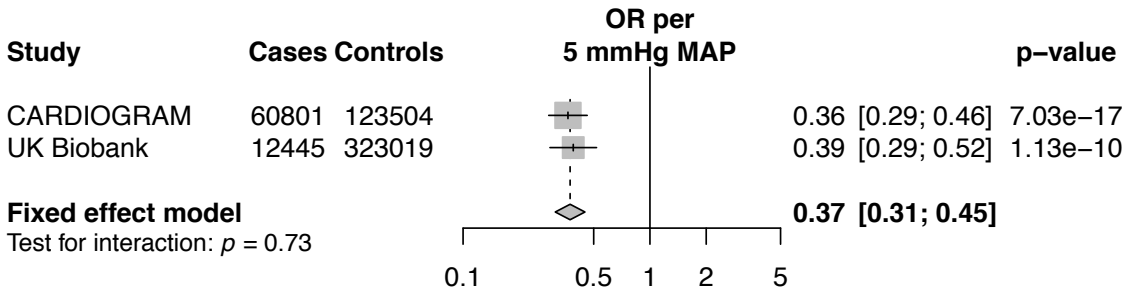
*Supplemental Figures and Figure Legends*



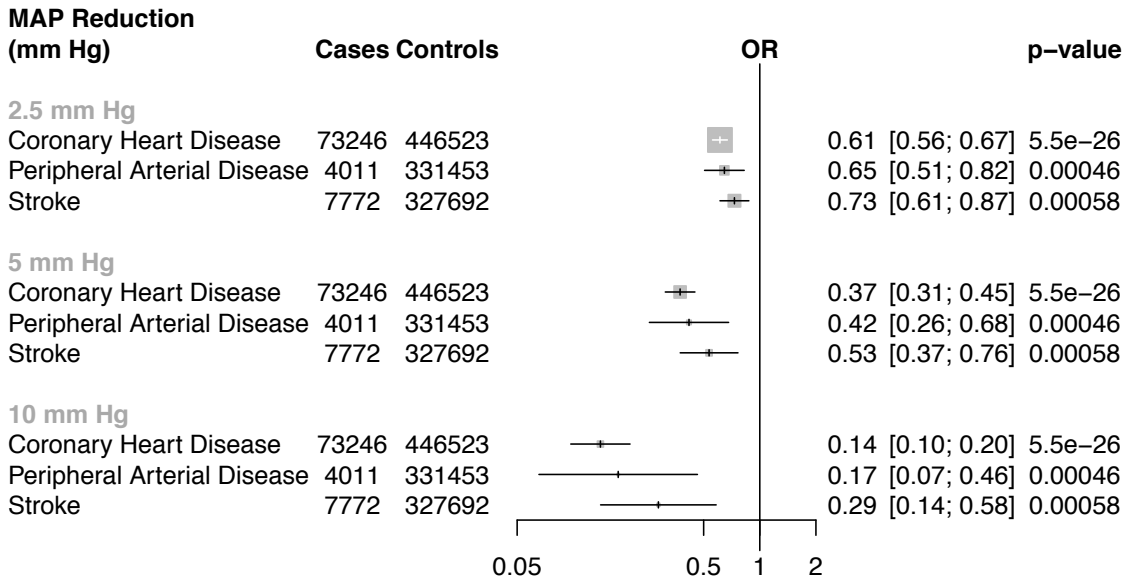

Supplemental Figure 1. Study design. Abbreviations: CARDIOGRAMplusC4D, Coronary ARtery DIsease Genome-wide Replication and Meta-analysis plus The Coronary Artery Disease Genetics consortium[7]; DIAGRAM, DIAbetes Genetics Replication And Meta-analysis[8]; GIANT, Genetic Investigation of ANthropometric Traits[4,5]; GLGC, Global Lipids Genetics Consortium[2]; MAGIC, Meta-Analyses of Glucose and Insulin-related traits Consortium[3]; CKDGen, Chronic Kidney Disease Genetics Consortium[6]; IHGC, International Headache Genetics Consortium.[9]



