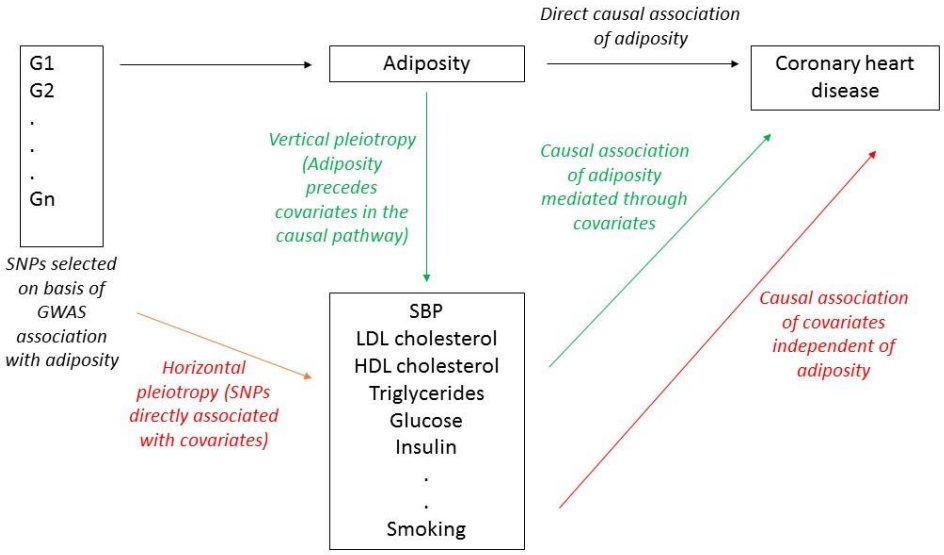
SUPPLEMENTAL MATERIAL

Supplemental Method 1: ECG DEFINITIONS

Definitions of the 12-lead ECG-LVH Indices Analyzed[1]:

- Sokolow-Lyon index (μV)=SV1+max (RV5, RV6)
- Cornell product (μV · s)=Cornell voltage×QRS Duration (where Cornell voltage=RaVL+SV3 (600 μV added for females)
- QRS voltage sum (μV)=the sum of |Q| +R+|S|+R'+|S|' amplitudes in all 12 leads
- QRS voltage product (μV · s)=QRS voltage sum×QRS duration

Supplemental Figure 1: Conceptual framework for the Mendelian randomisation analysis of adiposity and coronary heart disease



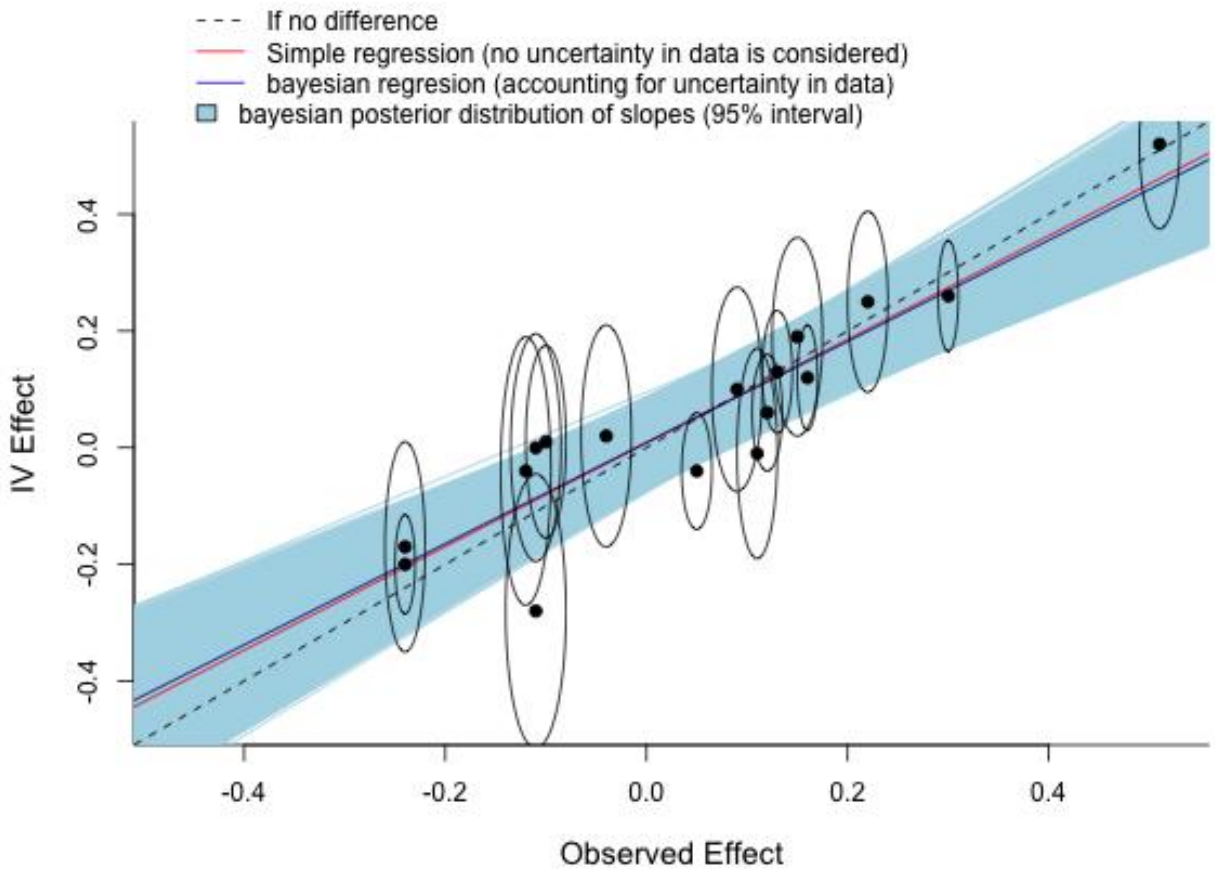
G_1-G_n are independent SNPs that together form the multilocus insrument for adiposity. Horizontal pleiotropy occurs when the instrument associates with traits that are independent mediators of the gene-coronary heart disease association (red pathway). Vertical pleiotropy occurs if adiposity causally influences the covariates (i.e. a downstream, pathway effect) and presence of such vertical pleiotropy does not invalidate Mendelian randomization analysis (green pathway), but rather, is informative of potential mediators. With a multi-SNP instrument, the horizontal pleiotropic effects may balance out (i.e. have equal and opposite effects on covariates), in contrast to unbalanced horizontal pleiotropy where the association of one or more SNPs in the instrument influences biomarkers on alternative pathways with this leading to a directionally biased effect with regards to the outcome when using conventional MR approaches. Recent methodological developments, including MR-Egger and weighted median MR,[2] allows investigation of pleiotropy and provision of MR estimates that are less sucseptible to first-order violations (i.e. pleiotropy) of MR. MR-Egger regression is used to provide a test for unbalanced pleiotropy and a valid causal estimate of adiposity on CHD in its presence. The weighted median estimator can give valid estimates even in the presence of horizontal pleiotropy provided at least 50 per cent of the information in the analysis comes from variants that are valid instruments.

Supplemental Figures 2a & 2b: Comparison of IV and observational estimates in IPD

We compared the observational estimates to the IV estimates for all cardiometabolic traits (except anthropometric) to investigate similarity between the two methodological approaches for calculating an effect. A consistently higher or lower IV estimate could help to illuminate the direction of confounding in observational estimates, under the hypothesis that the IV estimate is calculated with less bias from conventional sources. Similarity between the observational and IV approaches may indicate estimation of the true causal effect by both methods, although a consistent effect of bias(es) in both methods cannot be ruled out.

