Mild-to-moderate kidney dysfunction and cardiovascular disease: observational and Mendelian randomisation analyses

Running Title: Gaziano et al.; *Kidney dysfunction and CVDs*

Liam Gaziano*[1,2], PhD; Luanluan Sun*[2], PhD; Matthew Arnold*[2], PhD; Steven Bell[2,3,4], PhD; Kelly Cho [1,5], MD MPH; Stephen K Kaptoge[2], PhD; Rebecca J Song[1,6], MPH; Stephen Burgess[2,7,8], PhD; Daniel C Posner[1], PhD; Katja Mosconi[2], PhD; Cassianne Robinson-Cohen[9], PhD; Amy Mason[2], PhD; Thomas R Bolton[2,4], PhD; Ran Tao[10], PhD; Elias Allara[2,4], MD PhD; Petra Schubert[1], MPH; Lingyan Chen[2], PhD; James R Staley[2],PhD; Natalie Staplin[11], PhD; Servet Altay[12], MD; Pilar Amiano[13,14,15], PharmD MSc; Volker Arndt[16], PhD; Johan Ärnlöv[17,18], PhD; Elizabeth L M Barr[19,20], PhD; Cecilia Björkelund[21], MD; Jolanda M A Boer[22], PhD; Hermann Brenner[17,23], MD; Edoardo Casiglia[24], MD; Paolo Chiodini[25], PhD; Jackie A Cooper[26], MSc; Josef Coresh[27], MD PhD; Mary Cushman[28], MD; Rachel Dankner[29,30,31], MD; Karina W Davidson[31], PhD; Renate T de Jongh[32], MD PhD; Chiara Donfrancesco[33], PhD; Gunnar Engström[34], MD; Heinz Freisling[35], PhD; Agustin Gómez de la Cámara[15,36], PhD; Vilmundur Gudnason[37], MD; Graeme J Hankey[38], MD; Per-Olof Hansson[39,40], MD PhD; Alicia K Heath[41], PhD; Ewout J Hoorn[42], MD PhD; Hironori Imano[43], MD; Simerjot K Jassal[45], MD; Rudolf Kaaks[45], PhD; Verena Katzke[45], PhD; Jussi Kauhanen[46], MD; Stefan Kiechl[47,48], MD; Wolfgang Koenig[49,50,51], MD; Richard A Kronmal[52], PhD; Cecilie Kyrø[53], PhD; Deborah A Lawlor[54,55], FMedSci; Börje Ljungberg[56], MD; Conor MacDonald[57], PhD; Giovanna Masala[58], MD; Christa Meisinger[59], MD; Olle Melander[34], MD; Conchi Moreno Iribas[60,61], PhD; Toshiharu Ninomiya[62], PhD; Dorothea Nitsch[63], MD PhD; Børge G Nordestgaard[64,65,66], MD PhD; Charlotte Onland-Moret[67], PhD; Luigi Palmieri[33], PhD; Dafina Petrova[15,68,69], PhD; Jose Ramón Quirós Garcia[70], PhD; Annika Rosengren[39,40], MD; Carlotta Sacerdote[71], MD; Masaru Sakurai[72], MD; Carmen Santiuste[15,73], MD; Matthias B Schulze[74,75,76], PhD; Sabina Sieri[77], PhD; Johan Sundström[78], MD; Valérie Tikhonoff[79], MD PhD; Anne Tjønneland[53,80], MD; Tammy Tong[81], PhD; Rosario Tumino[82], MD; Ioanna Tzoulaki[41], PhD; Yvonne T van der Schouw[67], PhD; W M Monique Verschuren[22,67], PhD; Henry Völzke[83], MD; Robert B Wallace[84], MD; S Goya Wannamethee[85], PhD; Elisabete Weiderpass[35], PhD; Peter Willeit[2,48], MD PhD; Mark Woodward[86,87], PhD; Kazumasa Yamagishi[88], MD; Raul Zamora-Ros[89], PhD; Elvis A Akwo[9], MD PhD; Saiju Pyarajan[5,90], PhD; David R Gagnon[91], MD MPH PhD; Philip S Tsao[92,93], PhD; Sumitra Muralidhar[94], PhD; Todd L Edwards[95,96], PhD; Scott M Damrauer[97], MD; Jacob Joseph[1,98], MD PhD; Lisa Pennells[2], PhD; Peter WF Wilson[99,100], MD; Seamus Harrison[2], MD PhD; Thomas A Gaziano[98,101], MD PhD; Michael Inouye[2,6,20,102,103], PhD; the Million Veteran Program, Colin Baigent[11], FMedSci; Juan P Casas[1,5], MD PhD; Claudia Langenberg[104,105], PhD; Nick Wareham[104], MD; Elio Riboli[41], MD; J Michael Gaziano†[1,5], MD MPH; John Danesh†[2,4,7,102,106], FMedSci; Adriana M Hung†[107], MD MPH; Adam S Butterworth†[2,4,10,102], PhD; Angela M Wood†[2,4,7,102,103,108], PhD; Emanuele Di Angelantonio†[2,4,7,102,109], FRCP.

*Contributed equally.

†Contributed equally.

1. Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), VA Boston Healthcare System, Boston, MA, USA
2. BHF Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
3. Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK
4. NIHR Blood and Transplant Research Unit in Donor Health and Behaviour, University of Cambridge, UK
5. Division of Aging, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

6. Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA
7. BHF Centre of Research Excellence, School of Clinical Medicine, Addenbrooke's Hospital, University of Cambridge, UK
8. Medical Research Council Biostatistics Unit, University of Cambridge, UK
9. Division of Nephrology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA
10. Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, USA
11. Medical Research Council Population Health Research Unit, Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK
12. Department of Cardiology, Trakya University School of Medicine, Edirne Turkey
13. Ministry of Health of the Basque Government, Sub Directorate for Public Health and Addictions of Gipuzkoa, San Sebastián, Spain
14. Biodonostia Health Research Institute, Epidemiology of Chronic and Communicable Diseases Group, San Sebastián, Spain
15. Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain
16. Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany
17. Division of Family Medicine and Primary Care, Department of Neurobiology, Care Sciences and Society (NVS), Karolinska Institutet, Stockholm, Sweden
18. School of Health and Social Studies, Dalarna University, Falun, Sweden
19. Wellbeing & Preventable Chronic Diseases (WPCD) Division, Menzies School of Health Research, Charles Darwin University, Darwin, NT, Australia
20. Baker Heart and Diabetes Institute, Melbourne, VIC, Australia
21. Institute of Medicine, School of Public Health and Community Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
22. National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands
23. Network Aging Research (NAR), Heidelberg University, Heidelberg, Germany
24. Studium Patavinum, University of Padua, Italy
25. Dipartimento di Salute Mentale e Fisica e Medicina Preventiva, Università degli Studi della Campania 'Luigi Vanvitelli', Caserta, Italy
26. William Harvey Research Institute, NIHR Barts Biomedical Research Centre, Queen Mary University of London, London, UK
27. Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
28. Larner College of Medicine, The University of Vermont, Burlington, VT, USA
29. The Gertner Institute for Epidemiology and Health Policy Research, Sheba Medical Center, Tel Hashomer, Israel
30. School of Public Health, Department of Epidemiology and Preventive Medicine, Tel Aviv University, Ramat Aviv, Tel Aviv, Israel
31. Feinstein Institutes for Medical Research, Northwell Health, Manhasset, New York, NY, USA
32. Amsterdam University Medical Centers, VUMC, Amsterdam, the Netherlands
33. Department of Cardiovascular, Endocrine-metabolic Diseases and Aging, Istituto Superiore di Sanità, Rome, Italy
34. Department of Clinical Sciences, Malmö, Lund University, Sweden
35. International Agency for Research on Cancer (IARC), World Health Organization, Lyon, France
36. 12 Octubre Hospital Research Institute, Madrid, Spain
37. Faculty of Medicine, University of Iceland, Reykjavik, Iceland and Icelandic Heart Association, Kopavogur, Iceland
38. Medical School Faculty of Health & Medical Sciences, The University of Western Australia, Perth, WA, Australia
39. Region Västra Götaland, Sahlgrenska University Hospital, Department of Medicine Geriatrics and Emergency Medicine/Östra, Gothenburg, Sweden
40. Institute of Medicine, Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
41. School of Public Health, Imperial College London, London, UK
42. Department of Internal Medicine, Division of Nephrology and Transplantation, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands
43. Public Health, Department of Social Medicine, Osaka University Graduate School of Medicine, Suita, Japan
44. Division of General Internal Medicine, University of California, San Diego and VA San Diego Healthcare, San Diego, La Jolla, CA, USA
45. Department of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany
46. University of Eastern Finland (UEF), Kuopio, Finland
47. Department of Neurology & Neurosurgery, Medical University of Innsbruck, Innsbruck, Austria
48. Clinical Epidemiology Team, Institute of Health Economics, Medical University of Innsbruck, Innsbruck, Austria
49. Institute of Epidemiology and Medical Biometry, University of Ulm, Ulm, Germany
50. Deutsches Herzzentrum München, Technische Universität München, Munich, Germany
51. German Centre for Cardiovascular Research (DZHK), Partner Site Munich Heart Alliance, Munich, Germany
52. School of Public Health, University of Washington, Seattle, WA, USA
53. Danish Cancer Society Research Center, Copenhagen, Denmark
54. Medical Research Council Integrative Epidemiology Unit, University of Bristol, Bristol UK
55. Population Health Science, Bristol Medical School, Bristol, UK
56. Department of Surgical and Perioperative sciences, Urology and Andrology, Umeå University, Umeå, Sweden
57. University Paris-Saclay, UVSQ, Inserm, Villejuif, France
58. Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Florence, Italy
59. Helmholtz Zentrum München, Munich, Germany
60. Navarra Public Health Institute, IdiSNA, Pamplona, Spain
61. Red de Investigación en Servicios de Salud en Enfermedades Crónicas (REDISSEC), Pamplona, Spain
62. Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
63. London School of Hygiene & Tropical Medicine, London, UK
64. Herlev and Gentofte Hospital, Copenhagen University Hospital, Copenhagen, Denmark
65. Frederiksberg Hospital, Copenhagen University Hospital, Denmark
66. Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

67. Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
68. Escuela Andaluza de Salud Pública (EASP), Granada, Spain
69. Instituto de Investigación Biosanitaria ibs.GRANADA, Granada, Spain
70. Consejería de Sanidad del Principado de Asturias Oviedo, Asturias, Spain
71. Unit of Cancer Epidemiology, Città della Salute e della Scienza University-Hospital, Turin Italy
72. Department of Social and Environmental Medicine, Kanazawa Medical University, Uchinada, Japan
73. Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Murcia, Spain
74. German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany
75. German Center for Diabetes Research (DZD), Neuherberg, Germany
76. Institute of Nutritional Science, University of Potsdam, Potsdam, Germany
77. Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milano, Italy
78. Department of Medical Sciences, Uppsala University, Uppsala, Sweden
79. Department of Medicine, University of Padua, Padua, Italy
80. Department of Public Health, University of Copenhagen, Copenhagen, Denmark
81. Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK
82. Hyblean Association for Epidemiological Reserach AIRE - ONLUS, Ragusa, Italy
83. Universitätsmedizin Greifswald, Institut für Community Medicine, Abteilung SHIP/ Klinisch-Epidemiologische Forschung, Greifswald, Germany
84. College of Public Health, University of Iowa, Iowa, IA, USA
85. University College London, London, UK
86. The George Institute for Global Health, Camperdown, NSW, Australia
87. The George Institute for Global Health, Imperial College London, UK
88. Department of Public Health Medicine, Faculty of Medicine, and Health Services Research and Development Center, University of Tsukuba, Tsukuba, Japan
89. Unit of Nutrition and Cancer, Epidemiology Research Program, Catalan Institute of Oncology, Bellvitge Biomedical Research Institute (IDIBELL), L'Hospitalet de Llobregat (Barcelona), Spain
90. Center for Data and Computational Sciences, VA Boston Healthcare System, Boston, MA USA
91. Department of Biostatistics, Boston University School of Public Health, Boston, MA USA
92. VA Pal Alto Epidemiology Research and Information Center for Genomics, VA Palo Alto Health Care System, Palo Alto, CA USA
93. Medicine (Cardiovascular Medicine), Stanford University of School of Medicine, Stanford, CA USA
94. Office of Research and Development, Veterans Health Administration, Washington, DC USA
95. Department of Veterans Affairs, Tennessee Valley Health Care System, Vanderbilt University, Nashville, TN, USA
96. Medicine/Epidemiology, Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Nashville, TN, USA
97. Department of Surgery, Corporal Michael Crescenz VA Medical Center and Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
98. Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
99. Internal Medicine, VA Atlanta Healthcare System, Decatur, GA, USA
100. Emory University School of Medicine (Cardiology), Emory University, Atlanta, GA, USA
101. Center for Health Decision Science, Harvard T.H. Chan School of Public Health, Boston, MA USA
102. Health Data Research UK Cambridge, Wellcome Genome Campus and University of Cambridge, UK
103. The Alan Turing Institute, London, UK
104. MRC Epidemiology Unit, School of Clinical Medicine, University of Cambridge, Cambridge, UK
105. Computational Medicine, Berlin Institute of Health at Charité – Universitätsmedizin Berlin, Germany
106. Department of Human Genetics, Wellcome Sanger Institute, Hinxton, UK
107. Division of Nephrology & Hypertension, Department of Medicine, Tennessee Valley Health Care System and Vanderbilt University Medical Center, Nashville, TN, USA
108. Cambridge Centre for AI in Medicine, Cambridge, UK
109. Health Data Science Research Centre, Human Technopole, Milan, Italy

Corresponding author: Professor Emanuele Di Angelantonio

Department of Public Health and Primary Care

University of Cambridge

Strangeways Research Laboratory

Cambridge, CB1 8RN.

Tel. +44(0)1223748659

E-mail: ed303@medschl.cam.ac.uk; emanuele.diangelantonio@fht.org

Manuscript word count: 2,941

ABSTRACT (word count 259)

Background: End-stage renal disease is associated with a high risk of cardiovascular events. It is unknown, however, whether mild-to-moderate kidney dysfunction is causally related to coronary heart disease (CHD) and stroke.

Methods: Observational analyses were conducted using individual-level data from four population data sources (Emerging Risk Factors Collaboration, EPIC-CVD, Million Veteran Program, UK Biobank), comprising 648,135 participants with no history of cardiovascular disease or diabetes at baseline, yielding 42,858 and 15,693 incident CHD and stroke events, respectively, during 6.8 million person-years of follow-up. Using a genetic risk score (GRS) of 218 variants for estimated glomerular filtration rate (eGFR), we conducted Mendelian randomisation analyses involving 413,718 participants (25,917 CHD and 8,622 strokes) in EPIC-CVD, Million Veteran Program, and UK Biobank.

Results: There were U-shaped observational associations of creatinine-based eGFR with CHD and stroke, with higher risk in participants with eGFR values <60 or >105 mL/min/1.73m^2, compared to those with eGFR between 60 and 105 mL/min/1.73m^2. Mendelian randomization analyses for CHD showed an association among participants with eGFR <60 mL/min/1.73m^2, with a 14% (95%CI, 3%-27%) higher CHD risk per 5 mL/min/1.73m^2 lower genetically-predicted eGFR, but not for those with eGFR >105 mL/min/1.73m^2. Results were not materially different after adjustment for factors associated with the eGFR GRS, such as lipoprotein(a), triglycerides, hemoglobin A1c, and blood pressure. Mendelian randomization results for stroke were non-significant but broadly similar to those for CHD.

Conclusions: In people without manifest cardiovascular disease or diabetes, mild-to-moderate kidney dysfunction is causally related to risk of CHD, highlighting the potential value of preventive approaches that preserve and modulate kidney function.

Keywords: renal function, renal disease, cardiovascular diseases, coronary heart disease, stroke

CLINICAL PERSPECTIVE

What is new?

- In people without manifest cardiovascular disease or diabetes there is a non-linear causal relationship between kidney function and CHD.
- Even mildly reduced kidney function is causally associated with higher risk of coronary heart disease with a possible risk threshold for eGFR value of around 75 ml/min/1.73 m^2.
- The impact of reduced kidney function on coronary heart disease is independent of traditional cardiovascular risk factors.

What are the clinical implications?

- Preventive approaches that can preserve and modulate kidney function can help prevent cardiovascular diseases
- Given the non-linear causal relationship, it may be a preferable strategy to identify individuals in the population with mild-to-moderate kidney dysfunction and target them for renoprotective interventions alongside routine strategies to reduce cardiovascular risk.

Non-standard Abbreviations and Acronyms

Cardiovascular diseases (CVD)

Chronic kidney disease (CKD)

Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)

Coronary heart disease (CHD) a

Emerging Risk Factors Collaboration (ERFC),

Estimated glomerular filtration rate (eGFR)

European Prospective Investigation into Cancer and Nutrition – Cardiovascular Disease Study (EPIC-CVD),

Genetic risk score (GRS)

Hazard ratios (HRs) Million Veteran Program (MVP),

UK Biobank (UKB),

INTRODUCTION

Chronic kidney disease (CKD), a major public health burden, affects more than 10% of the adult population globally.[1,2] Kidney failure is associated with a high risk of cardiovascular diseases (CVD) and all-cause mortality.[3-5] Strong associations have also been reported between non-dialysis dependent CKD and these outcomes both in people without manifest CVD and in patients with ischemic cardiovascular disease, heart failure, high blood pressure, or diabetes.[2,6,7] These observations have led to guideline recommendations that patients with CKD should be regarded as being at very high risk of CVD.[8,9]

It is not known, however, whether mild-to-moderate kidney dysfunction is causally relevant to CVD or if the increase in CVD risk associated with kidney dysfunction is related to changes in known risk factors, such as blood pressure and dyslipidemia, which seem to be a direct result of kidney dysfunction.[10-12] An approach to help evaluate the causal relevance of kidney dysfunction to CVD is Mendelian randomization. Mendelian randomization uses genetic variants specifically related to a particular exposure to compare genetically-defined population subgroups with different average levels of the exposure. The independent segregation of alleles at conception means that these genetically-defined subgroups should not differ systematically with respect to confounding variables, creating a natural experiment analogous to a randomized trial. Therefore, compared with conventional observational analyses, Mendelian randomization analyses provide more reliable insights into causal relationships between risk factors and disease outcomes.[13-14]

Previous Mendelian randomization analysis that have assumed a linear dose-response relationship between kidney function and CVD have reported null associations.[14,15] However, observational analyses have reported *U-shaped* associations of CVD risk with creatinine-based estimated glomerular filtration rate (eGFR), a measure of kidney function. Therefore, drawing on multiple large-scale population bioresources, we evaluated the causal relevance of eGFR to coronary heart disease (CHD) and stroke, using Mendelian randomization methods tailored to non-linear

relationships[16-20], that require concomitant information on eGFR, genetic determinants of eGFR, and first-ever CVD outcomes in the same individuals.