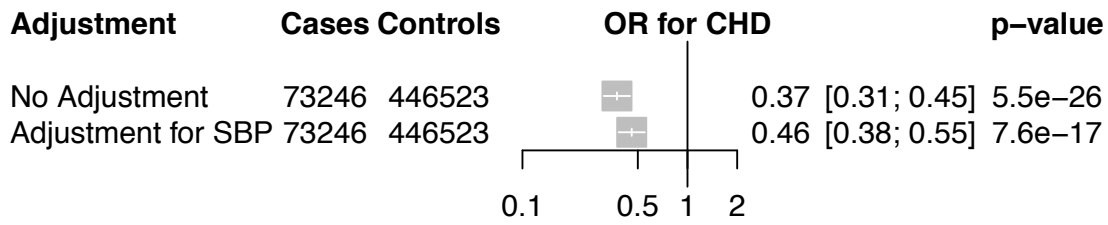

Supplemental Figure 2. Association of nitric oxide signaling genetic score (per 5 mm Hg lower MAP) with FEV1 by quartile of baseline pulmonary function. Estimates were derived in UK Biobank using linear regression, adjusted for age, sex, ten principal components of ancestry and a dummy variable for array type. Abbreviations: FEV1, forced expiratory volume in one second.



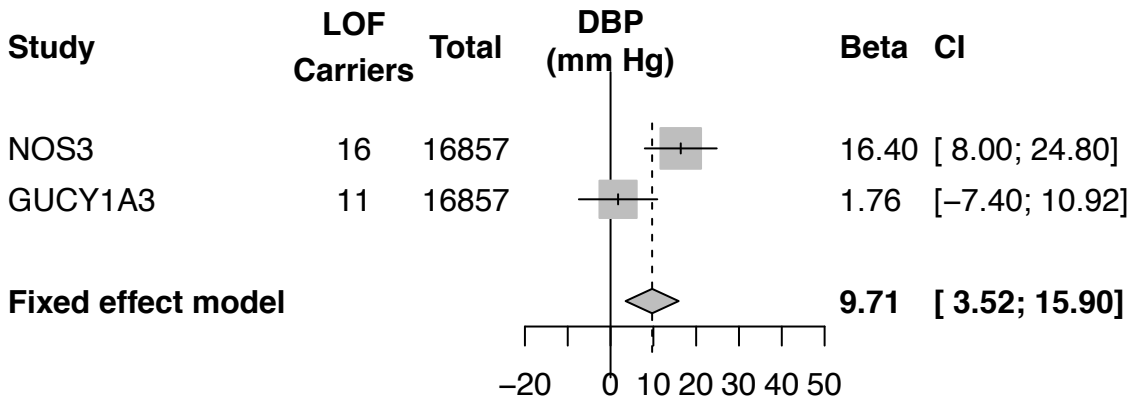

Supplemental Figure 3. Association of nitric oxide signaling genetic score with coronary heart disease. Estimate in UK Biobank was derived using logistic regression, adjusted for age, sex, ten principal components and array type. Estimate in CARDIOGRAM was derived using inverse variance weighted fixed effects meta-analysis. OR, odds ratio; CHD, coronary heart disease. CARDIOGRAM, Coronary ARtery DIsease Genome wide Replication and Meta-analysis.




Supplemental Figure 4. Association of nitric oxide signaling genetic score with coronary heart disease, peripheral arterial disease and stroke, standardized to a 2.5 mm Hg, 5 mm Hg and 10 mm Hg mean arterial pressure reduction. Estimates were derived in UK Biobank using logistic regression, adjusted for age, sex, ten principal components and array type. Estimates for coronary heart disease additionally included summary estimates from CARDIOGRAM and were pooled using inverse variance weighted fixed effects meta-analysis. OR, odds ratio; SD, standard deviation; COPD, chronic obstructive pulmonary disease. CARDIOGRAM, Coronary ARtery DIsease Genome wide Replication and Meta-analysis.




Supplemental Figure 5. Mediation analysis of the association of nitric oxide signaling genetic score with coronary heart disease. Estimates were derived through inverse variance weighted fixed effects meta-analysis of estimates in UK Biobank (derived using logistic regression, adjusted for age, sex, ten principal components and array type) and CARDIOGRAM. OR, odds ratio; SBP, systolic blood pressure; CHD, coronary heart disease. CARDIOGRAM, Coronary ARtery DIsease Genome wide Replication and Meta-analysis.




Supplemental Figure 6. Association of rare, predicted loss-of-function variants in the nitric oxide signaling pathway with diastolic blood pressure. Estimates for diastolic blood pressure from MIGen were derived using linear regression, with adjustment for sex, cohort and five principal components of ancestry. Estimates for diastolic blood pressure from T2D Genes were derived using linear regression with adjustment for five principal components of ancestry. Abbreviations: OR, odds ratio; DBP, diastolic blood pressure; MIGen, Myocardial Genetics Consortium.

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