We fitted a simple regression line of the instrumental variable estimated effects against the observational estimated effects of the cardiometabolic traits and compared this to the scenario of the two methods producing exactly the estimate (indicated by the black dotted diagonal line on the figures with slope equal to 1). In addition, we fitted a Bayesian regression model that takes into account the uncertainty associated with each of these two estimates. Each point estimate was assumed to arise from a normal distribution centred on the unknown true effect (instrumental variable or observational) with standard deviation equal to their estimated standard errors. The model was calculated using MCMC with a Gibbs sampling algorithm implemented in the software JAGS and we shaded a blue area covering the posterior 95% belief for the true regression line. These analyses were conducted in R.

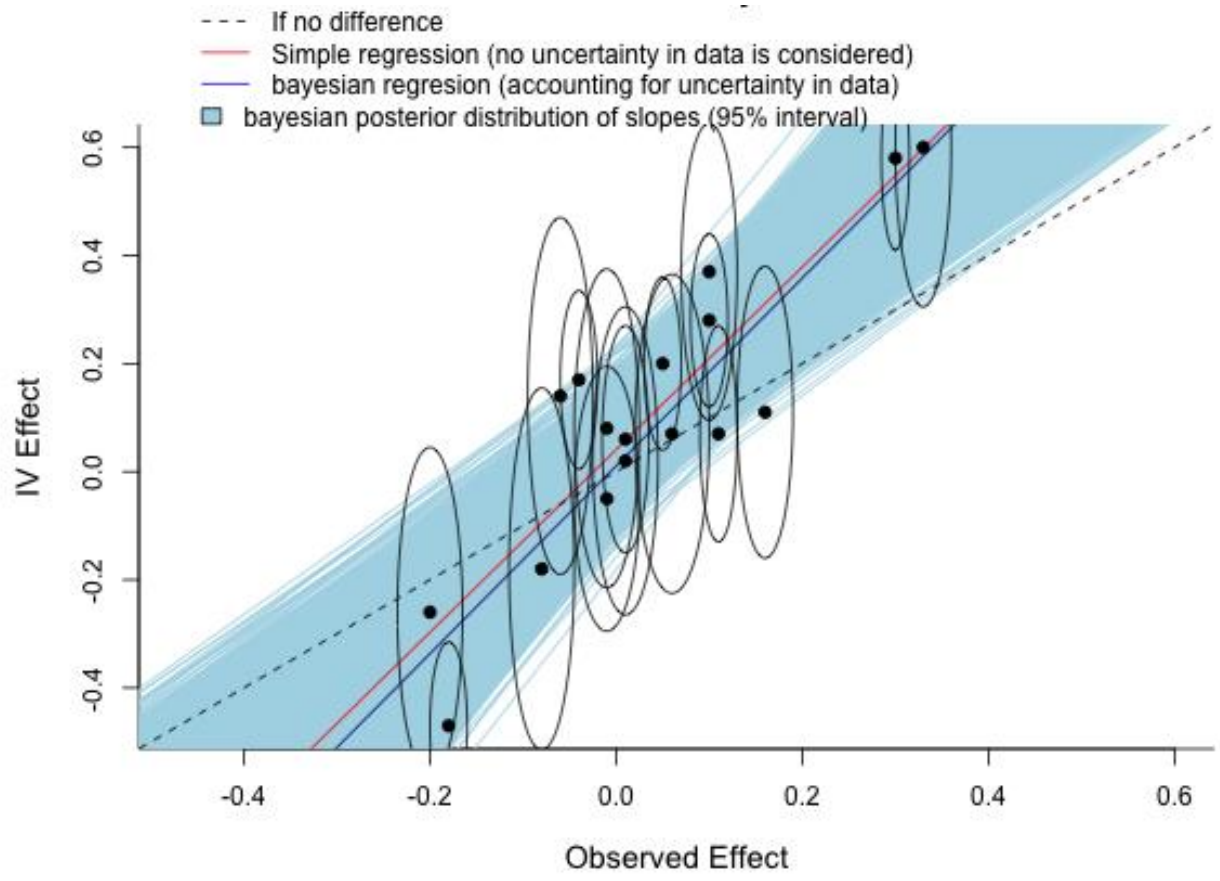
Supplemental Figure 2a: Comparison of association between BMI and cardiovascular traits derived from observational and MR estimates



Footnote: Each point represents SD change in CVD trait per 1SD increase in BMI

Overall, the linear relationship between observational and IV estimates across cardiometabolic traits, indicates that very similar estimates were produced by both methods for BMI. The difference between regression lines plotted with Bayesian regression (which accounts for uncertainty in the data) and without uncertainty was very small with the blue and red lines lying very close to each other. Furthermore, the black dotted line (indicating no difference) falls within the shaded blue area of the 95% posterior belief of the Bayesian regression slope.

Supplemental Figure 2b: Comparison of association between WHRadjBMI and cardiovascular traits derived from observational and MR estimates

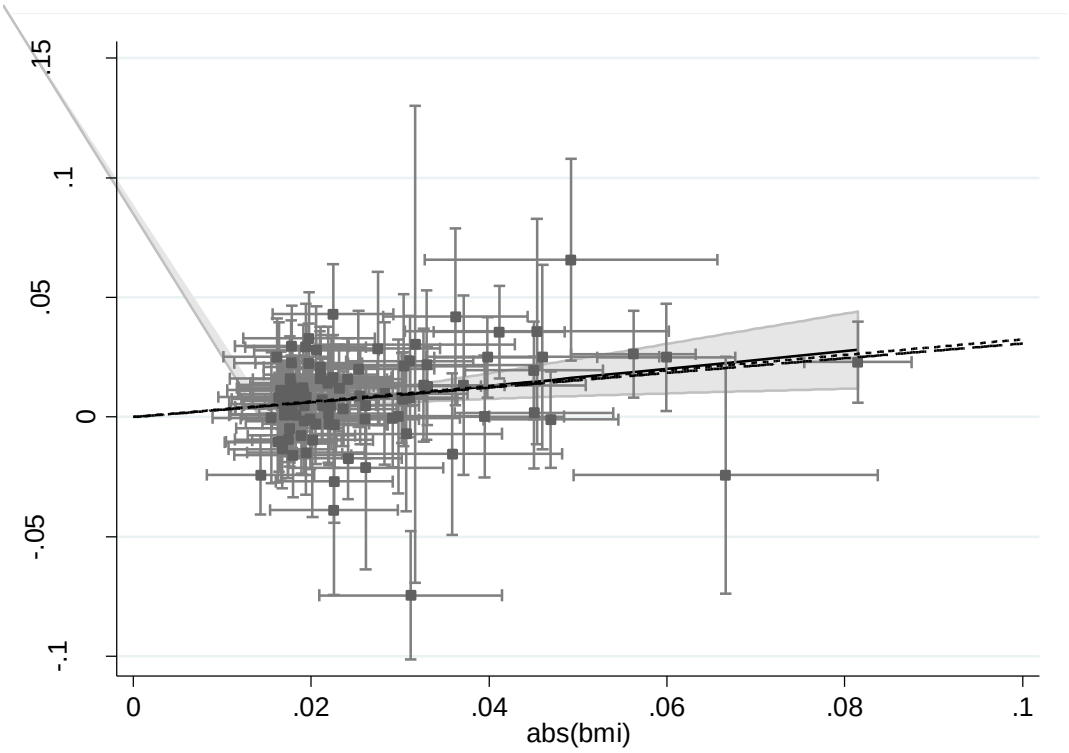


Footnote: Each point represents SD change in CVD trait per 1SD increase in WHRadjBMI