METHODS

The data, code, and study material that support the findings of this study are available from the corresponding author on reasonable request.

Study design and study overview

This study involved inter-related components (**Figure 1**). First, we characterized observational associations between eGFR and incident CHD or stroke, using data from the Emerging Risk Factors Collaboration (ERFC),[21] European Prospective Investigation into Cancer and Nutrition – Cardiovascular Disease Study (EPIC-CVD),[22] Million Veteran Program (MVP),[23] UK Biobank (UKB),[24] collectively involving 648,135 participants, who had serum creatinine measurements but no known CVD or diabetes at baseline. Second, we constructed a genetic risk score (GRS) for eGFR by computing a weighted sum of eGFR-associated index variants reported in a discovery GWAS from the CKDGen consortium comprising 567,460 European ancestry participants[25], none of whom were from MVP, EPIC-CVD, or UKB. Third, we used this GRS to conduct Mendelian randomization analyses in a total of 413,718 participants (i.e., EPIC-CVD, MVP, UKB), with concomitant individual-level information on genetics, serum creatinine, and disease outcomes. Fourth, to assess the potential for interference by horizontal pleiotropy[26] and explore potential mechanisms that could mediate associations between eGFR and CVD outcomes, we studied our GRS for eGFR in relation to several established and emerging risk factors for CVD.

Data sources

Information on each of the data sources used in the analysis is provided in the **Expanded Methods**. Briefly, ERFC, a global consortium of population cohort studies with harmonized individual-participant data for multiple CVD risk factors, has included 47 studies with available information on serum creatinine, and diabetes status at recruitment.[21] EPIC-CVD, a case-cohort study embedded

in the pan-European EPIC prospective study of over 500,000 participants, has recorded data on serum creatinine and imputed genome-wide array data from 21 of its 23 recruitment centers.[22] MVP, a prospective cohort study recruited from 63 Veterans Health Administration medical facilities throughout the US, has recorded serum creatinine and imputed genome-wide array data are available for a large subset of its participants.[23] UKB, a prospective study of 22 recruitment centers across the UK, has cohort-wide information on serum creatinine and imputed genome-wide array data.[24] Relevant ethical approval and participant consent were already obtained in all studies that contributed data to this work.

Estimation of kidney function

Kidney function was estimated using creatinine-based eGFR, calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[27] Creatinine concentration was multiplied by 0.95 for studies where measurements were not standardized to isotope-dilution mass spectrometry.[25,28] In a subset of participants with available data, kidney function was also defined using the CKD-EPI cystatin-C-based equation[29] and albuminuria measured as spot urine albumin-to-creatinine ratio (**Expanded Methods**).

Observational analyses

Primary outcomes were incident CHD and stroke. Details of endpoint definitions for each study are provided in **Table S1**. Participants in the contributing studies were eligible for inclusion in the current analysis if they met all of the following criteria: (1) aged 30-80 years old at recruitment; (2) had recorded information on age, sex, circulating creatinine, and diabetes status; (3) had a creatinine-based eGFR of <300 mL/min/1.73 m^2; (4) did not have a known history of CVD or diabetes at baseline; (5) had complete information on the following risk factors: smoking status, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, and body-mass index; and (6) had at least 1 year of follow-up data following recruitment.

Hazard ratios (HRs) for associations of creatinine-based eGFR with incident CHD and stroke were calculated using Cox regression, stratified by sex and study center, and where appropriate, adjusted for traditional vascular risk factors (defined here as systolic blood pressure, smoking status, total cholesterol, high-density lipoprotein cholesterol, body-mass index) on a "complete-case" basis. To account for EPIC-CVD's case-cohort design, Cox models were adapted using Prentice weights.[30] To avoid overfitting models, studies contributing fewer than 20 incident events to the analysis of a particular outcome were excluded from the analysis. Fractional polynomials were used to characterize non-linear relationships of creatinine-based eGFR with risk of CHD, and stroke, adjusted for age and CVD risk factors.[31] Study-specific estimates for each outcome were pooled across studies using multivariable random-effects meta-analysis, using a reference point of 90 mL/min/1.73 m^2. When information on urinary biomarkers in UKB was available, participants were grouped into tenths based on levels of urinary albumin-to-creatinine ratio to assess the shapes of associations between urinary biomarkers and CVD risk, using participants without albuminuria as the reference group.[32]

Genetic risk score for kidney function

Using individual-participant data from EPIC-CVD, MVP and UKB, we calculated a genetic risk score (GRS)[33] weighted by the conditional effect-estimated of the genetic variants associated ($P<5x10^{-8}$) with creatinine-based eGFR in CKDGen,[25] a global genetics consortium that has published GWAS summary statistics for creatinine-based eGFR. Of the 262 variants associated with creatinine-based eGFR, 37 were excluded due to ancestry-heterogeneity as reported in CKDGen,[25] 4 were excluded due to associations ($P<5x10^{-8}$) with vascular risk factors as reported in previous GWAS studies (i.e., smoking status, alcohol consumption, education attainment),[34] and 3 were excluded due to missingness in at least one of the contributing studies, leaving 218 variants for the primary GRS for creatinine-based eGFR.

In sensitivity analysis, we constructed two restricted GRSs using 126 and 121 genetic variants that were likely to be relevant for kidney function on the basis of their associations with cystatin-C-based

eGFR,[35] and blood urine nitrogen (BUN)[25], respectively. Sensitivity analysis was also conducted using a GRS that included all 262 trans-ancestry eGFR-associated index variants. Furthermore, to evaluate traits that could mediate or confound (through horizontal pleiotropy) the associations between genetically-predicted eGFR and outcomes, we tested associations of GRSs for eGFR with a range of cardiovascular risk factors in UKB and EPIC-CVD, and with 167 metabolites measured using targeted high-throughput NMR metabolomics (Nightingale Health Ltd) in UKB.

Mendelian randomization analyses

To account for the non-linear relationship between eGFR and risk of CVD outcomes in observational analyses, we performed a stratified Mendelian randomization analysis, using methods previously described.[16-20] For each participant, we calculated the residual eGFR by subtracting the genetic contribution determined by the GRS from observed eGFR. Participants were grouped based on their residual eGFR into 5-unit categories between 45 to <105 mL/min/1.73 m^2, plus <45 and ≥105 mL/min/1.73 m^2. By stratifying on residual eGFR we compare individuals in the population who would have an eGFR in the same category if they had the same genotype and reduce the potential influence of collider bias. We then calculated Mendelian randomization estimates for each eGFR category using the ratio method with the GRS as an instrumental variable, adjusting for age, age-squared, sex, study center, the first 10 principal components. Stratum-specific estimates were combined across studies using fixed-effect meta-analysis and plotted as a piecewise-linear function of eGFR, with point-wise confidence intervals calculated by resampling the stratum-specific estimates. Detailed methods describing statistical analysis are in the **Expanded Methods**. Analyses used Stata 15.1 and R 3.6.1.

RESULTS

Among the 648,135 participants without history of CVD or diabetes at baseline, the mean age was 57 years, 57% were men, and 4.4% had creatinine-based eGFR <60 mL/min/1.73 m^2 (**Table 1**, **Tables S2-S3**). During 6.8 million person-years of follow-up, there were 42,858 incident CHD outcomes and 15,693 strokes. Up to 413,718 European-ancestry participants from EPIC-CVD, MVP and UKB contributed to the main genetic analyses (**Figure 1**). Distributions of serum creatinine concentration and creatinine-based eGFR were broadly similar across studies (**Figures S1-2**).

Observational associations of eGFR with cardiovascular outcomes

For both CHD and stroke, there were U-shaped associations of creatinine-based eGFR. Compared with participants with creatinine-based eGFR values between 60 and 105 mL/min/1.73m^2, risks of both CHD and stroke were higher in people with eGFR <60 or >105 mL/min/1.73 m^2 (**Figure 2** and **Figure S3**). The shapes of these associations did not change substantially after adjustment for several traditional risk factors (**Figure 2**). Associations were similar in men and women, in clinically relevant subgroups (i.e., smokers, people with obesity, or hypertension; **Figure S4**), in the different studies contributing to this analysis (**Figure S5**), and when participants with a history of diabetes or missing information on cardiovascular risk factors were included (**Figures S6-S7**). Similar associations were also observed for ischemic stroke (**Figure S3**).

In the 338,044 participants in UKB with available data on serum cystatin C and urinary albumin-creatinine ratio, there were broadly similar associations of CHD or stroke with *cystatin-C*-based eGFR as *creatinine*-based eGFR equations - but only when eGFR values were lower than approximately 90 mL/min/1.73 m^2. However, there was no evidence of higher risk of CHD in participants with *cystatin-C*-based eGFR values above 105 mL/min/1.73 m^2 (**Figure S8**), in contrast with *creatinine*-based eGFR values above 105 mL/min/1.73 m^2. Levels of urinary microalbumin and urinary albumin-creatinine ratio showed approximately linear associations with risk of CHD and stroke, which were somewhat attenuated after adjustment for traditional risk factors (**Figure S9**).

Compared with participants with a creatinine-based eGFR of 75 to<90 mL/min/1.73 m^2 and without albuminuria, participants with albuminuria had higher risk of CHD and stroke (**Figure S10**).

Mendelian randomization of genetically-predicted eGFR with cardiovascular outcomes

The GRS for eGFR (**Table S4)** explained 2.0% of variation in creatinine-based eGFR in EPIC-CVD, 2.2% in MVP, and 3.2% in UKB. A one SD increase in the GRS for eGFR was associated with 0.18 SD higher creatinine-based eGFR (**Table S5** and **Figure S11**). The GRS for eGFR was not associated with body-mass index, diabetes, smoking status, or LDL-cholesterol concentrations, but showed modest associations with lipoprotein(a), triglycerides, blood pressure, and hemoglobin A1c measurement (**Figure S11**). Modest associations were also observed between the GRS for eGFR and triglyceride-related lipoprotein subclasses in a subset of participants with available data (**Figure S12**).

In non-linear Mendelian randomization analysis, we observed a curvilinear relationship between genetically-predicted eGFR and CHD (**Figure 3**). Among participants with eGFR <60 mL/min/1.73 m^2, each 5 mL/min/1.73 m^2 lower genetically-predicted eGFR was associated with 14% (95% CI: 3%-27%) higher risk of CHD (**Table 2**). There was no clear evidence of association among participants with eGFR above 75 mL/min/1.73 m^2 (**Figure 3**). Similar, but not statistically significant, associations were observed for stroke (**Table 2, Figure 3**). Overall, stratum-specific localized average causal estimates and non-linear Mendelian randomization estimates were compatible across the studies contributing to this analysis (**Table S6**, **Figure S13**). Similar associations were observed in analyses that adjusted for systolic blood pressure, lipoprotein(a), hemoglobin A1c, and triglycerides (**Figure S14**), included participants with a history of diabetes at baseline (**Figure S15**), or used ischemic stroke as the stroke outcome (**Figure S16**). Results were also similar using GRSs for cystatin-C-based eGFR, BUN, or variants associated with creatinine-based eGFR regardless of ancestry heterogeneity (**Figure S17**).

DISCUSSION

In analyses combining genetic, biomarker and clinical data in about 640,000 participants, our study has suggested that in people without manifest cardiovascular disease or diabetes even mildly reduced kidney function are causally associated with higher risk of CVD outcomes. Our results provide novel etiological insights and highlight the wider potential value of preventive approaches that can preserve and modulate kidney function.

First, our study estimated a dose-response curve for genetically-predicted eGFR and CHD, identifying an eGFR value of around 75 ml/min/1.73 m^2 as a possible risk threshold. The causal relationship of kidney function with CHD is, therefore, non-linear in shape, in contrast with those for blood pressure and LDL-cholesterol, which each have log-linear relationships with CHD risk across their range of values. An implication of this finding is that, in contrast with population-wide strategies to improve blood pressure and LDL-cholesterol levels, it may be a preferable strategy to identify those in the population with mild-to-moderate kidney dysfunction and target them for renoprotective interventions alongside routine strategies to reduce cardiovascular risk. For example, the use of renoprotective interventions such as renin angiotensin aldosterone system inhibitors,[36] and inhibitors of sodium-glucose cotransporter 2 might provide a potential means to do so.[37] Our findings encourage further evaluation of such agents in patients with CKD without manifest cardiovascular disease or diabetes.[38,39]

Second, we found that our GRS for eGFR was modestly associated with several established and emerging CVD risk factors, including plasma concentration of pro-atherogenic lipids (e.g., lipoprotein(a), triglycerides, triglycerides-related lipoprotein sub-classes), hemoglobin A1c values and blood pressure, consistent with previous studies.[11,40] However, adjustment for such factors did not materially alter the associations between eGFR and atherosclerotic CVD, indicating that they are unlikely to mediate or confound the associations between genetically-predicted kidney dysfunction and CHD or stroke, and limiting the likelihood that results are subject to influences of horizontal pleiotropy. These results suggest that the impact of reduced kidney function on CVD is independent

of traditional cardiovascular risk factors and underscores the potential importance of direct preservation of renal function to prevent CVD, in addition to control of known risk factors.

Third, our data help to resolve controversies about the relevance to CHD of higher-than-average eGFR. In contrast with the observation that higher-than-average creatinine-based eGFR values are associated with higher CHD risk at above 105 mL/min/1.73 m^2, we found genetically-predicted higher eGFR values were not associated with CHD risk in this same group. This discordance implies different pathophysiological meanings of creatinine-based eGFR values above 105 mL/min/1.73 m^2 (which may represent a transient state of hyperfiltration before progression to poorer kidney function and CKD) and *genetically-predicted* higher eGFR values (which represent a lifelong tendency toward exposure to better kidney function). This explanation is supported by our findings showing that the association between higher creatinine-based eGFR values and higher CHD risk was principally in participants who had albuminuria (and, therefore, pre-existing kidney damage) at entry into the study.

Fourth, our results are broadly consistent with a causal relationship between eGFR and stroke. The lack of statistically significant findings in our Mendelian randomization analysis for stroke outcomes principally reflects our study's lower power to evaluate a genetic risk score with stroke compared to CHD. It may also be due to etiological heterogeneity in stroke diagnoses (e.g., cardioembolic, small vessel disease and hemorrhagic subtypes may be less driven by atherosclerotic pathology than other ischemic stroke subtypes).[41,42]

Our study had major strengths, including a large sample size, access to individual-participant data, use of genetic causal inference methods tailored to the evaluation of non-linear disease associations, and an updated GRS that explains more variation in eGFR than previous analyses.[14] However, there are also potential limitations. First, Mendelian randomization assumptions state that the only causal pathway from the genetic variants to the outcome is via eGFR. Although we assessed the potential for interference by horizontal pleiotropy, there is the possibility of residual confounding by unrecognized effects of genotypes on other risk factors and by adaptation during early life to

compensate for genetically lower eGFR. Second, to reduce the scope for confounding by ancestry (population stratification), our analyses were limited to participants of European ancestries. This limitation means that our findings might not be applicable to other populations, and further studies on this topic are needed especially in non-European ancestry populations. Third, although serum creatinine is routinely used for estimating eGFR, true measurement of GFR requires the use of inulin, iohexol, or iothalamate. Assay of serum creatinine is liable to interference from other serum components (e.g., bilirubin, glucose),[43,44] autoimmune activation,[45] and is sensitive to changes in individuals' muscle mass (e.g., sarcopenia). Assessment of cystatin C, an analyte that enables an alternative calculation of eGFR without the potential limitations of creatinine, was available only in a subset of the participants we studied. However, our genetic analyses restricted to genetic variants additionally associated with other biomarkers of kidney function showed consistent results with that for creatinine-based eGFR. Finally, we used the 2009 CKD-EPI equation to calculate eGFR. However, our analysis was limited to European ancestry populations, in which the 2009 and 2021 CKD-EPI equations provide similar estimates of eGFR[46].

CONCLUSIONS

In conclusion, in people without manifest cardiovascular disease or diabetes, mild-to-moderate kidney dysfunction was causally related to cardiovascular outcomes, highlighting the potential cardiovascular benefit of preventive approaches that improve kidney function.

REFERENCES

1. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2020;395:709-33.
2. Levey AS, Coresh J. Chronic kidney disease. *Lancet.* 2012;379:165-80.
3. Di Angelantonio E, Chowdhury R, Sarwar N, Aspelund T, Danesh J, Gudnason V. Chronic kidney disease and risk of major cardiovascular disease and non-vascular mortality: prospective population based cohort study. *BMJ*. 2010;341:c4986.
4. Fox CS, Matsushita K, Woodward M, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet.* 2012;380:1662-73.
5. Baigent C, Burbury K, Wheeler D. Premature cardiovascular disease in chronic renal failure. *Lancet.* 2000;356:147-52.
6.Webster AC, Nagler EV, Morton RL, Masson P. Chronic Kidney Disease. *Lancet.* 2017; 389:1238-52.
7. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet.* 2010;375:2073-81.
8. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42:3227-3337.
9.Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* 2019;139: e1082-e143.
10. Said S, Hernandez GT. The link between chronic kidney disease and cardiovascular disease. *J Nephropathol*. 2014;3:99-104.
11. Yu Z, Coresh J, Qi G, et al. A bidirectional Mendelian randomization study supports causal effects of kidney function on blood pressure. *Kidney Int.* 2020;98:708-16.
12. Bulbul MC, Dagel T, Afsar B, et al. Disorders of Lipid Metabolism in Chronic Kidney Disease. *Blood Purif.* 2018;46:144-52.
13. Davey Smith G, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol.* 2003;32:1-22.
14. Charoen P, Nitsch D, Engmann J, et al. Mendelian Randomisation study of the influence of eGFR on coronary heart disease. *Sci Rep.* 2016;6:28514.
15. Morris AP, Le TH, Wu H, et al. Trans-ethnic kidney function association study reveals putative causal genes and effects on kidney-specific disease aetiologies. *Nat Commun.* 2019;10:29.
16. Staley JR, Burgess S. Semiparametric methods for estimation of a nonlinear exposure-outcome relationship using instrumental variables with application to Mendelian randomization. *Genet Epidemiol.* 2017;41:341-52.
17. Sun YQ, Burgess S, Staley JR, et al. Body mass index and all cause mortality in HUNT and UK Biobank studies: linear and non-linear mendelian randomisation analyses. *BMJ.* 2019;364:l1042.
18. Biddinger KJ, Emdin CA, Haas ME, et al. Association of Habitual Alcohol Intake With Risk of Cardiovascular Disease. *JAMA Netw Open.* 2022;5:e223849.
19. Arvanitis M, Qi G, Bhatt DL, et al. Linear and Nonlinear Mendelian Randomization Analyses of the Association Between Diastolic Blood Pressure and Cardiovascular Events: The J-Curve Revisited. *Circulation.* 2021;143:895-906.
20. Emerging Risk Factors Collaboration/EPIC-CVD/Vitamin D Studies Collaboration. Estimating dose-response relationships for vitamin D with coronary heart disease, stroke, and all-cause mortality: observational and Mendelian randomisation analyses. *Lancet Diabetes Endocrinol.* 2021;9:837-46.
21. Danesh J, Erqou S, Walker M, et al. The Emerging Risk Factors Collaboration: analysis of individual data on lipid, inflammatory and other markers in over 1.1 million participants in 104 prospective studies of cardiovascular diseases. *Eur J Epidemiol.* 2007;22:839-69.

22. Danesh J, Saracci R, Berglund G, et al. EPIC-Heart: the cardiovascular component of a prospective study of nutritional, lifestyle and biological factors in 520,000 middle-aged participants from 10 European countries. *Eur J Epidemiol.* 2007;22:129-41.
23. Gaziano JM, Concato J, Brophy M, et al. Million Veteran Program: A mega-biobank to study genetic influences on health and disease. *J Clin Epidemiol.* 2016;70:214-23.
24. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med.* 2015;12: e1001779.
25. Wuttke M, Li Y, Li M, et al. A catalog of genetic loci associated with kidney function from analyses of a million individuals. *Nat Genet.* 2019;51:957-72.
26. Burgess S, Davey Smith G, Davies NM, et al. Guidelines for performing Mendelian randomization investigations. *Wellcome Open Res.* 2019;4:186.
27. Levey AS, Stevens LA, Schmid CH, et al. A New Equation to Estimate Glomerular Filtration Rate. *Ann Intern Med.* 2009;150:604-12.
28. Levey AS, Coresh J, Greene T, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem.* 2007;53:766-72.
29. Shlipak MG, Matsushita K, Arnlov J, et al. Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med.* 2013;369:932-43.
30. Prentice RL. A Case-Cohort Design for Epidemiologic Cohort Studies and Disease Prevention Trials. *Biometrika.* 1986;73:1-11.
31. White IR, Kaptoge S, Royston P, Sauerbrei W. Meta-analysis of non-linear exposure-outcome relationships using individual participant data: A comparison of two methods. *Stat Med.* 2019;38:326-38.
32. KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl.* 2012;2013:1-150.
33. Burgess S, Thompson SG. Use of allele scores as instrumental variables for Mendelian randomization. *Int J Epidemiol.* 2013;42:1134-44.
34. Kamat MA, Blackshaw JA, Young R, et al. PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations. *Bioinformatics.* 2019;35:4851-3.
35. Stanzick KJ, Li Y, Schlosser P, et al. Discovery and prioritization of variants and genes for kidney function in >1.2 million individuals. *Nat Commun.* 2021;12:4350.
36. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med.* 1993;329:1456-62.
37. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. *N Engl J Med*. 2021;384:117-128.
38. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med.* 2020;383:1436-46.
39. Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet.* 2020;396:819-29.
40. Aguilar-Ramirez D, Alegre-Díaz J, Herrington WG, et al. Association of Kidney Function With NMR-Quantified Lipids, Lipoproteins, and Metabolic Measures in Mexican Adults. *J Clin Endocrinol Metab.* 2021;106:2828-39.
41. Dichgans M, Pulit SL, Rosand J. Stroke genetics: discovery, biology, and clinical applications. *Lancet Neurol.* 2019;18:587-99.
42. Sun L, Clarke R, Bennett D, et al. Causal associations of blood lipids with risk of ischemic stroke and intracerebral hemorrhage in Chinese adults. *Nat Med.* 2019;25:569-74.
43. Bargnoux A-S, Kuster N, Cavalier E, et al. Serum creatinine: advantages and pitfalls. *Journal of Laboratory and Precision Medicine.* 2018;3:71.
44. Delanaye P, Cavalier E, Cristol JP, Delanghe JR. Calibration and precision of serum creatinine and plasma cystatin C measurement: impact on the estimation of glomerular filtration rate. *J Nephrol.* 2014;27:467-75.

45. Altay S, Onat A, Ozpamuk-Karadeniz F, Karadeniz Y, Kemaloglu-Oz T, Can G. Renal "hyperfiltrators" are at elevated risk of death and chronic diseases. *BMC Nephrol.* 2014;15:160.
46. Inker LA, Eneanya ND, Coresh J, et al. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. *N Engl J Med.* 2021;385:1737-49.
47. Hellwege JN, Velez Edwards DR, Giri A, et al. Mapping eGFR loci to the renal transcriptome and phenome in the VA Million Veteran Program. *Nat Commun*. 2019;10:3842.
48. Hunter-Zinck H, Shi Y, Li M, et al. Genotyping Array Design and Data Quality Control in the Million Veteran Program. *Am J Hum Genet.* 2020;106:535-48.
49. Das S, Forer L, Schönherr S, et al. Next-generation genotype imputation service and methods. *Nat Genet.* 2016;48:1284-7.
50. Auton A, Brooks LD, Durbin RM, et al. A global reference for human genetic variation. *Nature.* 2015; 526:68-74.
51. Loh PR, Danecek P, Palamara PF, et al. Reference-based phasing using the Haplotype Reference Consortium panel. *Nat Genet*. 2016;48:1443-8.
52. Fang H, Hui Q, Lynch J, et al. Harmonizing Genetic Ancestry and Self-identified Race/Ethnicity in Genome-wide Association Studies. *Am J Hum Genet*. 2019;105:763-72.
53. Bycroft C, Freeman C, Petkova D, et al. The UK Biobank resource with deep phenotyping and genomic data. *Nature*. 2018;562:203-9.
54. Allen N, Arnold M, Parish S, et al. Approaches to minimising the epidemiological impact of sources of systematic and random variation that may affect biochemistry assay data in UK Biobank. *Wellcome Open Research*. 2020;5:222.
55. McCarthy S, Das S, Kretzschmar W, et al. A reference panel of 64,976 haplotypes for genotype imputation. *Nat Genet*. 2016;48:1279-83.
56. Howie BN, Donnelly P, Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS Genet*. 2009;5:e1000529.
57. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med*. 2012;367:20-9.
58. Burgess S, Ference BA, Staley JR, et al. Association of LPA Variants With Risk of Coronary Disease and the Implications for Lipoprotein(a)-Lowering Therapies: A Mendelian Randomization Analysis. *JAMA Cardiol.* 2018;3:619-27.

Table 1: Study-level and participant-level characteristics of the contributing data sources

	ERFC	EPIC-CVD	UK Biobank	MVP
Location	47 cohorts from 19 countries	21 centers from 8 European countries	England, Scotland, and Wales	United States
Years of recruitment	1964-2008	1990-2002	2006-2010	2011-Present
No. of participants	129,601	20,985	350,193	147,356
Age at baseline	58.3 (8.9)	56.3 (9.0)	56.3 (8.1)	57.9 (11.9)
Men	68,278 (52.7)	9,670 (46.1)	155,284 (44.3)	128,610 (87.3)
Body-mass index, kg/m^2	26.3 (4.3)	26.1 (4.0)	27.1 (4.6)	29.0 (5.5)
Systolic blood pressure, mmHg	135 (20)	138 (21)	137 (19)	130 (16)
Current-smoker	38,381 (29.6)	6,233 (29.7)	36,422 (10.4)	14,394 (9.77)
HDL cholesterol, mmol/L	1.4 (0.4)	1.4 (0.4)	1.5 (0.4)	1.3 (0.4)
Total cholesterol, mmol/L	5.8 (1.1)	6.2 (1.2)	5.8 (1.1)	4.8 (1.0)
Creatinine, mg/dL	0.94 (0.22)	0.82 (0.23)	0.81 (0.18)	1.0 (0.4)
eGFR, mL/min/1.73 m^2				
≥105	11,121 (8.6)	3,113 (14.8)	44,303 (12.7)	17,988 (12.2)
90-<105	32,971 (25.4)	9,400 (44.8)	165,603 (47.3)	41,461 (28.1)
75-<90	44,654 (34.5)	5,524 (26.3)	100,351 (28.7)	46,200 (31.4)
60-<75	30,751 (23.7)	2,306 (11.0)	33,895 (9.7)	29,552 (20.1)
<60	10,105 (7.8)	642 (3.1)	6041 (1.7)	12,155 (8.2)
Mean eGFR	84.5 (16.6)	92.1 (14.8)	91.2 (13.1)	84.9 (18.1)
Incident CHD events	10,390 (8.0)	7,638 (36.4)	13,863 (4.0)	10,967 (7.4)
Incident stroke events	4,838 (3.7)	3,572 (17.0)	4,544 (1.3)	2739 (1.8)

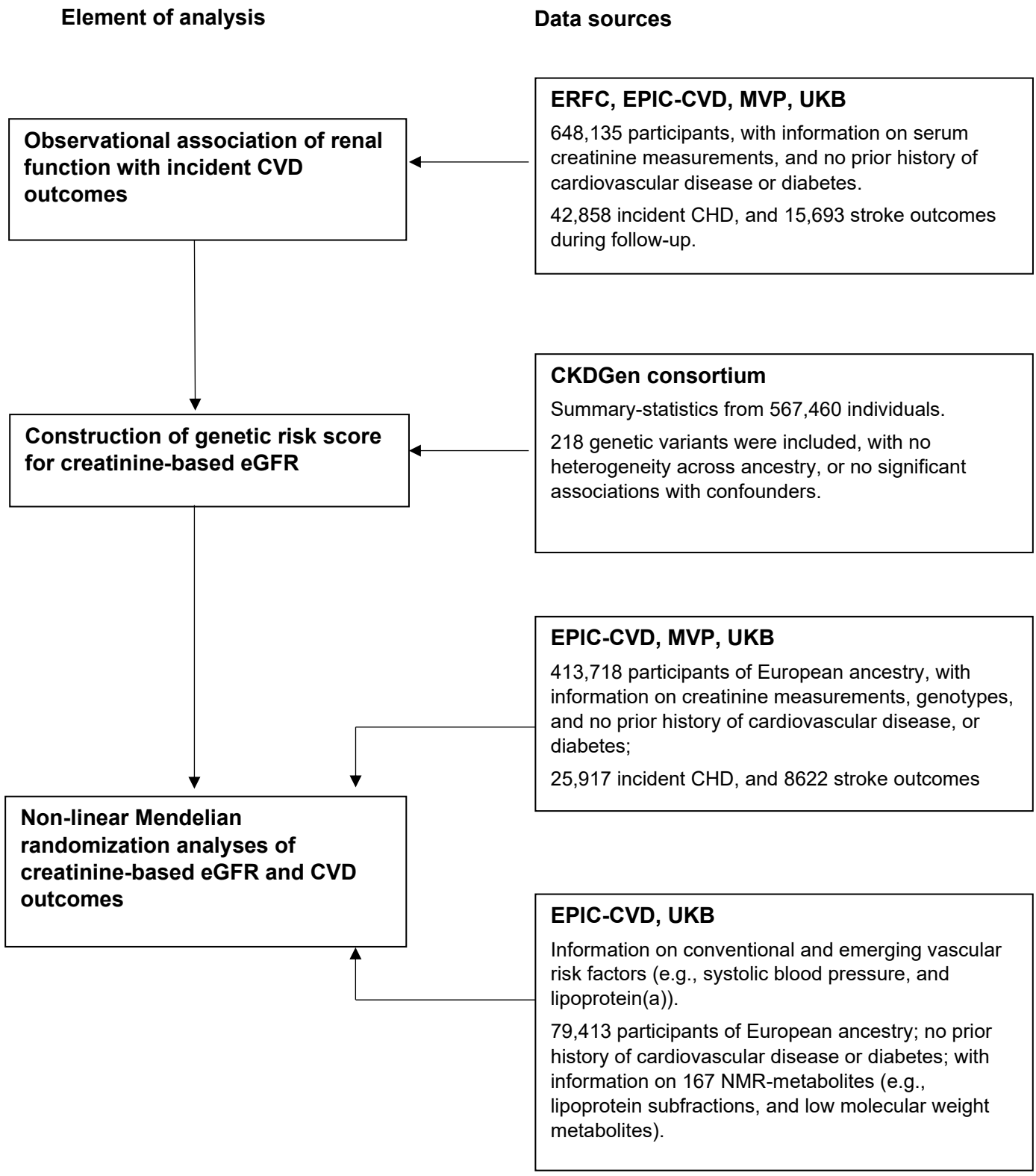
Data are n, n (%), or mean (SD). Participants with a history of diabetes or cardiovascular diseases at recruitment, or incomplete information on creatinine, BMI, SBP, smoking status, HDL cholesterol, or total cholesterol were excluded. ERFC= Emerging Risk Factors Collaboration. EPIC-CVD= European Prospective Investigation into Cancer and Nutrition-Cardiovascular Disease. MVP= Million Veteran Program. eGFR= estimated glomerular filtration rate. CHD= coronary heart disease. HDL= high-density lipoprotein.

Table 2: Mendelian randomization estimates per 5 mL/min/1.73 m^2 lower genetically-predicted eGFR with risk of coronary heart disease and stroke

eGFR mL/min/1.73m^2	Mean eGFR, mL/min/1.73m^2	No. of participants	Coronary heart disease		Stroke	
			No. of events	HR (95% CI)	No. of events	HR (95% CI)
<60	51.2	14,818	1749	1.14 (1.03, 1.27)	491	1.19 (0.97, 1.47)
60 to <75	68.9	53,256	4314	1.08 (1.01, 1.15)	1318	1.14 (1.01, 1.28)
75 to <90	83.3	123,664	8229	1.05 (1.00, 1.10)	2565	0.97 (0.89, 1.06)
90 to <105	96.9	176,180	9973	1.01 (0.96, 1.05)	3582	1.06 (0.98, 1.14)
≥105*	109.7	45,800	1652	0.91 (0.82, 1.02)	666	0.95 (0.79, 1.14)

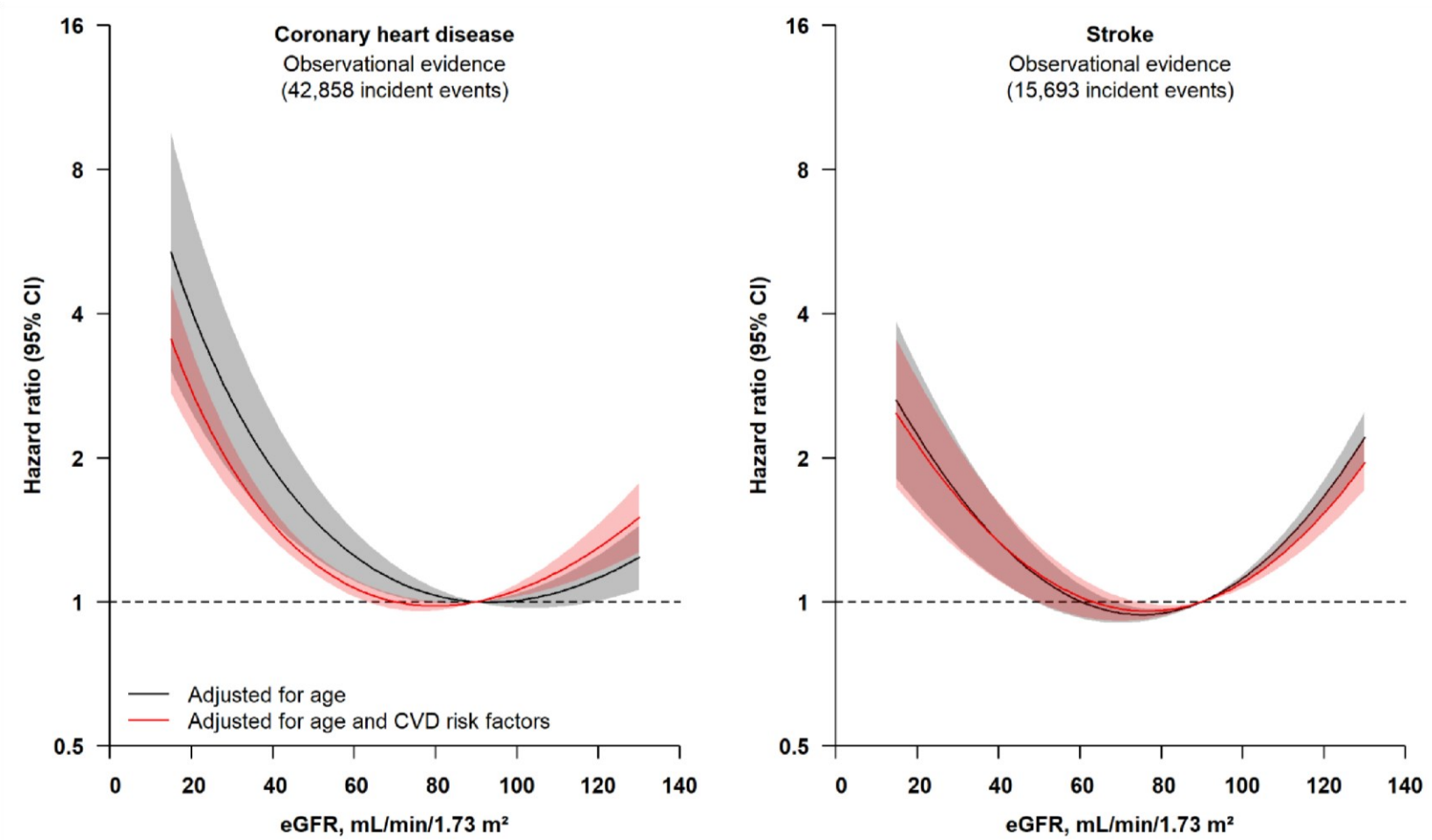
HRs are shown per 5 mL/min/1.73 m^2 lower genetically-predicted eGFR and are adjusted for age, age-squared, sex, study center, and the first ten principal components. *HRs in the group with eGFR above 105 were shown per 5 mL/min/1.73 m^2 *higher* genetically-predicted eGFR. Mean eGFR within each stratum was weighted by the number of participants from each contributing study, and MR estimates within each stratum were meta-analyzed using inverse variance weighting and fixed effects.