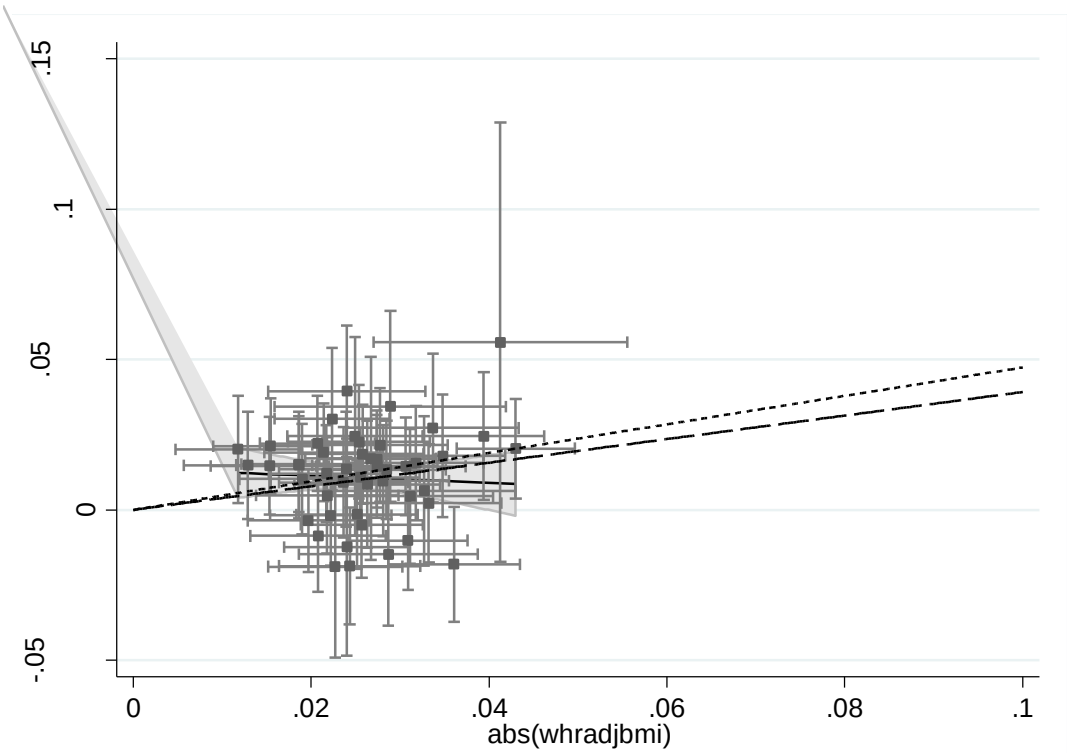
For WHRadjBMI, we observe a greater difference between the observational and IV estimates, particularly for cardiometabolic traits where effects are larger. However, the black dotted line remains mostly within the blue shaded area indicating that the data are consistent with no true difference between methodological approaches.

Supplemental Figures 3a-g: Scatter plots of MR-Egger model adding IVW line (long dash) and weighted median (short dash) for comparison

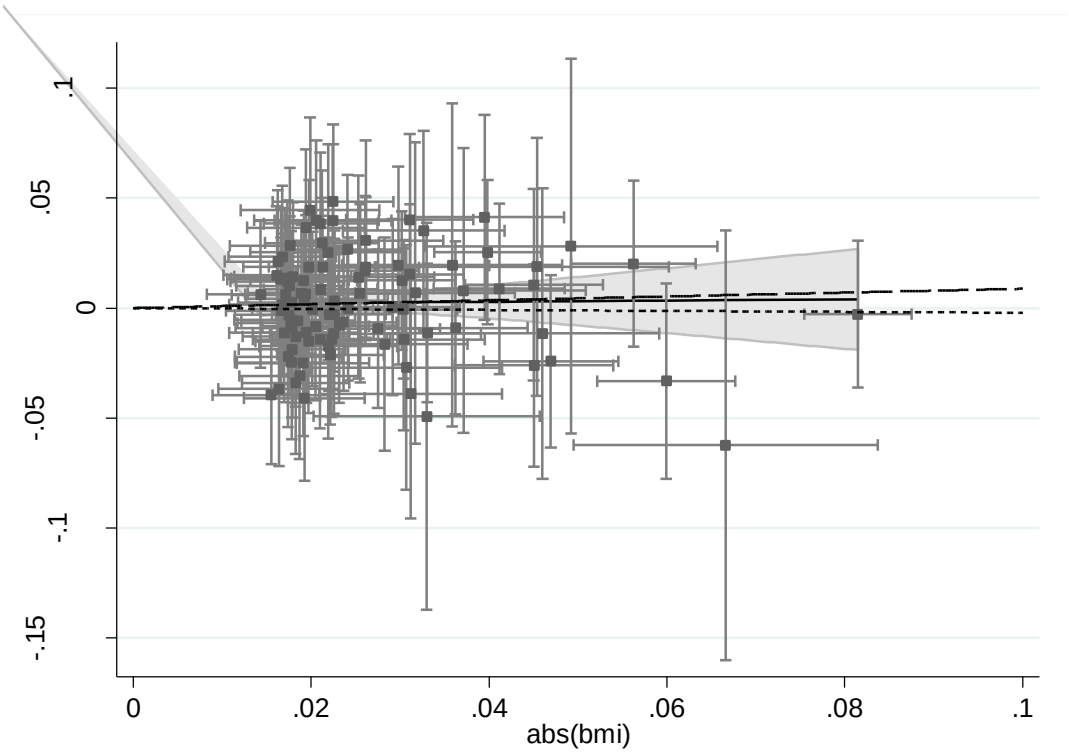
Supplemental Figure 3a: BMI SNPs and CHD



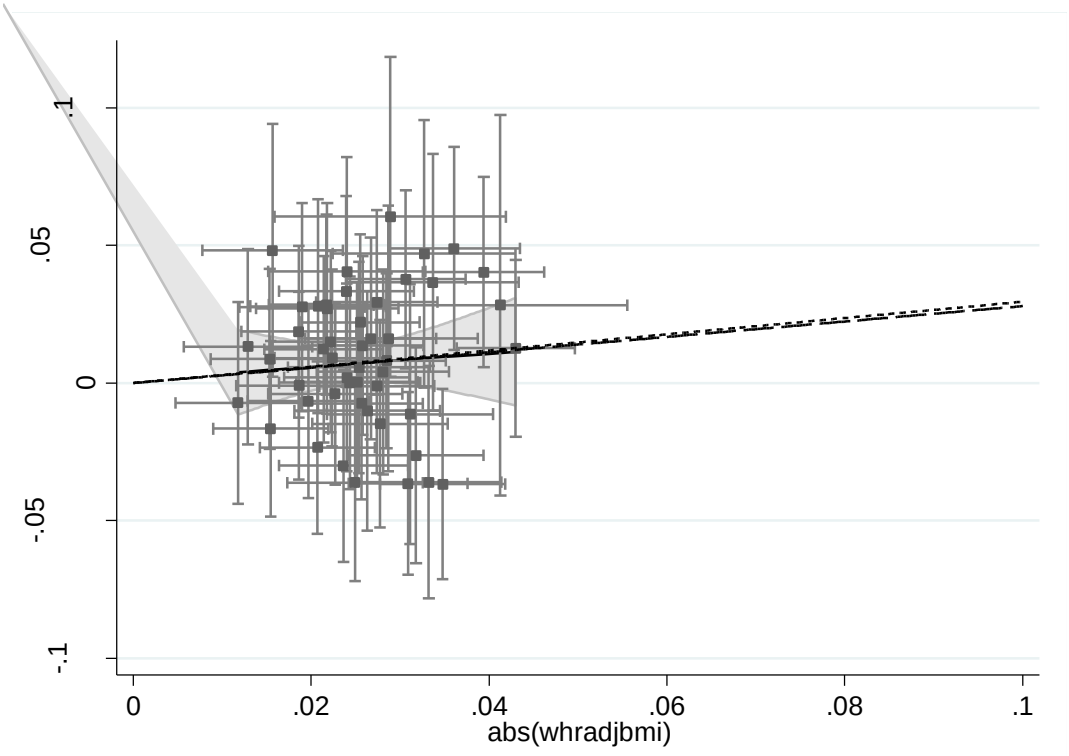
Supplemental Figure 3b: WHRadjBMI SNPs and CHD



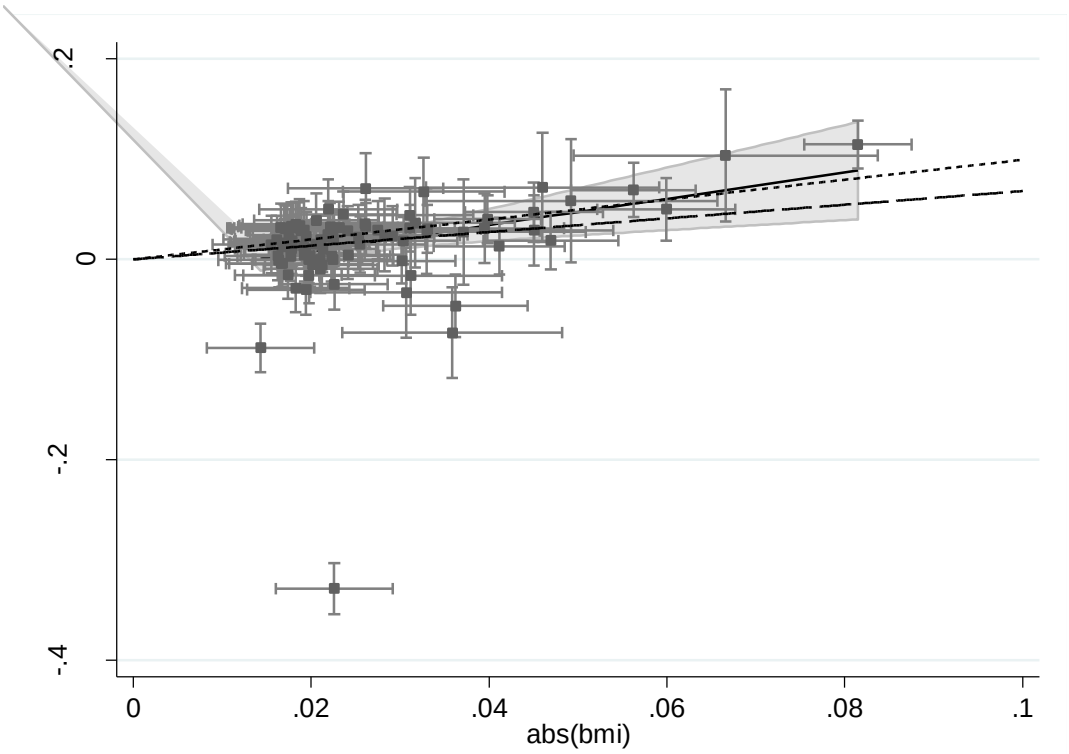
Supplemental Figure 3c: BMI SNPs and ischaemic stroke



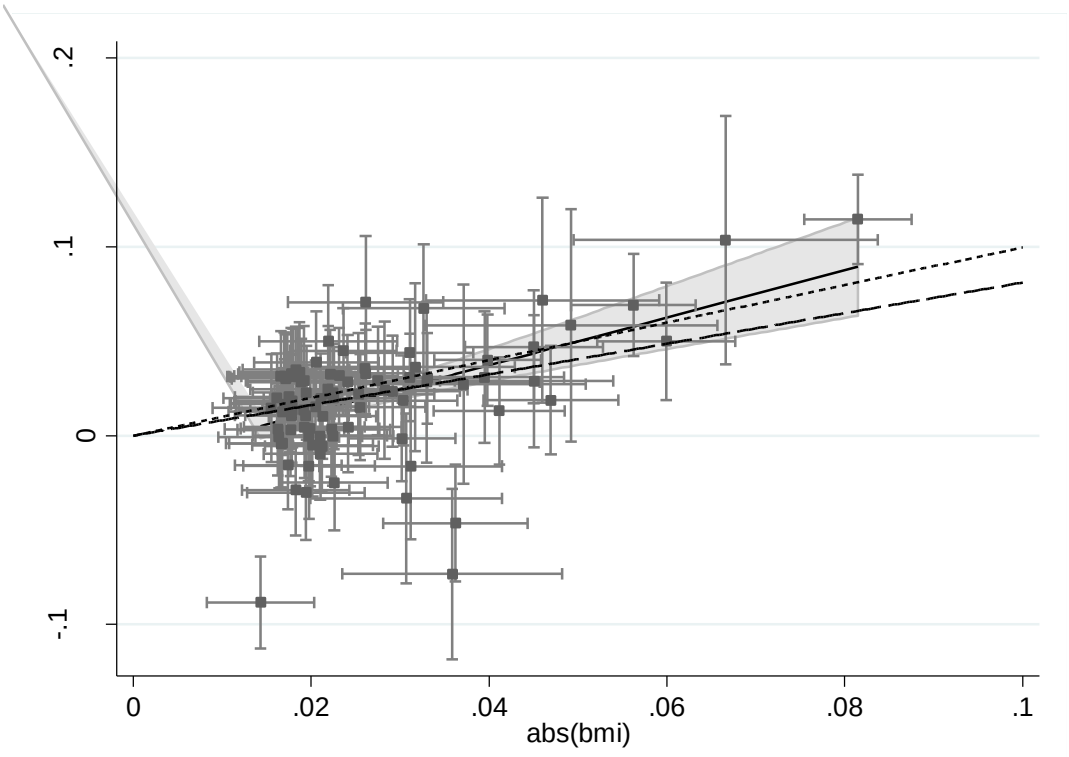
Supplemental Figure 3d: WHRadjBMI SNPs and ischaemic stroke