Figure 1: Study design and overview



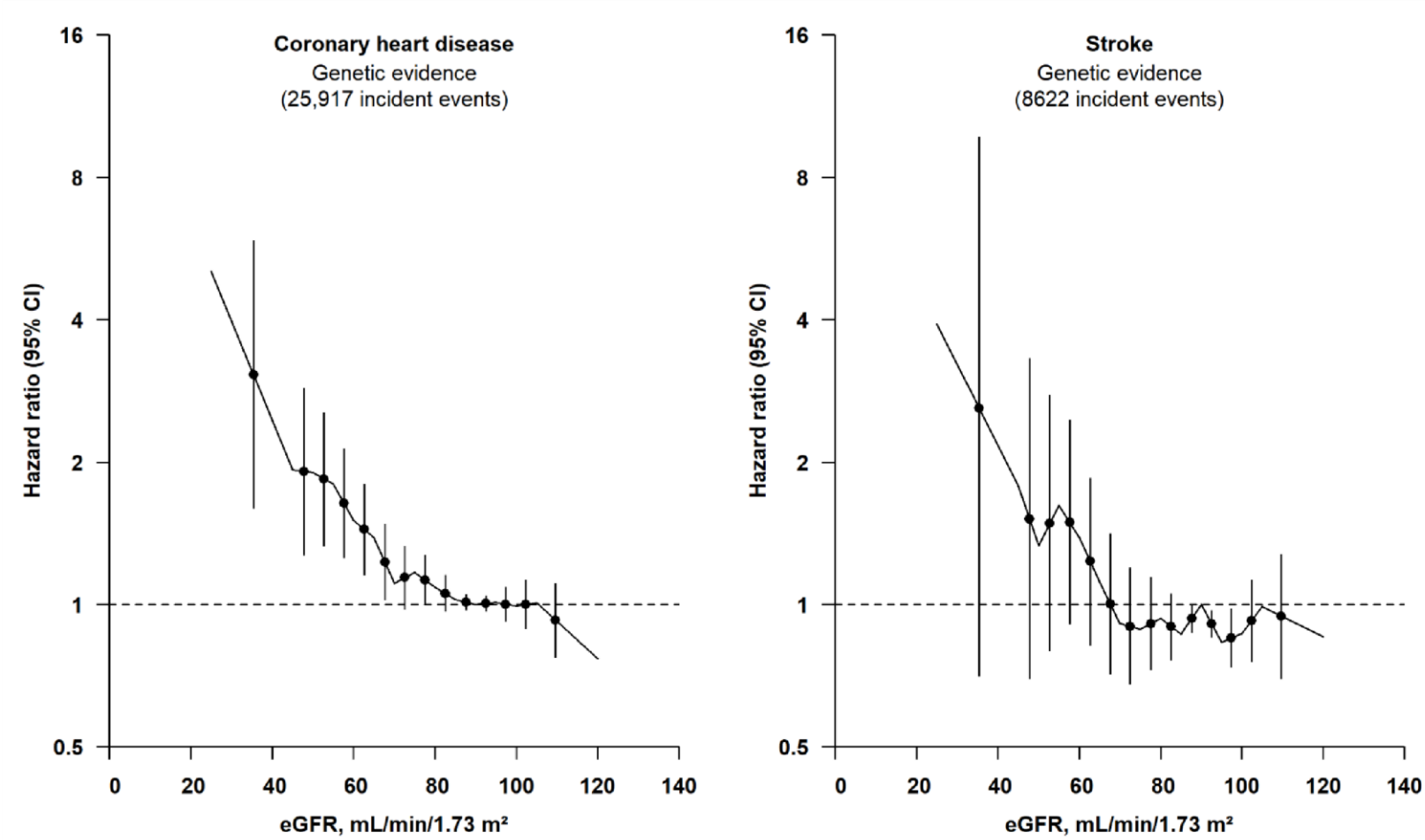
ERFC= Emerging Risk Factors Collaboration. EPIC-CVD= European Prospective Investigation into Cancer and Nutrition-Cardiovascular Disease. MVP= Million Veteran Program. UKB= UK Biobank. CKDGen= CKD Genetics consortium. eGFR= estimated glomerular filtration rate. CVD= Cardiovascular disease. CHD= coronary heart disease. NMR= nuclear magnetic resonance.

Figure 2: Observational associations of eGFR levels with risk of coronary heart disease and stroke (n=648,135)



Participants with missing information on age, and CVD risk factors (systolic blood pressure, total and high-density lipoprotein cholesterol, body-mass index, and smoking status) were excluded from the analyses. Hazard ratios were estimated using Cox regression, adjusting for age, and CVD risk factors (systolic blood pressure, total and high-density lipoprotein cholesterol, body-mass index, and smoking status), and stratified by sex and study center. The reference point is 90 mL/min/1.73 m^2. Shaded regions indicate 95% confidence intervals. CVD= cardiovascular disease. eGFR= estimated glomerular filtration rate. 95% CI= 95% confidence interval.

Figure 3: Associations of genetically-predicted eGFR with risk of coronary heart disease and stroke (n=413,718)



The reference point is 90 mL/min/1.73 m^2. Gradients at each point of the curve represented the localized average causal effect on coronary heart disease or stroke per 5 mL/min/1.73 m^2 change in genetically-predicted eGFR. The vertical lines represent 95% confidence intervals. Analyses were adjusted for age, age-squared, sex, study center, and the first ten principal components. eGFR= estimated glomerular filtration rate. 95% CI= 95% confidence interval

Acknowledgements

We thank investigators and participants of the several studies that contributed data to the Emerging Risk Factors Collaboration (ERFC). We thank all EPIC participants and staff for their contribution to the study, the laboratory teams at the Medical Research Council Epidemiology Unit for sample management and Cambridge Genomic Services for genotyping, Sarah Spackman for data management and the team at the EPIC-CVD Coordinating Centre for study co-ordination and administration. We thank the participants of the VA Million Veteran Program and VA MVP collaborators. Acknowledgment of VA Million Veteran Program leadership and staff contributions can be found in Supplementary Note.

This research has been conducted using the UK Biobank Resource under Application Number 31852.

Conflicts of interests
Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization. James Staley is now a full-time employee at UCB. Matthew Arnold is now an employee of AstraZeneca

Funding

The ERFC co-ordinating centre was underpinned by programme grants from the British Heart Foundation (SP/09/002; RG/13/13/30194; RG/18/13/33946), BHF Centre of Research Excellence (RE/18/1/34212), the UK Medical Research Council (MR/L003120/1), and the National Institute for Health Research (NIHR) Cambridge Biomedical Research Centre (BRC-1215-20014), with project specific support received from the UK NIHR [*], British United Provident Association UK Foundation and an unrestricted educational grant from GlaxoSmithKline.

*The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

This work was supported by Health Data Research UK, which is funded by the UK Medical Research Council, the Engineering and Physical Sciences Research Council, the Economic and Social Research Council, the Department of Health and Social Care (England), the Chief Scientist Office of the Scottish Government Health and Social Care Directorates, the Health and Social Care Research and Development Division (Welsh Government), the Public Health Agency (Northern Ireland), the British Heart Foundation, and Wellcome Trust.

A variety of funding sources have supported recruitment, follow-up, and laboratory measurements in the studies contributing data to the ERFC, which are listed on the ERFC website (www.phpc.cam.ac.uk/ceu/erfc/list-of-studies).

EPIC-CVD was funded by the European Research Council (268834), and the European Commission Framework Programme 7 (HEALTH-F2-2012-279233).

This research is based on data from the Million Veteran Program, Office of Research and Development, Veterans Health Administration, and was supported by award I01-BX004821(PIs: Wilson/Cho) and I01-BX003360 (PI: Hung). This publication does not represent the views of the Department of Veterans Affairs or the United States government.

S.M.D. is supported by IK2-CX001780. A.M.H. is supported by CX001897. P.S.T. is supported by BX003362-01 from VA Office of Research & Development. C.R.C. is supported by R01DK122075

Supplemental Materials

Expanded Methods

Tables S1 - 6

Figures S1 – 17

Emerging Risk Factors Collaboration Investigator list

ARIC: Anna Koettgen; **AUSDIAB**: Jonathan Shaw, Bob Atkins, Paul Zimmet; **BRHS**: Peter Whincup; **BRUN**: Peter Willeit, Johann Willeit, Christoph Leitner; **CASTEL**: Edoardo Casiglia, Valérie Tikhonoff; **COPEN**: Anne Tybjaerg-Hansen, Peter Schnohr, Shoaib Afzal; **DRECE**: David Lora Pablos, Cristina Martin Arriscado, Carmen Romero Ferreiro; **EPESEIOW**: Robert B Wallace; **ESTHER**: Hannah Stocker, Ben Schöttker, Bernd Holleczek; **GOH**: Angela Chetrit; **GOTO13**: Lennart Welin, Kurt Svärdsudd; **GOTO43**: Lennart Welin, Kurt Svärdsudd; **GOTOW**: Lauren Lissner, Dominique Hange, Kirsten Mehlig; **GRIPS**: Dorothea Nagel; **HIMS**: Paul Norman, Osvaldo Almeida, Leon Flicker; **HISAYAMA**: Jun Hata, Takanori Honda, Yoshihiko Furuta; **IKNS**: Hiroyasu Iso, Akihiko Kitamura, Isao Muraki; **KIHD**: Jukka T Salonen, Tomi-Pekka Tuomainen; **LASA**: E M van Zutphen, N M van Schoor; **MATISS83**: Chiara Donfrancesco, Cinzia Lo Noce; **MATISS87**: Luigi Palmieri, Cinzia Lo Noce; **MESA**: Mary Cushman, Richard Kronmal; **MONICA_KORA3:** Wolfgang Koenig, Christa Meisinger; **MOSWEGOT**: Georg Lappas; **MPP**: Peter M Nilsson Olle Melander, Bo Hedblad; **MRCOLD**: Dorothea Nitsch; **NPHSII**: Jackie A Cooper; **NSHS**: Jonathan Shaffer Joseph Schwartz, Daichi Shimbo; **OSAKA**: Shinichi Sato Hiroyasu Iso, Mina Hayama-Terada; **RANCHO**: Simerjot Jassal; **REYK**: Thor Aspelund Bolli Thorsson, Gunnar Sigurdsson; **RS_I:** Layal Chaker, M. Kamran Ikram, Maryam Kavousi; **SHHEC**: Hugh Tunstall-Pedoe, Mark Woodward; **SHIP**: Henry Völzke; **TARFS**: Günay Can, Hüsniye Yüksel, Uğur Özkan; **TOYAMA**: Hideaki Nakagawa, Yuko Morikawa, Masao Ishizaki; **ULSAM**: Johan Ärnlöv; **WCWC**: Volker Arndt; **ZUTE**: Edith Feskens, Johanna M Geleijnse, Daan Kromhout.

Mild-to-moderate kidney dysfunction and cardiovascular disease: observational and Mendelian randomisation analyses

Running Title: Gaziano et al.; *Kidney dysfunction and CVDs*

Supplementary Materials

EXPANDED METHODS

I. Description of contributing studies or consortium

Emerging Risk Factor Collaboration

Emerging Risk Factor Collaboration (ERFC) is a consortium of 112 prospective studies, involving a total of 1.2 million participants, that provided individual-level data.[21] These studies were approximately population-based (i.e., did not select participants on the basis of having previous cardiovascular disease); recorded cause-specific mortality or vascular morbidity using accepted criteria; and had accrued more than 1 year of follow-up. Coronary heart disease (CHD) and stroke were defined in each contributing study. Sixty-two studies used standard definitions of myocardial infarction (MI) based on World Health Organization criteria. Fifty-six studies reported diagnosis of strokes on the basis of typical clinical features and characteristic changes on brain imaging, and all attempted to provide attribution of stroke pathological types. In registering fatal outcomes, all contributing studies used coding from the *International Classification of Diseases* (ICD) to at least 3 digits and ascertainment was based on death certificates. Data on serum creatinine measurements were available in 48 studies, and were harmonized at the ERFC coordinating centers in consensus with the individual study collaborators. Genetic information was not available for the current analysis on any of the contributing studies, and therefore ERFC was not included in the Mendelian randomization (MR) analysis.

Million Veteran Program

Million Veteran Program (MVP) is a prospective biobank with ongoing recruitment from 63 Veterans Health Administration (VA) medical facilities that started in 2011.[23] Participant questionnaires and linkage to Electronic Health Records (EHR) from the VA healthcare system, national death index (NDI), and Centers for Medicare and Medicaid Services (CMS) were used to define baseline exposures and case status.[47-49] CHD was defined as ICD-9 410-414, or ICD-10 I20-I25 and stroke was defined as ICD-9 430-431 or 433-434, or ICD-10 I60-I61 or I63, I69. Creatinine was extracted from EHR as the value closest but prior to enrolment up to a year. Anyone with CHD or stroke codes prior to enrolment were excluded, along with amputees and individuals on HIV medications.[23] Genotyping was performed using an array similar to the UK Biobank Affymetrix Axiom array but with modifications tailored to the veteran population.[47] Genotypes were imputed with Minimac3,[48] using the 1000 Genomes Project reference panel (phase 3, version 5),[49] after phasing by EAGLE v2 software.[50] Ancestry was determined with HARE (harmonized ancestry and race/ethnicity) software, which allocates individuals into ancestry groups from a combination of self-identified race/ethnicity and genetic information.[51] The VA central

institutional review board and site-specific Research and Development committees approved the Million Veteran Program study.

UK Biobank

Details of the design, methods, and participants of UK Biobank (UKB) have been described previously.[52] Briefly, participants aged 40 to 75 years identified through primary care lists were recruited across 22 assessment centers throughout the UK between 2006 and 2010. At recruitment, information was collected via a standardized questionnaire and selected physical measurements. Data were subsequently linked to Hospital Episode Statistics (HES), as well as national death and cancer registries. HES uses ICD–9th and 10th Revisions to record diagnosis information, and *Office of Population, Censuses and Surveys: Classification of Interventions and Procedures*, version 4 (OPCS-4) to code operative procedures. Death registries include deaths in the UK, with both primary and contributory causes of death coded in ICD-10. CHD was defined as ICD-10 I20-I25 and stroke was defined as ICD-10 I60-I61 or I63, I64, I69. Genotyping was undertaken using a custom-built genome-wide array of ~826,000 markers.[24] Imputation to ~96 million markers was subsequently carried out using the Haplotype Reference Consortium and UK10K/1000Genomes reference panels.[24] Clinical biochemistry markers, including blood creatinine, total cholesterol, HDL-cholesterol, urinary albumin, and urinary creatinine, were measured in bio-samples collected at baseline. Full details of the biochemistry sampling, handling and quality control protocol, and assay method has been described previously.[53]

EPIC-CVD

EPIC-CVD is a case-cohort embedded in the European Prospective Investigation into Cancer and Nutrition (EPIC), to advance understanding about the separate and combined influence of lifestyle, biochemical, and genetic factors in the development of cardiovascular disease.[54] Briefly, between 1992 and 2000, 519,978 participants were recruited to the EPIC prospective study across 23 centers in ten European countries, via population-based registers, blood donors, screening clinics. CHD and stroke cases were ascertained at each recruiting center through death registries, hospital discharge codes, self-reported by questionnaires or through active follow-up by correspondence with relatives for fatal events. Within each of the contributing EPIC centers, information has been collected and centrally harmonized at the EPIC-CVD Coordinating Centre on: i) a random sample of the original center-specific cohort (i.e., the “sub-cohort”), and ii) all incident CHD and stroke cases. Participants were genotyped using either the Illumina 660W-Quad BeadChip at the Wellcome Trust Sanger Institute or the Illumina

HumanCoreExome BeadChip at Cambridge Genomic Services. Samples from each array were then imputed separately to the Haplotype Reference Consortium panel,[55] using IMPUTE2 software.[56]

II. ERFC study acronyms

Abbreviation	Full Name
ARIC	Atherosclerosis Risk in Communities Study
AUSDIAB	Australian Diabetes, Obesity and Lifestyle study'
BRHS	British Regional Heart Study
BRUN	Bruneck Study
BWHHS	British Women's Heart and Health Study
CASTEL	Cardiovascular Study in the Elderly
CHS1	Cardiovascular Health Study - 1
CHS2	Cardiovascular Health Study - 2
COPEN	Copenhagen City Heart Study
DRECE	Diet and Risk of Cardiovascular Disease in Spain
EPESEBOS	Established Populations for the Epidemiologic Study of the Elderly Studies, East Boston
EPESEIOW	Established Populations for the Epidemiologic Study of the Elderly Studies, Iowa
EPESENCA	Established Populations for the Epidemiologic Study of the Elderly Studies, North Carolina
EPESENHA	Established Populations for the Epidemiologic Study of the Elderly Studies, New Haven
ESTHER	Epidemiologische Studie zu Chancen der Verhutung und optimierten Therapie chronischer Erkrankungen in der alteren Bevolkerung
GOH	The Glucose Intolerance, Obesity and Hypertension Study
GOTO13	Goteborg Study 1913
GOTO43	Goteborg Study 1943
GOTOW	Population Study of Women in Göteborg, Sweden
GRIPS	Göttingen Risk Incidence and Prevalence Study
HIMS	Health in Men Study
HISAYAMA	Hisayama Study
IKNS	Ikawa, Kyowa, and Noichi Study
KIHD	Kuopio Ischaemic Heart Disease Study
LASA	Longitudinal Aging Study Amsterdam
MATISS83	Progetto CUORE
MATISS87	Progetto CUORE
MESA	Multi-Ethnic Study of Atherosclerosis
MONICA_KORA3	MONICA/KORA Augsburg Survey S3
MOSWEGOT	MONICA Göteborg Study
MPP	Malmö Preventive Project
MRCOLD	MRC Study of Older People
NHANESI	National Health and Nutrition Examination Survey I
NHANESIII	National Health and Nutrition Examination Survey III
NPHSII	Northwick Park Heart Study II
NSHS	Nova Scotia Health Survey
OSAKA	Osaka Study

RANCHO	Rancho Bernardo Study
REYK	Reykjavik Study
RS_I	The Rotterdam Study I
SHHEC	Scottish Heart Health Extended Cohort
SHIP	Study of Health in Pomerani
TARFS	Turkish Adult Risk Factor Study
TOYAMA	Toyama Study
ULSAM	Uppsala Longitudinal Study of Adult Men
WCWC	Wuertemberg Construction Workers Cohort
ZUTE	Zutphen Elderly Study

III. Estimators of glomerular filtration rates

We used eGFR from serum creatinine predicted from CKD-EPI formula in the primary analyses, and where available, we compared results with eGFR estimated using other formulae.