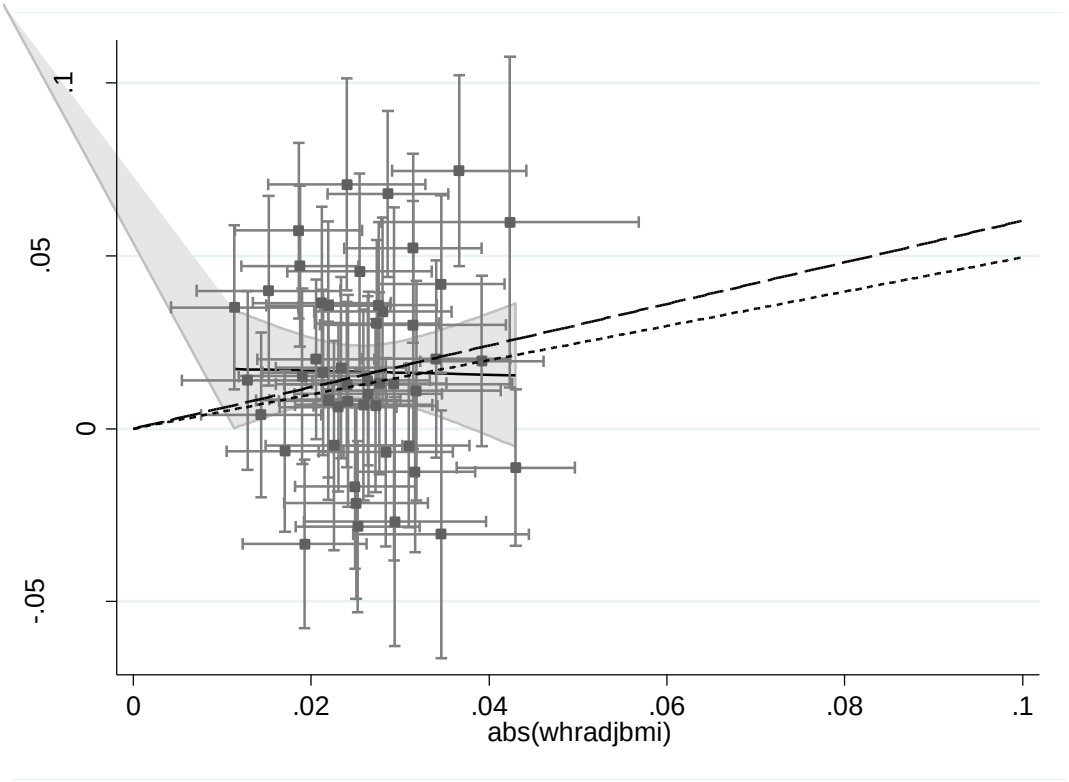
Supplemental Figure 3e: BMI SNPs and T2D



Supplemental Figure 3f: BMI snps (minus rs7903146) and T2D



Supplemental Figure 3g: WHRadjBMI SNPs and T2D



Supplemental References:

1. S S, Nelson Cp Fau - Gaunt TR, Gaunt Tr Fau - van der Harst P, van der Harst P Fau - Barnes T, Barnes T Fau - Braund PS, Braund Ps Fau - Lawlor DA, Lawlor Da Fau - Casas J-P, Casas Jp Fau - Padmanabhan S, Padmanabhan S Fau - Drenos F, Drenos F Fau - Kivimaki M, Kivimaki M Fau - Talmud PJ, Talmud Pj Fau - Humphries SE, Humphries Se Fau - Whittaker J, Whittaker J Fau - Morris RW, Morris Rw Fau - Whincup PH, Whincup Ph Fau - Dominiczak A, Dominiczak A Fau - Munroe PB, Munroe Pb Fau - Johnson T, Johnson T Fau - Goodall AH, Goodall Ah Fau - Cambien F, Cambien F Fau - Diemert P, Diemert P Fau - Hengstenberg C, Hengstenberg C Fau - Ouwehand WH, Ouwehand Wh Fau - Felix JF, Felix Jf Fau - Glazer NL, Glazer Nl Fau - Tomaszewski M, Tomaszewski M Fau - Burton PR, Burton Pr Fau - Tobin MD, Tobin Md Fau - van Veldhuisen DJ, van Veldhuisen Dj Fau - de Boer RA, de Boer Ra Fau - Navis G, Navis G Fau - van Gilst WH, van Gilst Wh Fau - Mayosi BM, Mayosi Bm Fau - Thompson JR, Thompson Jr Fau - Kumari M, Kumari M Fau - MacFarlane PW, MacFarlane Pw Fau - Day INM, Day In Fau - Hingorani AD, Hingorani Ad Fau - Samani NJ and NJ S. - Four genetic loci influencing electrocardiographic indices of left ventricular hypertrophy. *Circ Cardiovasc Genet*. 2011;4:626-35.
2. Bowden J, Davey Smith G, Haycock PC and Burgess S. Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. *Genetic epidemiology*. 2016;40:304-14.

Appendix

Consortia details

UCLEB

The UCLEB consortium consists of the following studies: Northwick Park Heart Study II (NPHS II), British Regional Heart Study (BRHS), Whitehall II Study (WHII), English Longitudinal Study of Ageing (ELSA), Medical Research Council National Survey of Health and Development (MRC NSHD), 1958 Birth cohort (1958BC), Caerphilly Prospective Study (CaPS), British Women's Heart and Health Study (BWHHS), Edinburgh Artery Study (EAS), Edinburgh Heart Disease Prevention Study (EHDPS), Edinburgh Type 2 Diabetes Study (ET2DS), Southall And Brent REvisited (SABRE), UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), and Asymptomatic Atherosclerosis Aspirin Trial (AAAT).

UCLEB consortium members include: Ben-Shlomo Y, Borges C, Casas JP, Charoen P, Chaturvedi N, Cooper J, Dale CE, Drenos F, Dudbridge F, Engmann JE, Fatemifar G, Finan C, Garfield V, Gaunt TR, Gentry-Maharaj A, Hingorani AD, Hughes A, Humphries SE, Hypponen E, Jefferis BJ, Kivimaki M, Kuh D, Kumari M, Langenberg C, Lawlor DA, Mclachlan S, Menon U, Plagnol V, Power C, Price JF, Price A, Schmidt AF, Shah T, Sofat R, Talmud P, Tillin T, Walker A, Wannamethee G, Whincup P, Whittaker J, Wong A

METASTROKE

Ischaemic stroke data were obtained from the METASTROKE consortium. The METASTROKE study consists of combined data from 15 GWAS of IS (12 389 cases vs 62 004 controls). We used TOAST criteria17 to classify IS as large artery stroke (LAS) (2167 cases/49 159 controls from 11 studies), cardioembolic stroke (CE) (2365 cases/ 56,140 controls from 13 studies), and small vessel disease (SVD) (1894 cases/51 976 controls from 12 studies). METASTROKE studies consisted of independently performed genome-wide single nucleotide polymorphism (SNP) genotyping using standard technologies and imputation to HapMap release 21 or 22 CEU phased genotype18 or 1000 Genomereference panels. Investigators contributed summary statistical data from association analyses using frequentist additive models for metaanalysis after application of appropriate quality control measures.

METASTROKE consortium members include: Rosand J, Rost NS, Meschia JF, Worrall BB, Markus HS, Bevan S, Hopewell JC, Sharma P, Boncoraglio G, Maguire JM, Holliday E, Pulit SL, Seshadri S,

Hopewell JC, Debette S, Reiner AP, Kooperberg CL, Kittner SJ, Cole J, Dichgans M, Malik R, Williams SR, Attia J, Levi CR

GIANT

BMI and WHRadjBMI data were obtained from the GIANT consortium. The **G**enetic **I**nvestigation of **AN**thropometric **T**raits (**GIANT**) consortium is an international collaboration that seeks to identify genetic loci that modulate human body size and shape, including height and measures of obesity. The GIANT consortium is a collaboration between investigators from many different groups, institutions, countries, and studies, and the results represent their combined efforts. The primary approach has been meta-analysis of genome-wide association data and other large-scale genetic data sets. Anthropometric traits that have been studied by GIANT include body mass index (BMI), height, and traits related to waist circumference (such as waist-hip ratio adjusted for BMI, or WHRadjBMI). Thus far, the GIANT consortium has identified common genetic variants at hundreds of loci that are associated with anthropometric traits.https://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium

CARDIoGRAMplusC4D

CARDIoGRAMplusC4D (Coronary ARtery DIsease Genome wide Replication and Meta-analysis (CARDIoGRAM) plus The Coronary Artery Disease (C4D) Genetics) 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.CARDIoGRAMplusC4D Metabochip is a two stage meta-analysis of Metabochip and GWAS studies of European and South Asian descent involving 63,746 cases and 130,681 controls. The CARDIoGRAM GWAS data was used as Stage 1 - data as published in: CARDIoGRAMplusC4D Consortium, Deloukas P, Kanoni S, Willenborg C, Farrall M, Assimes TL, Thompson JR, Ingelsson E, Saleheen D, Erdmann J, Goldstein BA, Stirrups K, König IR,Cazier JB, Johansson A, Hall AS, Lee JY, Willer CJ, Chambers JC, Esko T, Folkersen L, Goel A, Grundberg E, Havulinna AS, Ho WK, Hopewell JC, Eriksson N, Kleber ME, Kristiansson K,Lundmark P, Lyytikäinen LP, Rafelt S, Shungin D, Strawbridge RJ, Thorleifsson G, Tikkanen E,Van Zuydam N, Voight BF, Waite LL, Zhang W, Ziegler A, Absher D, Altshuler D, Balmforth AJ,Barroso I, Braund PS, Burgdorf C, Claudi-Boehm S, Cox D, Dimitriou M, Do R, DIAGRAM Consortium, CARDIOGENICS Consortium, Doney AS, El Mokhtari N, Eriksson P, Fischer K,Fontanillas P, Franco-Cereceda A, Gigante B, Groop L, Gustafsson S, Hager J, Hallmans G,Han BG, Hunt SE, Kang HM, Illig T, Kessler T, Knowles JW, Kolovou G, Kuusisto J,Langenberg C, Langford C, Leander K, Lokki ML, Lundmark A, McCarthy MI, Meisinger C,Melander O, Mihailov E, Maouche S, Morris AD, Müller-Nurasyid M, MuTHER Consortium,Nikus K, Peden JF, Rayner NW, Rasheed A, Rosinger S, Rubin D, Rumpf MP, Schäfer A,Sivananthan M, Song C, Stewart AF, Tan ST, Thorgeirsson G, van der Schoot CE, Wagner PJ,Wellcome Trust Case Control Consortium, Wells GA, Wild PS, Yang TP, Amouyel P, Arveiler D,Basart H, Boehnke M, Boerwinkle E, Brambilla P, Cambien F, Cupples AL, de Faire U,Dehghan A,

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DIAGRAM

The DIAGRAM (DIAbetes Genetics Replication And Meta-analysis) consortium is a grouping of researchers with shared interests in performing large-scale studies to characterise the genetic basis of type 2 diabetes, and a principal focus on samples of European descent. The membership and scope of DIAGRAM has developed as the scale of collaboration in the field has increased. The initial instance of DIAGRAM (retrospectively termed "DIAGRAM v1") enabled the combination of T2D genome wide association (GWA) studies from the UK (WTCCC), DGI and FUSION groups: this meta-analysis, and consequent replication, resulted in identification of six novel signals influencing T2D risk (Zeggini E, Scott LJ, Saxena R, Voight BF, Marchini JL, Hu T, de Bakker PI, Abecasis GR, Almgren P, Andersen G, Ardlie K, Boström KB, Bergman RN, Bonnycastle LL, Borch-Johnsen K, Burtt NP, Chen H, Chines PS, Daly MJ, Deodhar P, Ding CJ, Doney AS, Duren WL, Elliott KS, Erdos MR, Frayling TM, Freathy RM, Gianniny L, Grallert H, Grarup N, Groves CJ, Guiducci C, Hansen T, Herder C, Hitman GA, Hughes TE, Isomaa B, Jackson AU, Jørgensen T, Kong A, Kubalanza K, Kuruvilla FG, Kuusisto J, Langenberg C, Lango H, Lauritzen T, Li Y, Lindgren CM, Lyssenko V, Marvelle AF, Meisinger C, Midthjell K, Mohlke KL, Morken MA, Morris AD, Narisu N, Nilsson P, Owen KR, Palmer CN, Payne F, Perry JR, Pettersen E, Platou C, Prokopenko I, Qi L, Qin L, Rayner NW, Rees M, Roix JJ, Sandbaek A, Shields B, Sjögren M, Steinthorsdottir V, Stringham HM, Swift AJ, Thorleifsson G, Thorsteinsdottir U, Timpson NJ, Tuomi T, Tuomilehto J, Walker M, Watanabe RM, Weedon MN, Willer CJ; Wellcome Trust Case Control Consortium, Illig T, Hveem K, Hu FB, Laakso M, Stefansson K, Pedersen O, Wareham NJ, Barroso I, Hattersley AT, Collins FS, Groop L, McCarthy MI, Boehnke M, Altshuler D., Nature Genetics 2008;40(5):638-45). An incremental meta-analysis ("DIAGRAM v2" or "DIAGRAM+") adding GWA data from a further five studies (DGDG, KORA, Rotterdam, DeCODE, EUROSPAN for a total of 8,130 cases and 38,987 controls) together with extensive replication involving 20 other cohorts, was central to identification of a further 17 loci (Voight BF, Scott LJ, Steinthorsdottir V, Morris AP, Dina C, Welch RP, Zeggini E, Huth C, Aulchenko YS, Thorleifsson G, McCulloch LJ, Ferreira T, Grallert H, Amin N, Wu

G, Willer CJ, Raychaudhuri S, McCarroll SA, Langenberg C, Hofmann OM, Dupuis J, Qi L, Segrè AV, van Hoek M, Navarro P, Ardlie K, Balkau B, Benediktsson R, Bennett AJ, Blagieva R, Boerwinkle E, Bonnycastle LL, Bengtsson Boström K, Bravenboer B, Bumpstead S, Burtt NP, Charpentier G, Chines PS, Cornelis M, Couper DJ, Crawford G, Doney AS, Elliott KS, Elliott AL, Erdos MR, Fox CS, Franklin CS, Ganser M, Gieger C, Grarup N, Green T, Griffin S, Groves CJ, Guiducci C, Hadjadj S, Hassanali N, Herder C, Isomaa B, Jackson AU, Johnson PR, Jørgensen T, Kao WH, Klopp N, Kong A, Kraft P, Kuusisto J, Lauritzen T, Li M, Lieverse A, Lindgren CM, Lyssenko V, Marre M, Meitinger T, Midthjell K, Morken MA, Narisu N, Nilsson P, Owen KR, Payne F, Perry JR, Petersen AK, Platou C, Proença C, Prokopenko I, Rathmann W, Rayner NW, Robertson NR, Rocheleau G, Roden M, Sampson MJ, Saxena R, Shields BM, Shrader P, Sigurdsson G, Sparsø T, Strassburger K, Stringham HM, Sun Q, Swift AJ, Thorand B, Tichet J, Tuomi T, van Dam RM, van Haeften TW, van Herpt T, van Vliet-Ostaptchouk JV, Walters GB, Weedon MN, Wijmenga C, Witteman J, Bergman RN, Cauchi S, Collins FS, Gloyn AL, Gyllensten U, Hansen T, Hide WA, Hitman GA, Hofman A, Hunter DJ, Hveem K, Laakso M, Mohlke KL, Morris AD, Palmer CN, Pramstaller PP, Rudan I, Sijbrands E, Stein LD, Tuomilehto J, Uitterlinden A, Walker M, Wareham NJ, Watanabe RM, Abecasis GR, Boehm BO, Campbell H, Daly MJ, Hattersley AT, Hu FB, Meigs JB, Pankow JS, Pedersen O, Wichmann HE, Barroso I, Florez JC, Frayling TM, Groop L, Sladek R, Thorsteinsdottir U, Wilson JF, Illig T, Froguel P, van Duijn CM, Stefansson K, Altshuler D, Boehnke M, McCarthy MI; MAGIC investigators; GIANT Consortium., Nature Genetics 2010;42(7):579-89). Whilst in the Voight (2010) paper, GWA data from the Framingham, ARIC and NHS studies was only used for in silico replication, the full data from these studies was subsequently combined to constitute the largest current GWA dataset in samples of European descent ("DIAGRAMv3": 12,171 cases and 56,862 controls). This data set was used as the basis for the selection of SNPs for T2D replication for the Metabochip custom array, and a manuscript describing the integration of DIAGRAM v3 and Metabochip data (a combined total of ~150k individuals) was published in 2012 (Morris AP, Voight BF, Teslovich TM, Ferreira T, Segrè AV, Steinthorsdottir V, Strawbridge RJ, Khan H, Grallert H, Mahajan A, Prokopenko I, Kang HM, Dina C, Esko T, Fraser RM, Kanoni S, Kumar A, Lagou V, Langenberg C, Luan J, Lindgren CM, Müller-Nurasyid M, Pechlivanis S, Rayner NW, Scott LJ, Wiltshire S, Yengo L, Kinnunen L, Rossin EJ, Raychaudhuri S, Johnson AD, Dimas AS, Loos RJ, Vedantam S, Chen H, Florez JC, Fox C, Liu CT, Rybin D, Couper DJ, Kao WH, Li M, Cornelis MC, Kraft P, Sun Q, van Dam RM, Stringham HM, Chines PS, Fischer K, Fontanillas P, Holmen OL, Hunt SE, Jackson AU, Kong A, Lawrence R, Meyer J, Perry JR, Platou CG, Potter S, Rehnberg E, Robertson N, Sivapalaratnam S, Stancáková A, Stirrups K, Thorleifsson G, Tikkanen E, Wood AR, Almgren P, Atalay M, Benediktsson R, Bonnycastle LL, Burtt N, Carey J, Charpentier G, Crenshaw AT, Doney AS, Dorkhan M, Edkins S, Emilsson V, Eury E, Forsen T, Gertow K, Gigante B, Grant GB, Groves CJ, Guiducci C, Herder C, Hreidarsson AB, Hui J, James A, Jonsson A, Rathmann W, Klopp N, Kravic J, Krjutskov K, Langford C, Leander K, Lindholm E, Lobbens S, Männistö S, Mirza G, Mühleisen TW, Musk B, Parkin M, Rallidis L, Saramies J, Sennblad B, Shah S, Sigurðsson G, Silveira A, Steinbach G,