Estimating equations using serum creatinine in mg/dL (to convert serum creatinine in mmol/L to mg/dL, divide by 88.4):

1. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)[57]:

$$\text{eGFR} = 141 \times \left\{\min\left(\frac{\text{creatinine}}{k}, 1\right)\right\}^{\alpha} \times \left\{\max\left(\frac{\text{creatinine}}{k}, 1\right)\right\}^{-1.209} \times 0.993^{\text{age}} \times [1.018 \text{ if female}] \times [1.159 \text{ if black}]$$

where $k = 0.7$ and $\alpha = -0.329$ for females, and $k = 0.9$ and $\alpha = -0.411$ for males.

Estimating equations using serum cystatin C in mg/L[27]:

1. CKD-EPI

$$\text{eGFR} = 130 \times \left(\frac{\text{cystatin C}}{0.8}\right)^{\alpha} \times 0.996^{\text{age}} \times [0.932 \text{ if female}]$$

where $\alpha = -0.499$ if cystatin C ≤ 0.8, and $\alpha = -1.328$ otherwise.

Estimating equations using serum creatinine and serum cystatin C:

1. CKD-EPI

$$\text{eGFR} = 135 \times \left\{\min\left(\frac{\text{creatinine}}{k}, 1\right)\right\}^{\alpha} \times \left\{\max\left(\frac{\text{creatinine}}{k}, 1\right)\right\}^{-0.601} \times \left(\frac{\text{cystatin C}}{0.8}\right)^{\beta} \times 0.995^{\text{age}} \times [0.969 \text{ if female}] \times [1.08 \text{ if black}]$$

where $k = 0.7$ and $\alpha = -0.248$ for females, and $k = 0.9$ and $\alpha = -0.207$ for males, and $\beta = -0.375$ if cystatin C ≤ 0.8, and $\beta = -0.711$ otherwise

IV. Non-linear Mendelian randomization analysis

Mendelian randomization (MR) methods typically assume that the exposure-outcome relationship is linear when estimating a causal association. However, large-scale prospective epidemiological studies among different populations, and the present study performed among participants without prior history of cardiovascular disease or diabetes, have demonstrated that there is a reversed J-shaped association between creatinine-based eGFR and risk of CHD and stroke. To account for the non-linear relationship when investigating the causal relevance of kidney function for risk of CHD, and stroke, we applied a tailored novel method, i.e., the non-linear MR approach.[16-17,58]

Genetically-predicted eGFR and cardiovascular outcomes

Within each study (i.e., EPIC-CVD, MVP, and UKB), we calculated the residual variation in creatinine-based eGFR (henceforth, termed as *IV-free* eGFR) by subtracting the genetically-determined eGFR from the creatinine-based eGFR. The IV-free eGFR can be interpreted as the expected value of a participant's eGFR if their GRS was 0. Based on the IV-free eGFR, all study participants were then stratified into 5-unit groups between 45-105 mL/min/1.73 m^2, plus <45 and ≥105 mL/min/1.73 m^2. Within stratum, linear MR estimates were calculated using the ratio method. These stratum-specific MR estimates are localized average causal effect (LACE) estimates and were pooled across studies using fixed-effects meta-analysis within each stratum. The stratum-specific MR estimates were plotted as a piecewise-linear function of eGFR, where the slope in each piece is the LACE estimate in that stratum. The estimated risk was plotted against the mean eGFR in each stratum, relative to the risk at 90 mL/min/1.73 m^2. Point-wise confidence intervals were calculated by re-sampling the MR estimates and re-calculating the full piecewise-linear shape. Interpretation of graphical representations of these non-linear genetic associations must focus on the slope in the neighborhood of an eGFR value of interest, rather than comparisons of absolute risk made across the range of the eGFR distribution.

Genetically-predicted eGFR and other vascular risk factors

To assess the specificity of the GRSs for eGFR, we tested associations of GRSs with a range of vascular risk factors (e.g., systolic blood pressure, LDL-cholesterol, and diabetes status) in UKB and EPIC-CVD studies, and with 167 metabolites measured using targeted high-throughput NMR metabolomics (Nightingale Health Ltd) in UKB. The analyses were conducted among participants with no prior history of vascular diseases or diabetes, and not on lipid-lowering treatments. NMR-measured metabolites were standardized for comparison via rank-based inverse normal transformation. Linear regression was used

to relate GRSs to continuous traits, and logistic regression was used for binary outcomes, adjusted for age, age-squared, sex, study center, and the first ten principal components.

Table S1: Definitions of coronary heart diseases and stroke

Outcome (includes both fatal and non-fatal)	ICD-10 codes
All cardiovascular	I20-I25, I60-I64, I69
Coronary heart disease	I20-I25
All stroke	I60-I64, I69
Ischemic stroke	I63, I69.3
Intracerebral hemorrhage	I61, I69.1
Subarachnoid hemorrhage	I60, I69.0
Unclassified stroke †	I64, I69.4

† Unclassified stroke refers to ICD codes I64 (ICD-10), 436 (ICD-9) or earlier ICD equivalents, or strokes no specified as ischemic or hemorrhagic stroke in study specific codes. Corresponding ICD-6, 7 or 8 codes are used for ERFC studies that recorded outcomes using earlier ICD versions.

Table S2: Number of participants by eGFR category and contributing study

Cohort	Total	creatinine-based eGFR categories, mL/min/1.73 m^2						
		<45	45-<60	60-<75	75-<90	90-<105	105-<120	>120
ARIC	11,421	64	1,271	5,134	3,719	1,054	164	15
AUSDIAB	8,307	35	338	1,807	3,502	2,176	447	2
BRHS	6,406	15	180	1,529	2,785	1,646	249	2
BRUN	756	4	20	98	265	297	72	-
BWHHS	2,503	17	306	1,137	885	157	1	-
CASTEL	1,793	54	224	464	746	292	10	3
CHS1	2,936	127	613	1,048	896	246	6	-
CHS2	312	9	28	91	89	75	19	1
COPEN	6,569	94	819	2,277	2,192	1,004	179	4
DRECE	2,058	4	27	312	762	663	265	25
EPESEBOS	437	55	179	138	61	4	-	-
EPESEIOW	708	112	304	193	94	5	-	-
EPESENCA	609	105	260	197	42	5	-	-
EPESENHA	341	46	134	108	43	8	2	-
ESTHER	3,995	134	372	646	984	1,425	349	85
GOH	867	12	42	200	248	257	106	2
GOTO43	723	-	1	56	303	350	12	1
GRIPS	5,645	14	184	1,160	2,720	1,266	297	4
HIMS	1,823	47	152	480	984	158	2	-
HISAYAMA	2,236	12	173	825	858	334	34	-
IKNS	4,204	12	68	415	1,139	1,847	708	15
KIHD	1,792	5	13	209	627	796	137	5
LASA	124	3	26	66	27	2	-	-
MATISS83	2,403	10	70	297	576	899	479	72
MATISS87	1,876	17	46	268	500	669	341	35
MESA	5,696	56	319	1,204	2,021	1,672	381	43
MONICA_KORA3	3,902	16	39	154	457	1,387	1,441	408
MOSWEGOT	309	5	93	137	63	11	-	-
NHANESIII	8,946	156	853	2,322	3,079	1,896	544	96
NSHS	913	6	16	75	168	374	230	44
OSAKA	3,476	9	39	477	1,296	1,244	394	17

RANCHO	1,406	71	424	546	286	76	3	-
REYK	11,808	38	388	2,640	4,650	3,551	529	12
RS_I	3,371	18	213	915	1,434	777	13	1
SHHEC	9,643	23	282	2,402	4,270	2,276	383	7
SHIP	1,743	4	42	287	639	575	192	4
TARFS	561	6	17	80	131	207	109	11
TOYAMA	4,303	7	10	103	695	2,040	1,405	43
ULSAM	1,728	2	2	70	186	959	495	14
WCWC	551	-	-	11	111	277	148	4
ZUTE	401	9	85	173	121	13	-	-
MVP	147,356	2,698	9,457	29,552	46,200	41,461	15,176	2,812
EPICCVD	20,985	139	503	2,306	5,524	9,400	2,942	171
UKBIOBANK	350,193	809	5,232	33,895	100,351	165,603	43,124	1,179

Data are number of participants.

Table S3: Characteristics of participants by categories of eGFR

	Categories of eGFR (mL/min/1.73 m^2)								
	<15	**15-<30**	**30-<45**	**45-<60**	**60-<75**	**75-<90**	**90-<105**	**105-<120**	**>120**
Age	60.2 (4.7)	65.4 (4.4)	66.7 (3.6)	65.6 (3.7)	62.2 (4.1)	59.2 (4.5)	55.7 (4.3)	47 (3.5)	41.6 (3.2)
Sex									
Men	271	609	2,552	13,919	55,794	114,660	133,631	37,506	2,899
Women	58	193	1,395	9,945	40,710	82,069	115,804	33,882	2,238
Creatinine	7.1 (1.7)	2.6 (0.3)	1.7 (0.1)	1.3 (0.1)	1.1 (0.1)	0.9 (0.1)	0.8 (0.1)	0.8 (0.1)	0.6 (0.1)
Incident CHD events	90	142	523	2,693	8,303	13,614	14,619	2,706	168
Incident stroke events	8	34	214	1,087	3,186	4,793	5,298	1,002	71
BMI, kg/m2	26.4 (2.4)	27.4 (2.7)	27.7 (2.5)	27.8 (2.4)	27.8 (2.3)	27.5 (2.4)	27.3 (2.5)	27.3 (2.7)	27.1 (3)
SBP, mmHg	137 (11)	138 (10)	137 (10)	135 (9)	134 (9)	132 (8)	131 (8)	127 (8)	126 (8)
Smoking status									
Not current	303	730	3,567	21,245	84,160	169,933	212,106	56,731	3,939
Current	26	72	380	2,619	12,344	26,796	37,329	14,657	1198
HDL cholesterol, mmol/L	1.2 (0.2)	1.2 (0.2)	1.3 (0.2)	1.3 (0.2)	1.3 (0.2)	1.3 (0.2)	1.3 (0.2)	1.3 (0.2)	1.4 (0.2)
Total cholesterol, mmol/L	5.0 (0.5)	5.0 (0.6)	5.2 (0.6)	5.3 (0.5)	5.3 (0.5)	5.3 (0.5)	5.3 (0.5)	5.1 (0.5)	5.0 (0.5)

Data are n, or mean (SD). Participants with missing information on age, sex systolic blood pressure, total and high-density lipoprotein cholesterol, body-mass index, and smoking status were excluded. CHD= coronary heart disease. BMI= body-mass index. SBP= systolic blood pressure. HDL= high-density lipoprotein. eGFR= estimated glomerula filtration rate

Table S4: Variants used to make the genetic risk score for eGFR (using creatinine in the CKD-EPI equation).

RSID	Chromosome and base pair	Effect allele	Other allele	European ancestry		Trans-ancestry	
				Effect size (beta)	SE	Effect size (beta)	SE
rs11166440	1:100808363	A	G	0.0021	0.0004	0.002	0.0003
rs74748843	1:10730910	C	T	0.006	0.0013	0.0048	0.0008
rs12736457	1:113258293	C	G	0.0056	0.0005	0.0054	0.0005
rs3118119	1:150159616	T	C	0.0031	0.0005	0.003	0.0005
rs267738	1:150940625	G	T	0.005	0.0004	0.0048	0.0004
rs10159261	1:15912987	G	T	0.0038	0.0004	0.0034	0.0003
rs3845534	1:163738950	G	A	0.0019	0.0003	0.0019	0.0003
rs4656220	1:170649277	T	C	0.0021	0.0004	0.002	0.0003
rs1011731	1:172346548	G	A	0.0019	0.0003	0.0019	0.0003
rs3795503	1:180905694	T	C	0.0022	0.0004	0.002	0.0003
rs78444298	1:184672098	G	A	0.0107	0.0014	0.0105	0.0014
rs78329830	1:186769572	G	A	0.0051	0.001	0.0054	0.0009
rs12061708	1:18809916	G	A	0.0027	0.0004	0.0026	0.0003
rs3850625	1:201016296	A	G	0.0048	0.0006	0.0046	0.0005
rs2808454	1:207231751	A	T	0.0019	0.0003	0.0019	0.0003
rs75625374	1:208039431	C	G	0.0043	0.0007	0.0045	0.0007
rs7535253	1:214744893	T	C	0.0023	0.0004	0.0021	0.0004
rs2577134	1:220224321	T	C	0.0021	0.0004	0.002	0.0003
rs61830291	1:221001142	C	A	0.0036	0.0006	0.0036	0.0006
rs417237	1:228532195	T	G	0.002	0.0004	0.0018	0.0003
rs2749153	1:23699340	G	A	0.003	0.0004	0.0033	0.0003
rs2490391	1:243469669	C	A	0.0025	0.0003	0.0024	0.0003
rs688540	1:48002447	G	A	0.0031	0.0006	0.003	0.0005
rs17413465	1:55718708	A	C	0.0025	0.0004	0.0025	0.0004
rs1757915	1:56615809	A	G	0.002	0.0004	0.0021	0.0003
rs7536433	1:78023173	T	C	0.0018	0.0004	0.0021	0.0004
rs679843	1:78707493	T	C	0.002	0.0004	0.0021	0.0003
rs17050272	2:121306440	G	A	0.0022	0.0004	0.0022	0.0003
rs11694902	2:121988884	A	G	0.0041	0.0005	0.0041	0.0005
rs7425436	2:148759656	A	G	0.0026	0.0004	0.0024	0.0003
rs4664475	2:152387553	C	T	0.002	0.0004	0.002	0.0003
rs807624	2:15782471	T	G	0.0034	0.0004	0.0032	0.0003
rs35472707	2:169995581	C	T	0.0075	0.0008	0.0073	0.0008
rs187355703	2:176993583	C	G	0.0101	0.0011	0.01	0.0011
rs35284526	2:178121524	A	C	0.0029	0.0004	0.0029	0.0003
rs4666821	2:183077254	T	G	0.0018	0.0003	0.002	0.0003
rs4491726	2:18676276	A	G	0.0032	0.0004	0.0032	0.0004
rs60980181	2:188168567	T	A	0.0029	0.0005	0.0027	0.0004
rs1047891	2:211540507	C	A	0.0065	0.0004	0.0065	0.0004
rs1548945	2:217665788	T	C	0.0037	0.0004	0.0036	0.0003
rs1050816	2:220358198	T	C	0.0029	0.0004	0.0026	0.0003
rs35669853	2:227287718	A	G	0.0026	0.0004	0.0024	0.0004
rs13003198	2:234257105	T	C	0.0017	0.0004	0.0018	0.0003
rs2301343	2:40680149	G	T	0.0023	0.0004	0.0023	0.0004

RSID	Chromosome and base pair	Effect allele	Other allele	European ancestry		Trans-ancestry	
				Effect size (beta)	SE	Effect size (beta)	SE
rs10865189	2:43433257	C	G	0.0025	0.0004	0.0024	0.0003
rs2971880	2:54885640	T	A	0.0026	0.0004	0.0024	0.0003
rs10197255	2:67874553	A	T	0.0018	0.0004	0.0018	0.0003
rs6546869	2:73895765	A	G	0.0061	0.0004	0.0059	0.0004
rs2289746	3:105455955	C	T	0.0016	0.0004	0.0019	0.0003
rs9868185	3:121657593	A	G	0.0027	0.0003	0.0026	0.0003
rs10934754	3:125906237	T	C	0.0017	0.0003	0.002	0.0003
rs35320690	3:135932494	C	T	0.0025	0.0004	0.0025	0.0004
rs9828976	3:136536835	G	C	0.0024	0.0004	0.0024	0.0004
rs7624084	3:141093285	T	C	0.0015	0.0003	0.0017	0.0003
rs1397764	3:141750810	A	G	0.0047	0.0004	0.0043	0.0003
rs76272256	3:168888112	T	C	0.0024	0.0005	0.0024	0.0004
rs56065557	3:185354216	G	C	0.003	0.0004	0.0029	0.0003
rs9823161	3:193811168	A	G	0.0021	0.0004	0.0022	0.0004
rs6779998	3:30749965	G	A	0.0019	0.0003	0.0017	0.0003
rs3774726	3:63974477	C	T	0.0023	0.0004	0.0021	0.0003
rs3775932	4:10090930	C	A	0.002	0.0003	0.0018	0.0003
rs223471	4:103698786	C	G	0.0028	0.0004	0.0028	0.0003
rs55929207	4:109703549	C	G	0.002	0.0003	0.0019	0.0003
rs16874073	4:23743962	C	T	0.0041	0.0008	0.0045	0.0007
rs75501914	4:3449781	A	G	0.0042	0.0008	0.0039	0.0006
rs4864890	4:52686513	C	T	0.0023	0.0004	0.0023	0.0004
rs12509595	4:81182554	C	T	0.0032	0.0004	0.0035	0.0003
rs12777	5:131671662	C	G	0.005	0.0009	0.005	0.0009
rs11743174	5:148524820	T	C	0.0019	0.0004	0.0019	0.0003
rs3812036	5:176813404	C	T	0.0069	0.0004	0.0065	0.0004
rs13157326	5:34504277	G	A	0.0027	0.0004	0.0027	0.0003
rs495237	5:39950266	T	G	0.0029	0.0004	0.0027	0.0003
rs11746506	5:44812566	T	C	0.0018	0.0004	0.0017	0.0003
rs79760705	5:53298716	T	G	0.0056	0.0006	0.0056	0.0005
rs72759880	5:67750213	G	T	0.0057	0.0005	0.0056	0.0005
rs2010352	5:68656327	G	A	0.0019	0.0003	0.0018	0.0003
rs3797537	5:78322650	A	G	0.0021	0.0004	0.0019	0.0003
rs1857859	6:100894587	A	G	0.0014	0.0004	0.0019	0.0003
rs1268168	6:109008158	A	G	0.0027	0.0004	0.0024	0.0003
rs7740107	6:130374461	A	T	0.0027	0.0004	0.0027	0.0004
rs9375818	6:131882078	G	A	0.0026	0.0004	0.0031	0.0004
rs3822939	6:133849789	G	A	0.0028	0.0003	0.0025	0.0003
rs9397738	6:154986664	A	G	0.0025	0.0005	0.0027	0.0004
rs12207180	6:160633107	T	A	0.0085	0.0005	0.0085	0.0005
rs3765502	6:24354045	T	C	0.0017	0.0006	0.0024	0.0004
rs144100226	6:34180297	T	C	0.006	0.0011	0.0059	0.001
rs13200335	6:41690823	A	C	0.0024	0.0003	0.0024	0.0003
rs77915916	6:43287722	A	T	0.0047	0.0006	0.0046	0.0006
rs881858	6:43806609	G	A	0.0056	0.0004	0.0054	0.0003
rs720989	6:44765535	T	G	0.0023	0.0004	0.0021	0.0004
rs6458868	6:52630153	C	T	0.0021	0.0004	0.002	0.0003
rs3925003	6:55422618	C	T	0.0019	0.0003	0.0018	0.0003

RSID	Chromosome and base pair	Effect allele	Other allele	European ancestry		Trans-ancestry	
				Effect size (beta)	SE	Effect size (beta)	SE
rs11755724	6:7118990	A	G	0.0027	0.0004	0.0027	0.0004
rs72912510	6:90118764	G	A	0.002	0.0004	0.0024	0.0004
rs3757387	7:128576086	T	C	0.0029	0.0004	0.003	0.0003
rs62435145	7:1286567	G	T	0.0055	0.0004	0.006	0.0004
rs62491533	7:129564134	C	T	0.0027	0.0005	0.0027	0.0004
rs10254101	7:151415536	C	T	0.0068	0.0004	0.0068	0.0004
rs12671694	7:155665959	T	C	0.0028	0.0004	0.0025	0.0003
rs868822	7:156252939	T	G	0.0032	0.0004	0.0029	0.0003
rs6968554	7:17287106	G	A	0.0022	0.0004	0.0019	0.0003
rs3750081	7:32930876	G	T	0.0019	0.0004	0.0022	0.0003
rs55773927	7:65337902	T	C	0.002	0.0003	0.0019	0.0003
rs41301394	7:75612803	T	C	0.002	0.0004	0.0023	0.0003
rs11783418	8:10841858	G	A	0.002	0.0004	0.002	0.0004
rs10098664	8:11417493	C	T	0.0024	0.0004	0.0021	0.0003
rs2954017	8:126476873	T	C	0.0026	0.0004	0.0024	0.0003
rs34861762	8:23748420	C	T	0.0043	0.0003	0.0043	0.0003
rs10102889	8:32435620	G	C	0.005	0.0013	0.0036	0.0006
rs2980423	8:8142575	C	T	0.0025	0.0004	0.0023	0.0003
rs1533059	8:8684953	A	G	0.0028	0.0004	0.0025	0.0003
rs2976178	8:87332552	G	C	0.0027	0.0004	0.0025	0.0003
rs35353426	8:9297246	C	T	0.0026	0.0004	0.0026	0.0004
rs1321917	9:119324929	G	C	0.0025	0.0003	0.0023	0.0003
rs7024579	9:139100413	T	C	0.0023	0.0004	0.0023	0.0004
rs28404308	9:140103272	A	T	0.0027	0.0005	0.0024	0.0004
rs12377027	9:20554583	G	A	0.0027	0.0005	0.0026	0.0005
rs13287724	9:33169034	T	A	0.0029	0.0006	0.003	0.0006
rs544169	9:33956791	A	G	0.0024	0.0004	0.0022	0.0003
rs284859	10:104573017	T	G	0.0027	0.0004	0.0026	0.0004
rs1536225	10:105202318	G	T	0.0019	0.0004	0.0021	0.0003
rs6481598	10:29781798	C	G	0.0023	0.0004	0.0024	0.0004
rs7072591	10:35150364	A	G	0.0019	0.0004	0.0019	0.0003
rs8474	10:51026705	C	G	0.0019	0.0003	0.002	0.0003
rs10821905	10:52646093	A	G	0.0039	0.0004	0.0037	0.0004
rs7475348	10:69965177	T	C	0.0027	0.0004	0.0031	0.0003
rs12240572	10:75016365	T	A	0.0034	0.0007	0.0032	0.0006
rs816850	10:79252446	G	C	0.002	0.0004	0.002	0.0004
rs7095954	10:82209232	T	A	0.0019	0.0003	0.0018	0.0003
rs9420446	10:88880689	T	C	0.0022	0.0005	0.0023	0.0004
rs80282103	10:899071	A	T	0.0081	0.0006	0.0078	0.0006
rs2068888	10:94839642	G	A	0.0026	0.0003	0.0024	0.0003
rs4918943	10:97278922	G	A	0.0023	0.0005	0.0022	0.0004
rs6589750	11:119326726	A	G	0.0017	0.0004	0.002	0.0003
rs10790452	11:121584931	T	C	0.002	0.0004	0.002	0.0003
rs11564722	11:2178330	T	C	0.0038	0.0004	0.0033	0.0004
rs63934	11:2789062	A	G	0.0042	0.0004	0.0041	0.0004
rs963837	11:30749090	C	T	0.0055	0.0004	0.0057	0.0003
rs61897431	11:47427667	T	C	0.0028	0.0004	0.0029	0.0004
rs7127946	11:48250675	T	C	0.0023	0.0004	0.0023	0.0003

RSID	Chromosome and base pair	Effect allele	Other allele	European ancestry		Trans-ancestry	
				Effect size (beta)	SE	Effect size (beta)	SE
rs2727040	11:49057603	C	T	0.0026	0.0006	0.0026	0.0004
rs1813937	11:50468801	T	C	0.0019	0.0004	0.0022	0.0004
rs1541937	11:5578558	C	A	0.0029	0.0004	0.0029	0.0004
rs1783827	11:57409538	G	A	0.0021	0.0004	0.002	0.0003
rs948493	11:65552154	C	T	0.0032	0.0004	0.0033	0.0003
rs11237450	11:78023356	A	C	0.003	0.0005	0.0032	0.0004
rs117113238	12:12209203	A	G	0.0039	0.0006	0.0039	0.0006
rs10846157	12:15325031	C	A	0.0036	0.0004	0.0034	0.0004
rs632887	12:3392351	A	G	0.0033	0.0004	0.0032	0.0003
rs11062167	12:364739	G	A	0.0042	0.0003	0.0039	0.0003
rs4238020	12:4616642	T	C	0.0028	0.0005	0.0029	0.0005
rs2634675	12:48740855	A	G	0.0028	0.0004	0.0025	0.0003
rs12313306	12:57751854	T	C	0.0031	0.0004	0.0029	0.0004
rs41284816	13:50655989	G	T	0.0079	0.0012	0.0078	0.0012
rs500830	13:72348768	T	C	0.0026	0.0003	0.0029	0.0003
rs61993680	14:100752644	C	A	0.0022	0.0004	0.0019	0.0003
rs72683923	14:50735947	C	T	0.0076	0.0014	0.0074	0.0013
rs6574652	14:81870100	C	T	0.0019	0.0003	0.0017	0.0003
rs1028455	14:88829975	A	T	0.0021	0.0004	0.002	0.0003
rs17184313	14:93102251	C	T	0.0028	0.0005	0.0029	0.0005
rs12913015	15:39305443	T	C	0.0028	0.0004	0.0027	0.0003
rs6492982	15:41399951	C	T	0.0032	0.0004	0.0033	0.0004
rs1994887	15:57793765	C	A	0.0024	0.0004	0.002	0.0004
rs956006	15:62808539	T	C	0.0022	0.0004	0.0019	0.0003
rs11071738	15:63580155	C	T	0.0025	0.0003	0.0025	0.0003
rs11071939	15:67463391	C	T	0.0038	0.0007	0.0039	0.0006
rs351237	15:74477239	G	A	0.0018	0.0004	0.0018	0.0003
rs2472297	15:75027880	T	C	0.0039	0.0004	0.0039	0.0004
rs4886696	15:75664570	T	A	0.0033	0.0004	0.0032	0.0004
rs4886755	15:76298132	A	G	0.0041	0.0003	0.0041	0.0003
rs166906	15:76802175	T	C	0.0039	0.0006	0.0033	0.0005
rs17507300	15:83722059	A	G	0.0024	0.0005	0.0024	0.0004
rs7169629	15:85191274	C	G	0.0019	0.0003	0.0018	0.0003
rs59646751	15:99276521	G	T	0.002	0.0004	0.0023	0.0003
rs193538	16:16127916	G	T	0.002	0.0004	0.002	0.0003
rs438339	16:2003425	T	C	0.0035	0.0007	0.0035	0.0006
rs77924615	16:20392332	A	G	0.0096	0.0005	0.0098	0.0004
rs1635404	16:3747042	G	T	0.0024	0.0004	0.0025	0.0004
rs9932625	16:51735746	G	A	0.003	0.0004	0.003	0.0003
rs7203398	16:53189672	A	C	0.0027	0.0004	0.0025	0.0003
rs7185391	16:68323115	G	T	0.0026	0.0004	0.0027	0.0004
rs62053077	16:71643669	G	T	0.0025	0.0004	0.0021	0.0004
rs1858800	16:73024276	T	C	0.0022	0.0004	0.002	0.0003
rs154656	16:89708003	T	A	0.0031	0.0003	0.003	0.0003
rs28735420	17:12139964	T	G	0.004	0.0008	0.0039	0.0006
rs2349648	17:17017267	G	T	0.0022	0.0004	0.0017	0.0003
rs9891340	17:17543846	T	C	0.0024	0.0004	0.0024	0.0004
rs2440165	17:19428719	T	C	0.0041	0.0004	0.004	0.0003

RSID	Chromosome and base pair	Effect allele	Other allele	European ancestry		Trans-ancestry	
				Effect size (beta)	SE	Effect size (beta)	SE
rs2411192	17:34882998	T	A	0.0024	0.0003	0.0024	0.0003
rs227731	17:54773238	T	G	0.0018	0.0004	0.0018	0.0003
rs35662455	17:56755223	C	G	0.003	0.0005	0.003	0.0005
rs9903801	17:58915261	C	G	0.0049	0.0005	0.0047	0.0004
rs9895661	17:59456589	T	C	0.0074	0.0005	0.0069	0.0004
rs8866	17:65373979	G	C	0.0018	0.0004	0.0018	0.0003
rs883541	17:66449122	G	A	0.0023	0.0004	0.0022	0.0003
rs1719934	18:5585158	A	G	0.0028	0.0003	0.0026	0.0003
rs2974751	19:13053034	A	C	0.0019	0.0004	0.0018	0.0003
rs7251730	19:36997147	T	C	0.0024	0.0004	0.0024	0.0003
rs78241494	19:37649748	C	T	0.0031	0.0004	0.003	0.0004
rs113445505	19:38157969	T	C	0.0038	0.0004	0.0037	0.0003
rs34647824	19:50138143	C	A	0.002	0.0004	0.0021	0.0004
rs62187537	20:1333060	T	C	0.0038	0.0007	0.0039	0.0007
rs1041606	20:14677788	C	T	0.002	0.0004	0.0021	0.0004
rs6087579	20:32985155	G	A	0.003	0.0003	0.0028	0.0003
rs2273684	20:33529766	T	G	0.0033	0.0003	0.0032	0.0003
rs17216707	20:52732362	C	T	0.0052	0.0005	0.0051	0.0004
rs2235826	20:56143169	T	A	0.0033	0.0005	0.003	0.0004
rs72629024	20:62152519	C	G	0.0034	0.0006	0.0035	0.0005
rs4408777	20:62706105	G	A	0.0021	0.0004	0.0021	0.0003
rs1509117	20:8303120	A	T	0.0025	0.0004	0.0024	0.0004
rs2823139	21:16576783	G	A	0.0027	0.0004	0.0026	0.0003
rs2834317	21:35356706	G	A	0.0031	0.0005	0.0035	0.0005
rs2244237	21:37818141	T	G	0.0027	0.0004	0.0027	0.0004
rs131263	22:30133045	T	C	0.0023	0.0004	0.0024	0.0004
rs80576	22:36539804	G	A	0.0027	0.0005	0.0028	0.0005
rs4820324	22:38599857	G	C	0.0023	0.0004	0.0023	0.0003
rs112880707	22:40884662	T	C	0.0056	0.0006	0.0052	0.0005
rs738527	22:43112961	T	C	0.0031	0.0004	0.0032	0.0003

SE= standard error. Weights were taken from the discovery GWAS of the CKDGen study.[20]

Table S5: Pairwise Pearson correlations of GRSs for eGFR and body-mass index, by study

	Creatinine-based eGFR	BMI	GRS	GRS (Cys)	GRS (BUN)
UKB					
GRS	0.1730*	-0.0037			
GRS (Cys)	0.1447*	-0.0031	0.8003*		
GRS (BUN)	0.1378*	0.0009	0.7626*	0.7661*	
GRS (Raw)	0.2005*	-0.0039	0.8898*	0.7062*	0.6731*
EPIC-CVD					
GRS	0.1357*	-0.0203			
GRS (Cys)	0.1183*	-0.0037	0.7954*		
GRS (BUN)	0.1025*	-0.0199	0.7591*	0.7564*	
GRS (Raw)	0.1598*	-0.0079	0.8851*	0.6972*	0.6612*
MVP					
GRS	0.1475*	-0.0021			
GRS (Cys)	0.1267*	0.0029	0.8032*		
GRS (BUN)	0.1240*	-0.0034	0.6507*	0.6626*	
GRS (Raw)	0.1670*	-0.0058	0.8894*	0.7090*	0.6934*

GRS was constructed using 218 European-specific eGFR (creatinine-based) associated genetic variants (n=567,460). GRS (Cys) included 127 genetic variants (out of the 218 genetic variants included in the GRS for eGFR) that were additionally associated with cystatin-C-based eGFR (n=460,826). GRS (BUN) included 121 genetic variants (out of the 218 genetic variants included in the GRS for eGFR) that were additionally associated with blood urine nitrogen (n=416,178). GRS (Raw) included all the 262 eGFR-associated index variants in CKDGen trans-ancestry analysis (n=765,348). * Bonferroni-corrected significance (P<0.01). GRS= genetic risk score. eGFR= estimated glomerular filtration rate. BMI= body-mass index.

Table S6: Mendelian randomization estimates of each 5 mL/min/1.73 m^2 lower genetically-predicted eGFR with risk of coronary heart disease and stroke

eGFR within studies,	Mean eGFR, mL/min/1.73m2	No. of participants	Coronary heart disease		Stroke	
mL/min/1.73m2			No. of events	HR (95% CI)	No. of events	HR (95% CI)
EPIC-CVD						
< 60	50.1	533	266	1.52 (1.09, 2.13)	103	2.30 (1.32, 4.02)
60 - 74	69.1	1979	847	1.10 (0.94, 1.29)	322	1.13 (0.86, 1.49)
75 - 89	83.3	4953	1760	1.08 (0.97, 1.21)	777	1.01 (0.85, 1.20)
90 - 104	97.6	8787	2619	1.11 (1.00, 1.23)	1382	1.01 (0.88, 1.16)
≥105*	111.0	3569	658	0.85 (0.71, 1.02)	376	0.83 (0.64, 1.09)
MVP						
< 60	50.6	9241	1146	1.18 (1.04, 1.34)	250	1.10 (0.84, 1.44)
60 - 74	68.3	22,916	2008	1.06 (0.97, 1.16)	484	1.17 (0.97, 1.41)
75 - 89	82.9	34,890	2752	1.05 (0.97, 1.14)	587	0.92 (0.78, 1.09)
90 - 104	96.4	30,130	2285	0.94 (0.86, 1.02)	514	1.10 (0.91, 1.33)
≥105*	111.7	8085	316	0.98 (0.77, 1.24)	79	1.41 (0.87, 2.27)
UK Biobank						
< 60	52.4	5044	337	0.84 (0.66, 1.08)	138	1.03 (0.70, 1.53)
60 - 74	69.4	28,361	1459	1.10 (0.97, 1.23)	512	1.11 (0.91, 1.34)
75 - 89	83.5	83,821	3717	1.04 (0.97, 1.11)	1201	0.98 (0.87, 1.11)

90 - 104	97.0	137,263	5069	1.00 (0.94, 1.07)	1686	1.07 (0.96, 1.20)
≥105*	109.1	34,146	678	0.94 (0.79, 1.11)	211	0.97 (0.71, 1.31)
Combined						
< 60	51.2	14,818	1749	1.14 (1.03, 1.27)	491	1.19 (0.97, 1.47)
60 - 74	68.9	53,256	4314	1.08 (1.01, 1.15)	1318	1.14 (1.01, 1.28)
75 - 89	83.3	123,664	8229	1.05 (1.00, 1.10)	2565	0.97 (0.89, 1.06)
90 - 104	96.9	176,180	9973	1.01 (0.96, 1.05)	3582	1.06 (0.98, 1.14)
≥105*	109.7	45,800	1652	0.91 (0.82, 1.02)	666	0.95 (0.79, 1.14)

HRs are shown per 5 mL/min/1.73 m^2 lower genetically-predicted eGFR and are adjusted for age, age-squared, sex, study center, and the first ten principal components. *HRs in the group with eGFR above 105 were shown per 5 mL/min/1.73 m^2 *higher* genetically-predicted eGFR. Mean eGFR within each stratum was weighted by the number of participants from each contributing study, and MR estimates within each stratum were meta-analyzed using inverse variance weighting and fixed effects.