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GLOBAL LIPIDS GENETICS CONSORTIUM

Lipids data were obtained from the Global Lipids Genetics Consortium website (GLGC). GLGC started in 2006 with a genome-wide association analysis for plasma lipids within the Diabetes Genetics Initiative Study led by D. Altshuler and L. Groop. The collaborative research network involves >200 investigators from more than 80 institutions. GLGC includes 94,595 individuals from 23 studies genotyped with genome-wide association study (GWAS) arrays and 93,982 individuals from 37 studies genotyped with the Metabochip array. The Genomics Platform at the Broad Institute, led by S. Gabriel, has performed the bulk of the genotyping and sequencing.

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Acknowledgements

Mika Kivimaki is funded by Medical Research Council (K013351), NordForsk.

Frank Dudbridge is funded by Medical Research Council grant MR/K006215/1.

SEH is a British Heart Foundation Professor, supported by the British Heart Foundation (RG008/08) and by the NIHR, University College London Hospitals Biomedical Research Centre.

The Medical Research Council Unit for Lifelong Health and Ageing at UCL is supported by the UK Medical Research Council (MR_UU_12019/1).

The Medical Research Council Integrative Epidemiology Unit is supported by grants MC_UU_12013/1-9 (GDS, TRG, DAL, YBS).

The British Regional Heart study is supported by British Heart Foundation grants (RG/08/013/25942, RG/13/16/30528). The British Women's Heart and Health Study has been supported by funding from the British Heart Foundation (PG/13/66/304422). The British Heart Foundation had no role in the design and conduct of the studies; collection, management, analysis, and interpretation of the data; preparation,

review, or approval of the manuscript; and decision to submit the manuscript for publication. BRHS investigators acknowledge the British Regional Heart Study team for data collection.
The Caerphilly Prospective Study (CaPS) was set up by Prof. Peter Elwood, Medical Research Council Unit (South Wales).
The Edinburgh Artery Study (EAS) is funded by the British Heart Foundation (Programme Grant RG/98002), with Metabochip genotyping funded by a project grant from the Chief Scientist Office of Scotland (Project Grant CZB/4/672).
The Edinburgh Type 2 Diabetes Study (ET2DS) is funded by the Medical Research Council (Project Grant G0500877); the Chief Scientist Office of Scotland (Programme Support Grant CZQ/1/38); Pfizer plc (Unrestricted Investigator Led Grant); and Diabetes UK (Clinical Research Fellowship 10/0003985).
1958 Birth Cohort: DNA collection was funded by Medical Research Council grant G0000934 and cell-line creation by Wellcome Trust grant 068545/Z/02. The work was supported by the NIHR Biomedical Research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London and also by the Department of Health Policy Research Programme through the Public Health Research Consortium (PHRC). The views expressed in the publication are those of the authors and not necessarily those of the Department of Health. Information about the wider programme of the PHRC is available from http://phrc.lshtm.ac.uk.
The Whitehall II study was supported by the Medical Research Council (K013351), the British Heart Foundation, and the NIH (R01HL36310).
UKCTOCS was core funded by the Medical Research Council, Cancer Research UK, and the Department of Health with additional support from the Eve Appeal, Special Trustees of Bart's and the London, and Special Trustees of UCLH. Funding for this study was obtained from the UCLH NIHR University College London Hospitals Biomedical Research Centre.
ASCOT was funded by an investigator-initiated grant from Pfizer, USA. The study was investigator led and was conducted, analysed and reported independently of the company. The Genomewide Association Scan was funded by the NIHR as part of the portfolio of translational research of the NIHR Biomedical Research Unit at Barts and the NIHR Biomedical Research Centre at Imperial College, the International Centre for Circulatory Health Charity and the Medical Research Council through G952010. On behalf of the ASCOT investigators, we thank all ASCOT trial participants, physicians, nurses, and practices in the participating countries for their important contribution to the study.
The NEO study is supported by the participating Departments, the Division and the Board of Directors of the Leiden University Medical Center, and by the Leiden University, Research Profile Area Vascular and Regenerative Medicine. Dennis Mook-Kanamori is supported by Dutch Science Organization (ZonMW-VENI Grant 916.14.023). Raymond Noordam was supported by the European Commission funded project HUMAN (Health-2013-INNOVATION-1-602757). The authors of the NEO study thank all individuals who participated in the Netherlands Epidemiology in Obesity study, all participating general practitioners for inviting eligible participants and all research nurses for collection of the data. We thank

the NEO study group, Pat van Beelen, Petra Noordijk and Ingeborg de Jonge for the coordination, lab and data management of the NEO study. We also thank Arie Maan for the analyses of the electrocardiograms. The genotyping in the NEO study was supported by the Centre National de Génotypage (Paris, France), headed by Jean-Francois Deleuze.

The METASTROKE consortium is supported by NINDS (NS017950). We thank all study participants, volunteers, and study personnel that made this consortium possible, including the following:

.*ASGC*: Australian population control data were derived from the Hunter Community Study. We also thank the University of Newcastle for funding and the men and women of the Hunter region who participated in this study. This research was funded by grants from the Australian National and Medical Health Research Council (NHMRC Project Grant ID: 569257), the Australian National Heart Foundation (NHF Project Grant ID: G 04S 1623), the University of Newcastle, the Gladys M Brawn Fellowship scheme, and the Vincent Fairfax Family Foundation in Australia. Elizabeth G Holliday was supported by a Fellowship from the National Heart Foundation and National Stroke Foundation of Australia (ID: 100071). Jane Maguire was supported by an Australian Postgraduate Award.