Figure S1: Distributions of creatinine measurements by study

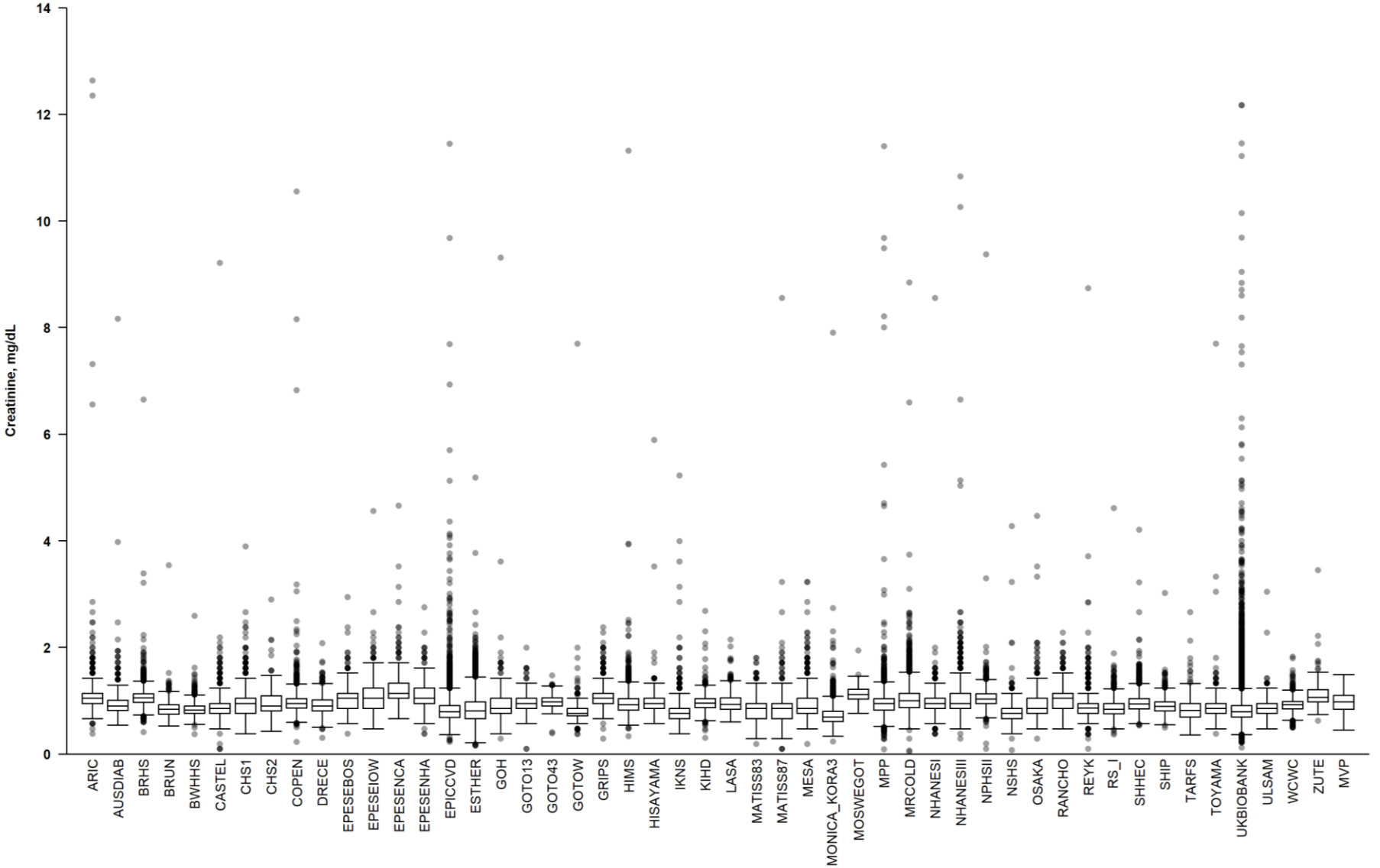
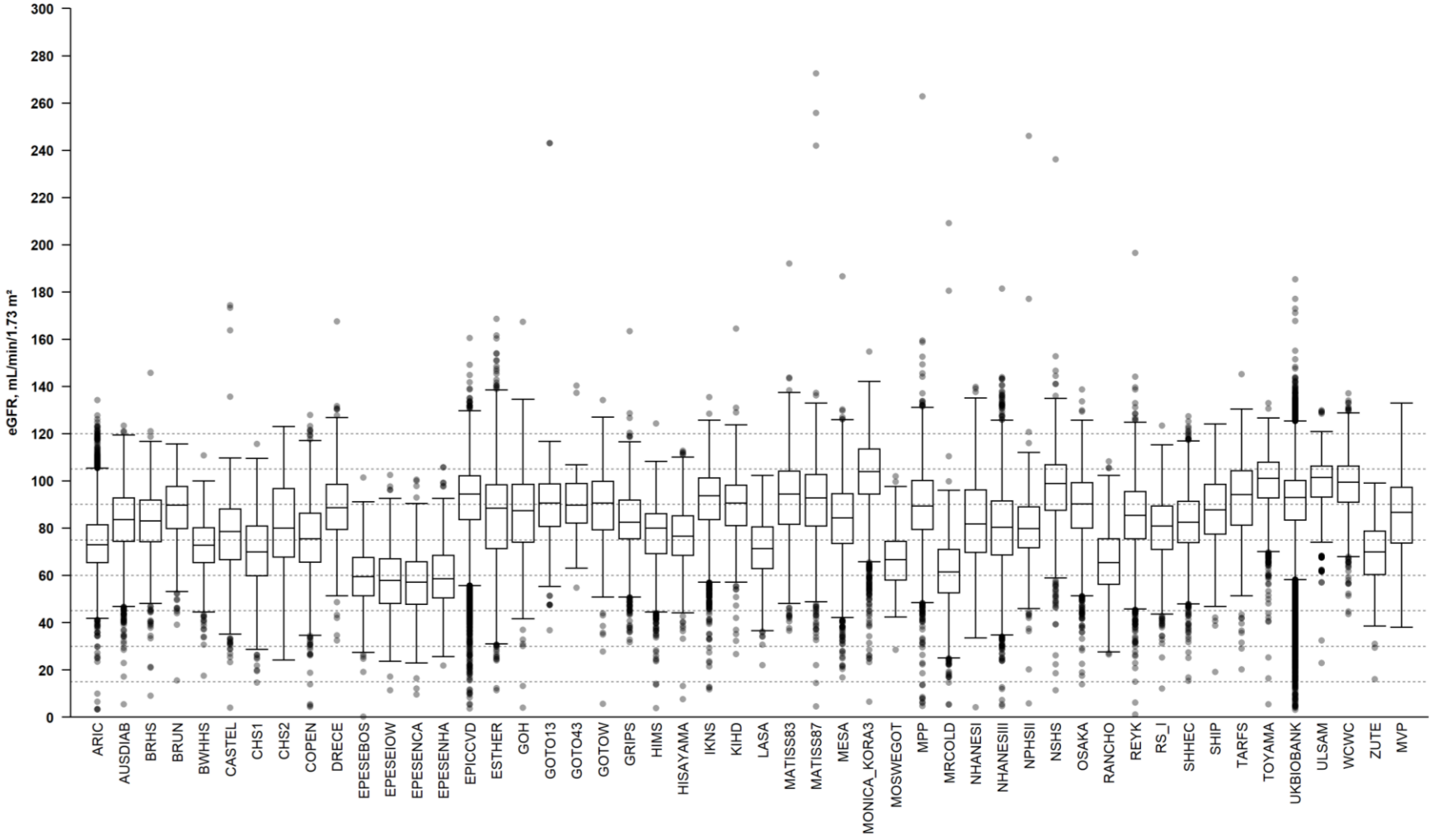
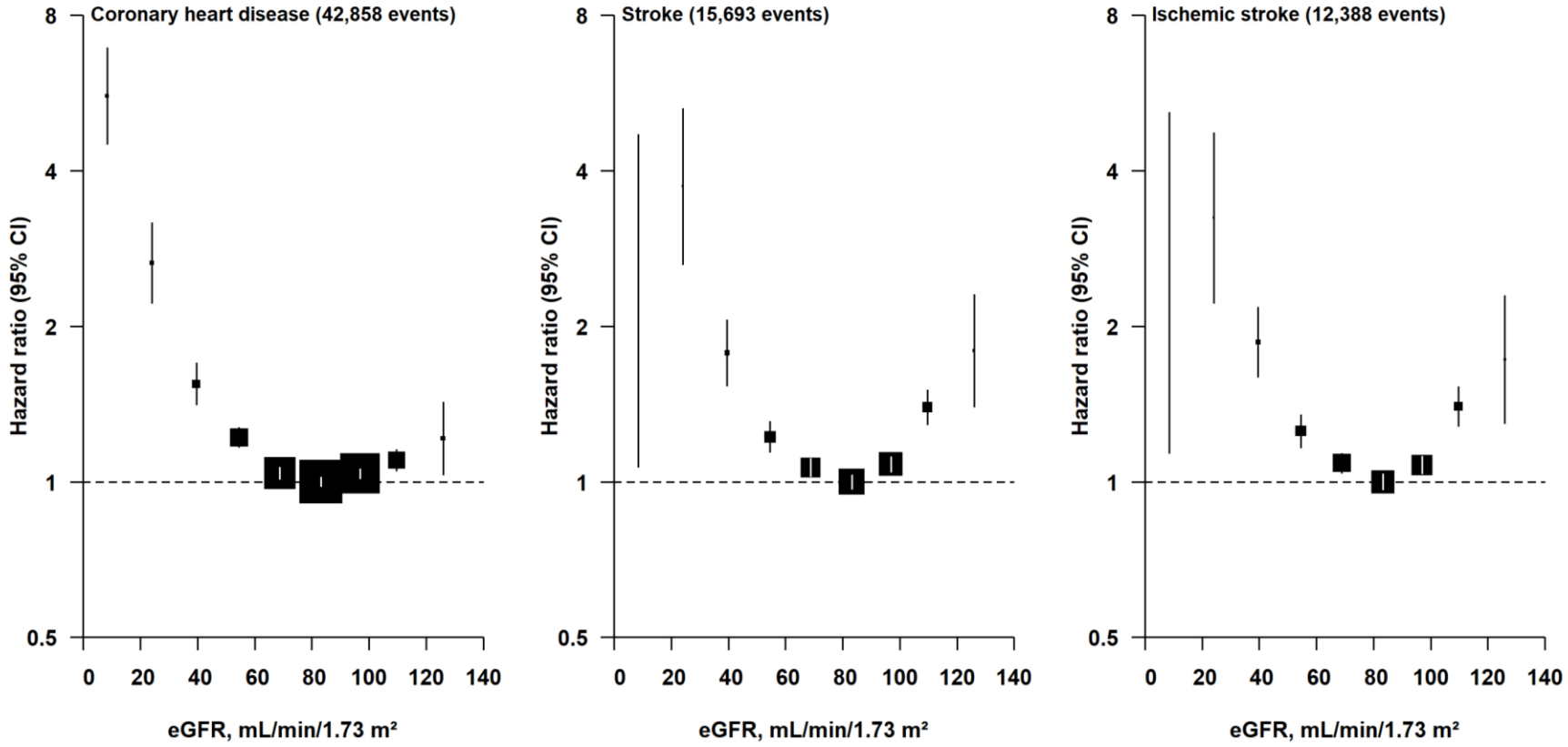

Creatinine, mg/dL
0
2
4
6
8
10
12
14
ARIC
AUSDIAB
BRHS
BRUN
BWHHS
CASTEL
CHS1
CHS2
COPEN
DRECE
EPESEBOS
EPESEIOW
EPESENCA
EPESENHA
EPICCVD
ESTHER
GOH
GOTO13
GOTO43
GOTOW
GRIPS
HIMS
HISAYAMA
IKNS
KIHD
LASA
MATISS83
MATISS87
MESA
MONICA_KORA3
MOSWEGOT
MPP
MRCOLD
NHANESI
NHANESIII
NPHSII
NSHS
OSAKA
RANCHO
REYK
RS_I
SHHEC
SHIP
TARFS
TOYAMA
UKBIOBANK
ULSAM
WCWC
ZUTE
MVP

Figure S2: Distributions of measured eGFR by study



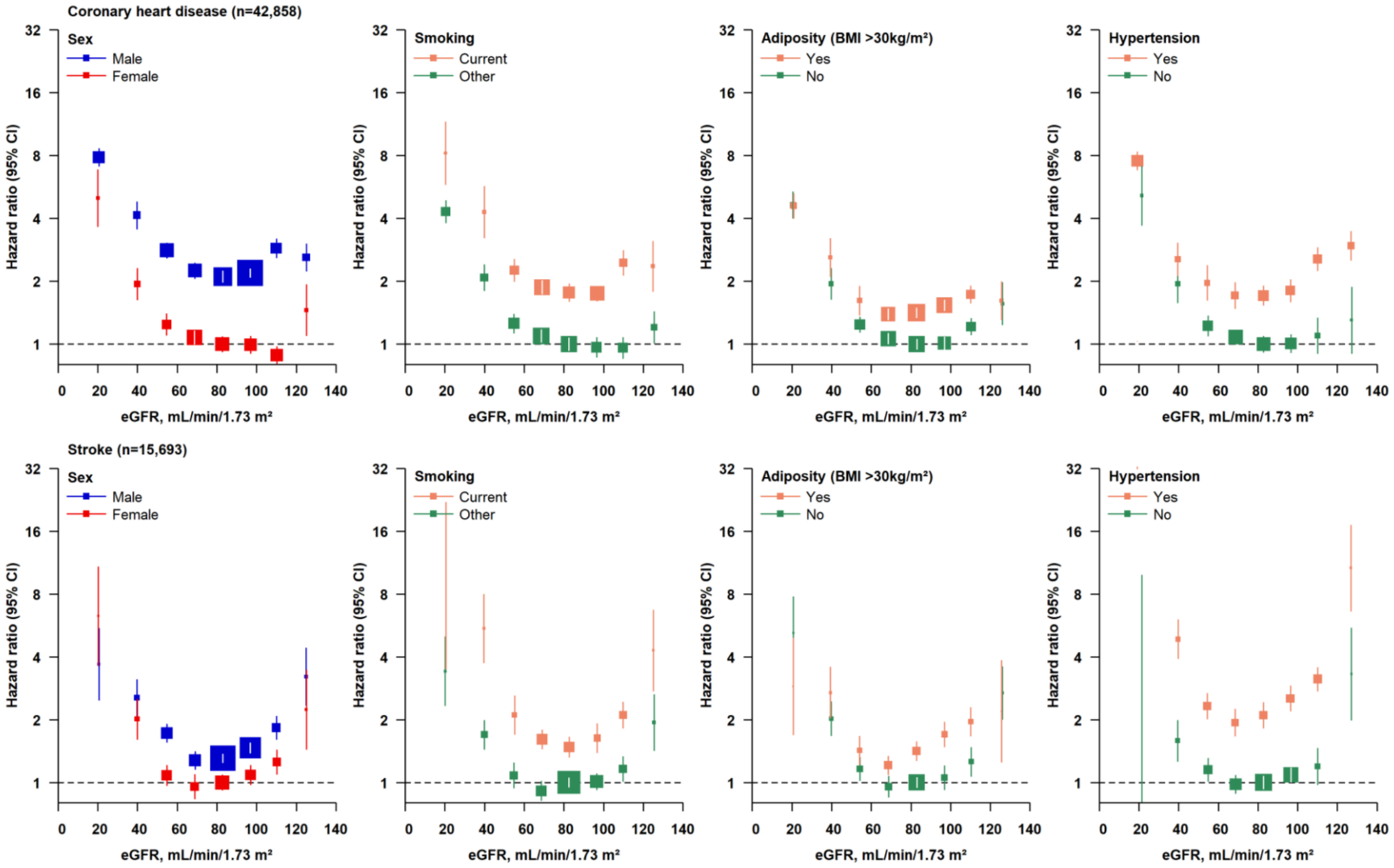
Participants with eGFR levels greater than 300 mL/min/1.73 m^2 were excluded from the analysis.

Figure S3: Observational associations of creatinine-based eGFR with risk of coronary heart disease and stroke (n=648,135)



Participants with missing information on age, sex, systolic blood pressure, total and high-density lipoprotein cholesterol, body-mass index, smoking status were excluded from the analysis. Hazards ratios were estimated using Cox regression, adjusted for age, sex and study centre, where appropriate. The eGFR was estimated using creatinine-based CKD-EPI formula. The categories of eGFR are <15, 15-<30, 30-<44, 45-<60, 60-<75, 75-<90, 90-<105, 105-<120, and ≥120 mL/min/1.73 m^2. The reference category is 75-<90 mL/min/1.73 m^2. Hazards ratios were plotted against the mean eGFR in each category. Sizes of the boxes are proportional to the inverse of the variance of the log risk within that specific group. Vertical lines represented 95% confidence intervals.

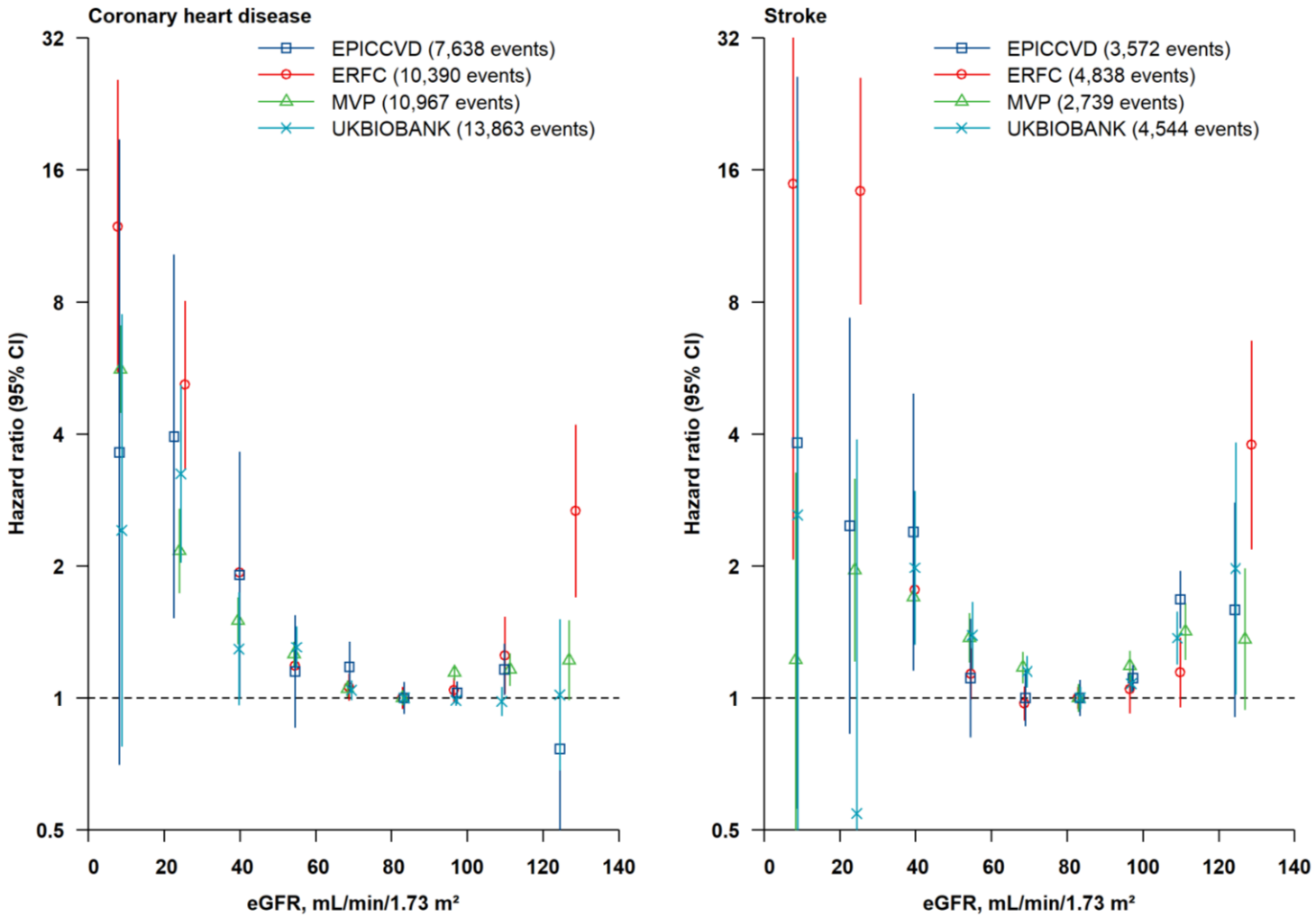
Figure S4: Observational associations of creatinine-based eGFR with risk of coronary heart disease and stroke by sex, smoking, adiposity and hypertension.