*BRAINS***:** Bio-Repository of DNA in Stroke (BRAINS) is partly funded by a Senior Fellowship from the Department of Health (UK) to P Sharma, the Henry Smith Charity and the UK-India Education Research Institutive (UKIERI) from the British Council.

*GEOS***:** Genetics of Early Onset Stroke (GEOS) Study, Baltimore, USA was supported by the NIH Genes, Environment and Health Initiative (GEI) Grant U01 HG004436, as part of the GENEVA consortium under GEI, with additional support provided by the Mid-Atlantic Nutrition and Obesity Research Center (P30 DK072488), and the Office of Research and Development, Medical Research Service, and the Baltimore Geriatrics Research, Education, and Clinical Center of the Department of Veterans Affairs. Genotyping services were provided by the Johns Hopkins University Center for Inherited Disease Research (CIDR), which is fully funded through a federal contract from the NIH to the Johns Hopkins University (contract number HHSN268200782096C). Assistance with data cleaning was provided by the GENEVA Coordinating Center (U01 HG 004446; PI Bruce S Weir). Study recruitment and assembly of datasets were supported by a Cooperative Agreement with the Division of Adult and Community Health, Centers for Disease Control and Prevention and by grants from NINDS and the NIH Office of Research on Women's Health (R01 NS45012, U01 NS069208-01).

*HPS***:** Heart Protection Study (HPS) (ISRCTN48489393) was supported by the UK Medical Research Council (MRC), British Heart Foundation, Merck and Co (manufacturers of simvastatin), and Roche Vitamins Ltd (manufacturers of vitamins). Genotyping was supported by a grant to Oxford University and CNG from Merck and Co. Jemma C Hopewell acknowledges support from the British Heart Foundation (FS/14/55/30806).

*ISGS***:** Ischemic Stroke Genetics Study (ISGS)/Siblings With Ischemic Stroke Study (SWISS) was supported in part by the Intramural Research Program of the NIA, NIH project Z01 AG-000954-06. ISGS/SWISS used samples and clinical data from the NIH-NINDS Human Genetics Resource Center

DNA and Cell Line Repository (http://ccr.coriell.org/ninds), human subjects protocol numbers 2003-081 and 2004-147. ISGS/SWISS used stroke-free participants from the Baltimore Longitudinal Study of Aging (BLSA) as controls. The inclusion of BLSA samples was supported in part by the Intramural Research Program of the NIA, NIH project Z01 AG-000015-50, human subjects protocol number 2003-078. The ISGS study was funded by NIH-NINDS Grant R01 NS-42733 (J F Meschia). The SWISS study was funded by NIH-NINDS Grant R01 NS-39987 (J F Meschia). This study used the high-performance computational capabilities of the Biowulf Linux cluster at the NIH (http://biowulf.nih.gov).

*MGH-GASROS***:** MGH Genes Affecting Stroke Risk and Outcome Study (MGH-GASROS) was supported by NINDS (U01 NS069208), the American Heart Association/Bugher Foundation Centers for Stroke Prevention Research 0775010N, the NIH and NHLBI's STAMPEED genomics research program (R01 HL087676), and a grant from the National Center for Research Resources. The Broad Institute Center for Genotyping and Analysis is supported by grant U54 RR020278 from the National Center for Research resources.

*MILANO***:** Milano - Besta Stroke Register Collection and genotyping of the Milan cases within CEDIR were supported by the Italian Ministry of Health (Grant Numbers: RC 2007/LR6, RC 2008/LR6; RC 2009/LR8; RC 2010/LR8; GR-2011-02347041). FP6 LSHM-CT-2007-037273 for the PROCARDIS control samples.

*WTCCC2***:** Wellcome Trust Case-Control Consortium 2 (WTCCC2) was principally funded by the Wellcome Trust, as part of the Wellcome Trust Case Control Consortium 2 project (085475/B/08/Z and 085475/Z/08/Z and WT084724MA). The Stroke Association provided additional support for collection of some of the St George's, London cases. The Oxford cases were collected as part of the Oxford Vascular Study which is funded by the MRC, Stroke Association, Dunhill Medical Trust, National Institute of Health Research (NIHR) and the NIHR Biomedical Research Centre, Oxford. The Edinburgh Stroke Study was supported by the Wellcome Trust (clinician scientist award to C Sudlow), and the Binks Trust. Sample processing occurred in the Genetics Core Laboratory of the Wellcome Trust Clinical Research Facility, Western General Hospital, Edinburgh. Much of the neuroimaging occurred in the Scottish Funding Council Brain Imaging Research Centre (www.sbirc.ed.ac.uk), Division of Clinical Neurosciences, University of Edinburgh, a core area of the Wellcome Trust Clinical Research Facility and part of the SINAPSE (Scottish Imaging Network—A Platform for Scientific Excellence) collaboration (www.sinapse.ac.uk), funded by the Scottish Funding Council and the Chief Scientist Office. Collection of the Munich cases and data analysis was supported by the Vascular Dementia Research Foundation. M Farrall and A Helgadottir acknowledge support from the BHF Centre of Research Excellence in Oxford and the Wellcome Trust core award (090532/Z/09/Z).

*VISP***:** The GWAS component of the Vitamin Intervention for Stroke Prevention (VISP) study was supported by the United States National Human Genome Research Institute (NHGRI), Grant U01 HG005160 (PI Michèle Sale & Bradford Worrall), as part of the Genomics and Randomized Trials Network (GARNET). Genotyping services were provided by the Johns Hopkins University Center for

Inherited Disease Research (CIDR), which is fully funded through a federal contract from the NIH to the Johns Hopkins University. Assistance with data cleaning was provided by the GARNET Coordinating Center (U01 HG005157; PI Bruce S Weir). Study recruitment and collection of datasets for the VISP clinical trial were supported by an investigator-initiated research grant (R01 NS34447; PI James Toole) from the United States Public Health Service, NINDS, Bethesda, Maryland. Control data obtained through the database of genotypes and phenotypes (dbGAP) maintained and supported by the United States National Center for Biotechnology Information, US National Library of Medicine.

WHI: Funding support for WHI-GARNET was provided through the NHGRI GARNET (Grant Number U01 HG005152). Assistance with phenotype harmonisation and genotype cleaning, as well as with general study coordination, was provided by the GARNET Coordinating Center (U01 HG005157). Funding support for genotyping, which was performed at the Broad Institute of MIT and Harvard, was provided by the NIH Genes, Environment, and Health Initiative (GEI; U01 HG004424).

SiGN: The Stroke Genetics Network (SiGN) study was funded by a cooperative agreement grant from the National Institute of Neurological Disorders and Stroke (NINDS) U01 NS069208. Genotyping services were provided by the Johns Hopkins University Center for Inherited Disease Research (CIDR), which is fully funded through a federal contract from the National Institutes of Health (NIH) to the Johns Hopkins University (contract No.HHSN268200782096C). The Biostatistics Department Genetics Coordinating Center at the University of Washington (Seattle) provided more extensive quality control of the genotype data through a subcontract with CIDR. Additional support to the Administrative Core of SiGN was provided by the Dean's Office, University of Maryland School of Medicine. This work was supported by grants received from the German Federal Ministry of Education and Research (BMBF) in the context of the e:Med program (e:AtheroSysMed), the FP7 European Union project CVgenes@target (261123), the DFG as part of the CRC 1123 (B3), the Corona Foundation and the Fondation Leducq (Transatlantic Network of Excellence on the Pathogenesis of Small Vessel Disease of the Brain).