Participants with missing information on age, sex, systolic blood pressure, total and high-density lipoprotein cholesterol, body-mass index, smoking status were excluded from the analysis. Hazards ratios were estimated using Cox regression, adjusted for age, sex and study centre. The categories of eGFR are <30, 30-<44, 45-<60, 60-<75, 75-<90, 90-<105, 105-<120, and ≥120 mL/min/1.73 m^2. The reference category is 75-<90 mL/min/1.73 m^2 in females, non-smokers, participants with no history of diabetes, or hypertension in the respective panels. Hazards ratios

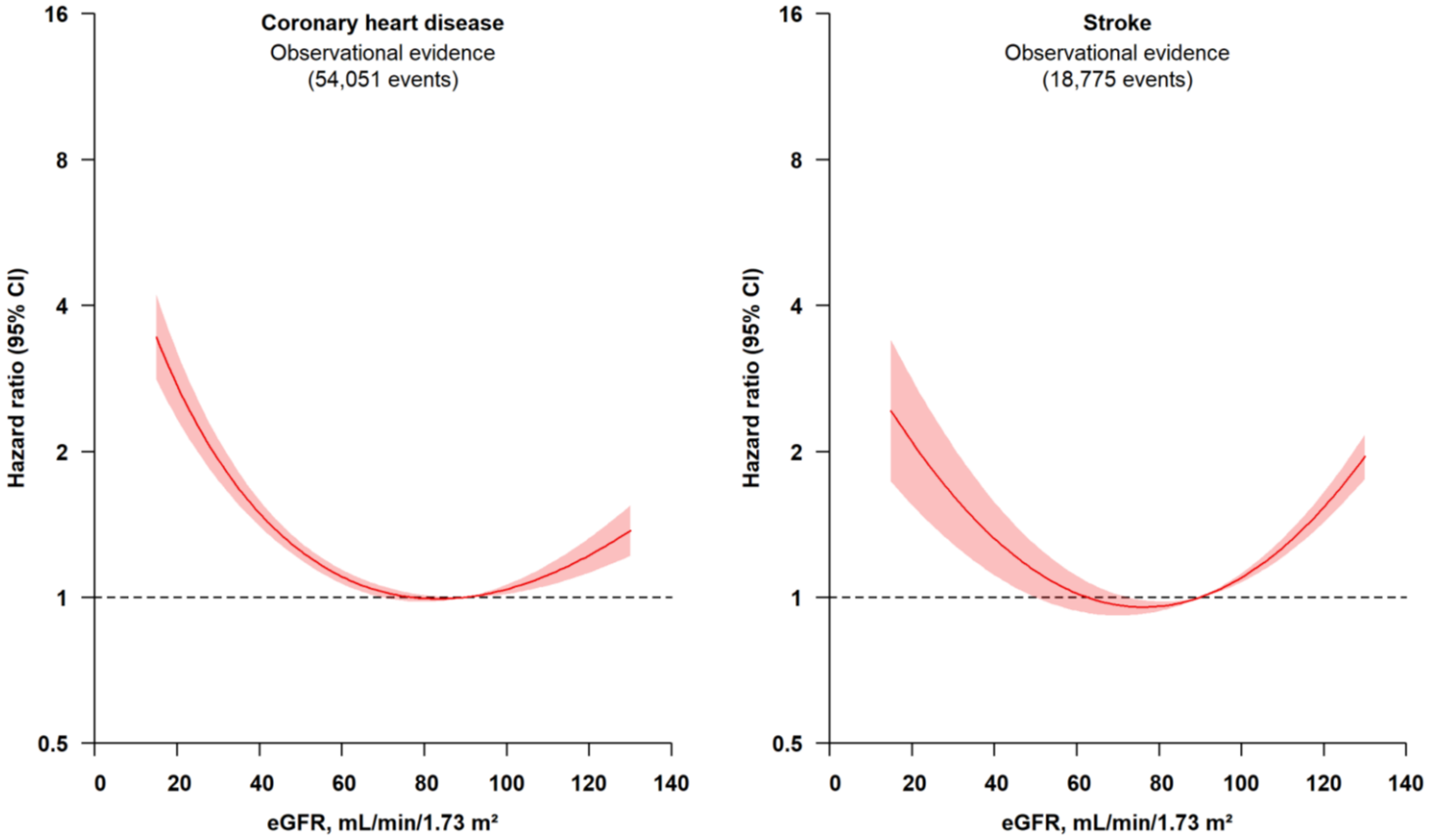
were plotted against the mean eGFR in each category. Sizes of the boxes are proportional to the inverse of the log risk in that specific group. Vertical lines represented 95% confidence intervals. Hypertension was defined as recorded prior history of hypertension or systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg.

Figure S5: Observational associations of creatinine-based eGFR with risk of coronary heart disease and stroke, by contributing study



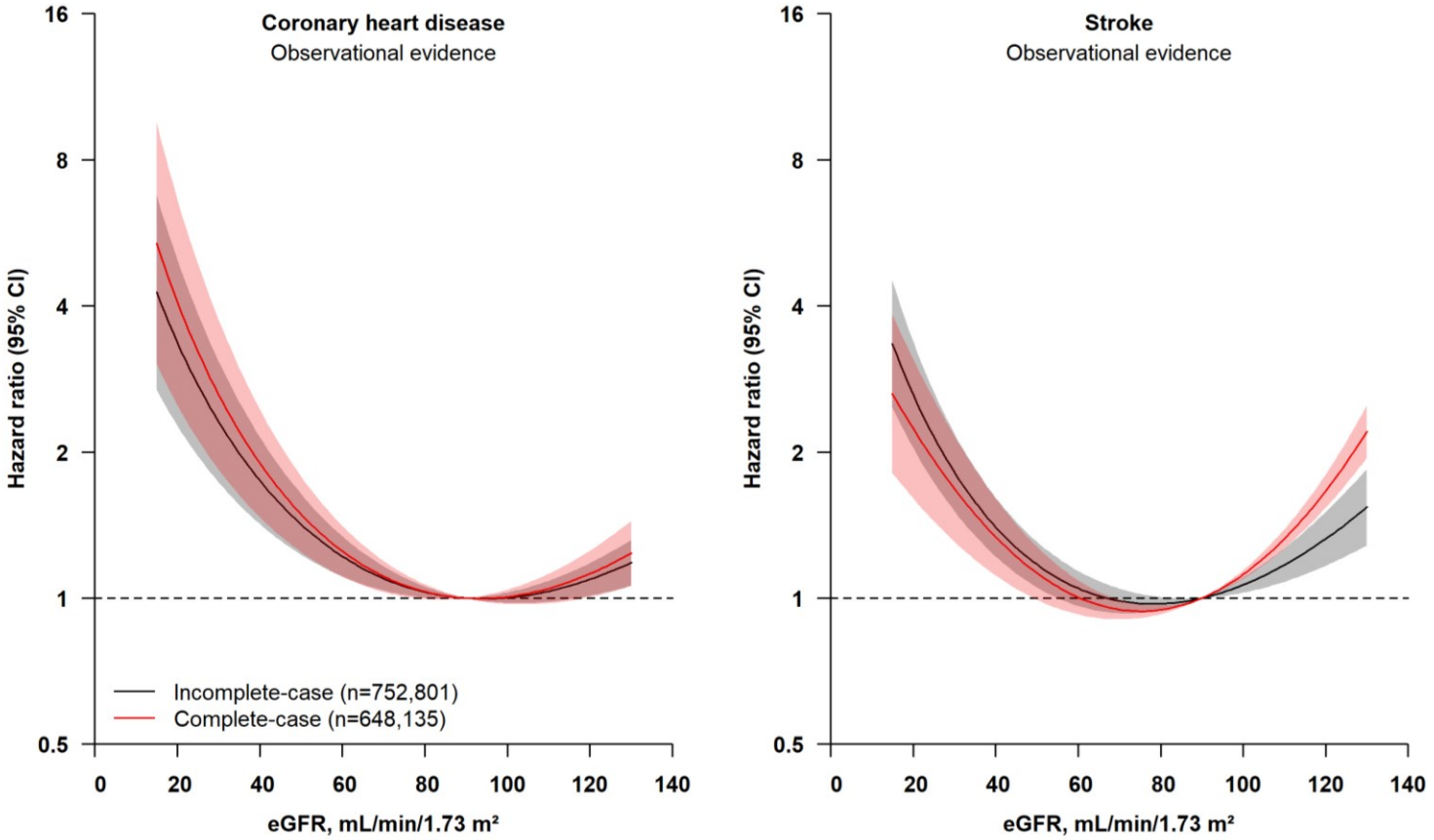
Participants with missing information on age, sex, systolic blood pressure, total and high-density lipoprotein cholesterol, body-mass index, smoking status were excluded from the analysis. Hazards ratios were estimated using Cox regression, adjusted for age, and systolic blood pressure, total and high-density lipoprotein cholesterol, body-mass index, and smoking status, and stratified by sex and study center, where appropriate. The eGFR was estimated using creatinine-based CKD-EPI formula. The categories of eGFR are <15, 15-<30, 30-<44, 45-<60, 60-<75, 75-<90, 90-<105, 105-<120, and ≥120 mL/min/1.73 m^2. The reference category is 75-<90 mL/min/1.73 m^2. Hazards ratios were plotted against the mean eGFR in each category, with vertical lines representing 95% confidence intervals.

Figure S6: Observational association of creatinine-based eGFR with risk of coronary heart disease and stroke, *irrespective of diabetes status at recruitment* (n=732,808)



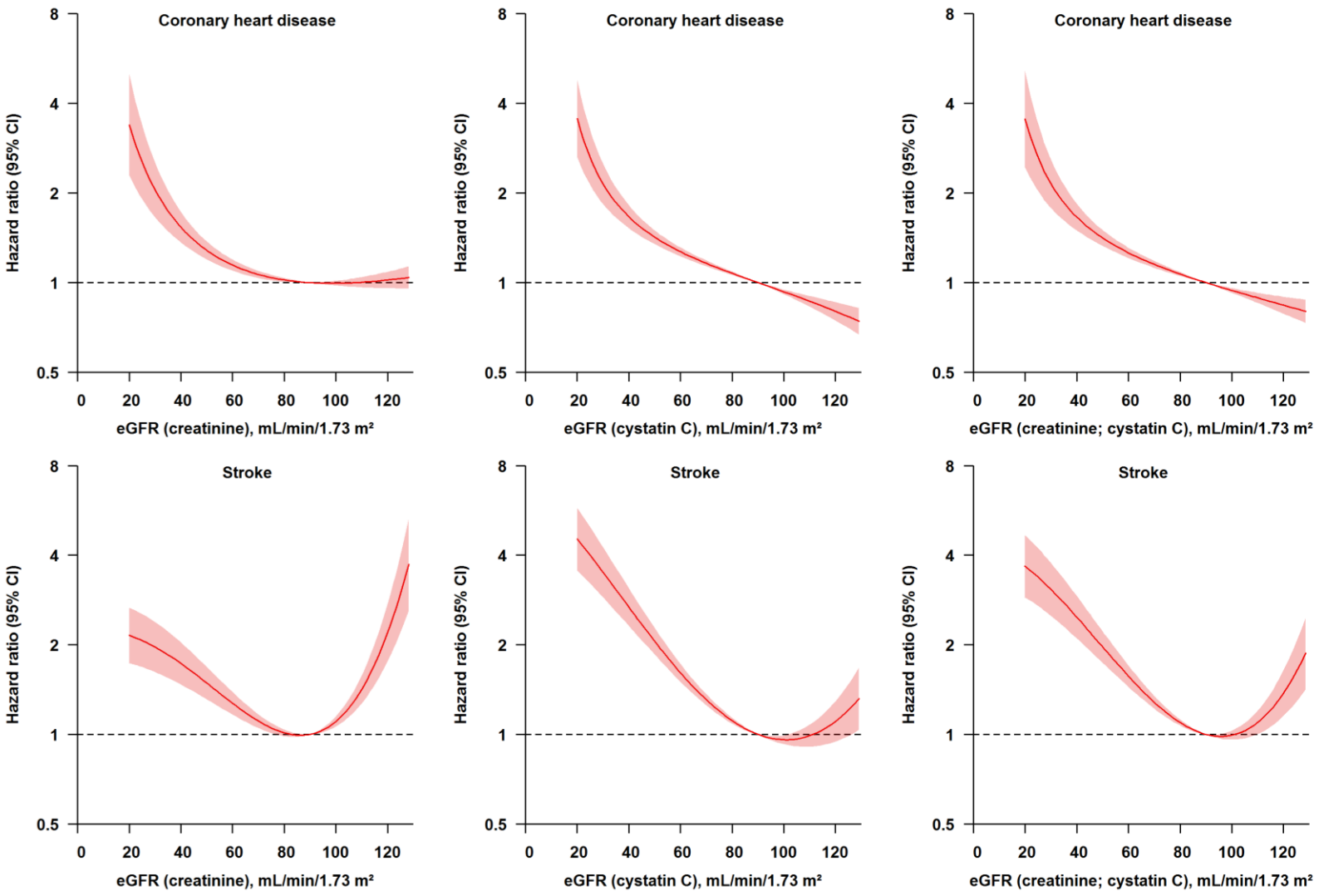
Participants with missing information on age, sex, systolic blood pressure, total and high-density lipoprotein cholesterol, body-mass index, smoking status were excluded from the analysis. Hazards ratios were estimated using Cox regression, adjusted for age, and systolic blood pressure, total and high-density lipoprotein cholesterol, body-mass index, and smoking status, and stratified by sex and study center. eGFR was estimated using creatinine-based CKD-EPI formula. The reference point is 90 mL/min/1.73 m^2. Shaded regions indicate 95% confidence intervals.

Figure S7: Observational association of creatinine-based eGFR with risk of coronary heart disease and stroke, with / without complete information on vascular risk factors



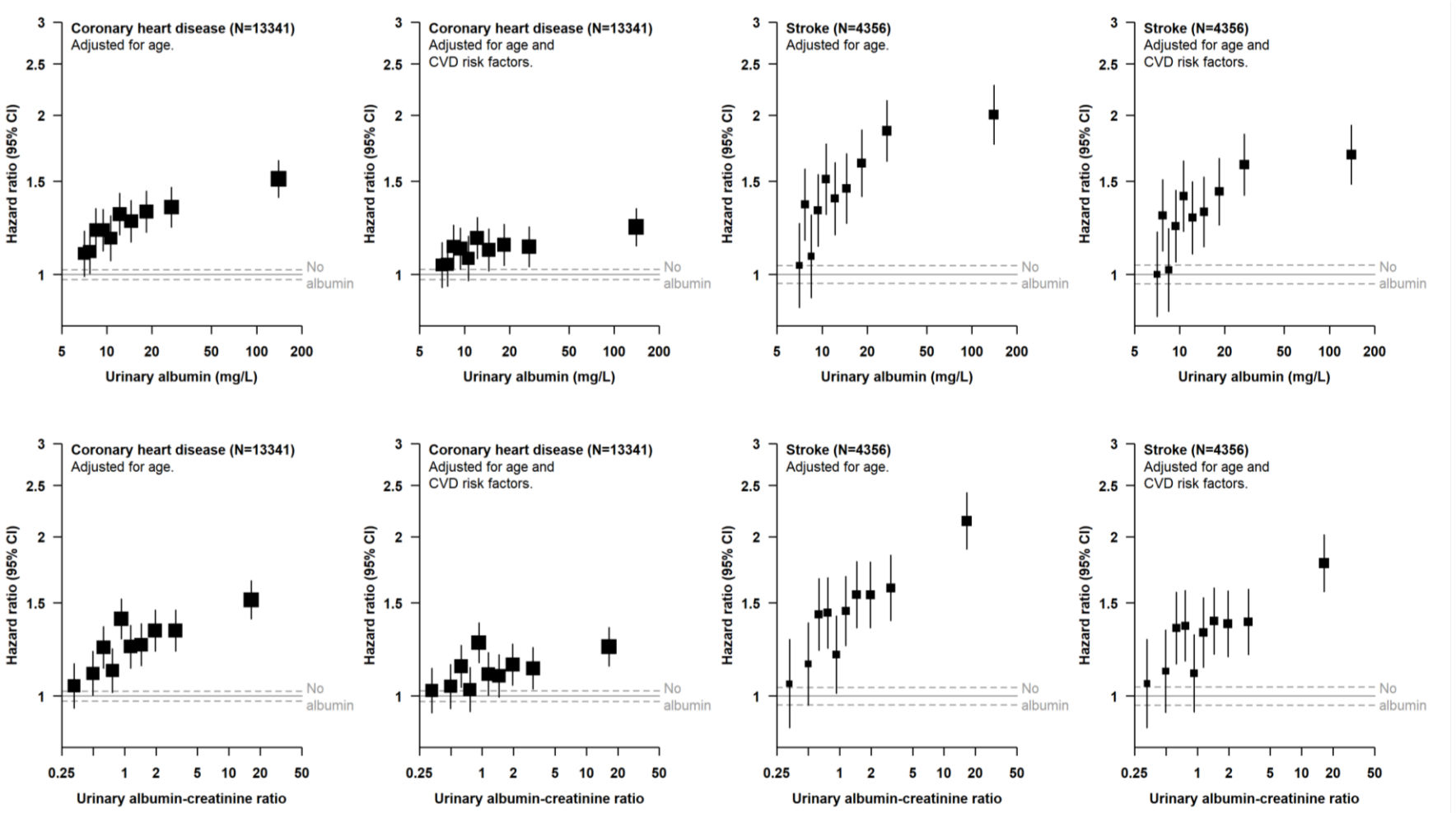
Incomplete-case included participants with information on age, sex, creatinine measurements; and complete-case included participants with complete information on age, sex, creatinine measurement, systolic blood pressure, total and high-density lipoprotein cholesterol, body-mass index, smoking status. Hazards ratios were estimated using Cox regression, adjusted for age, and systolic blood pressure, total and high-density lipoprotein cholesterol, body-mass index, and smoking status, and stratified by sex and study center. eGFR was estimated using creatinine-based CKD-EPI formula. The reference point is 90 mL/min/1.73 m^2. Shaded regions indicate 95% confidence intervals.

Figure S8: Observational associations of eGFR, estimated using creatinine or cystatin-C, with risk of coronary heart disease and stroke



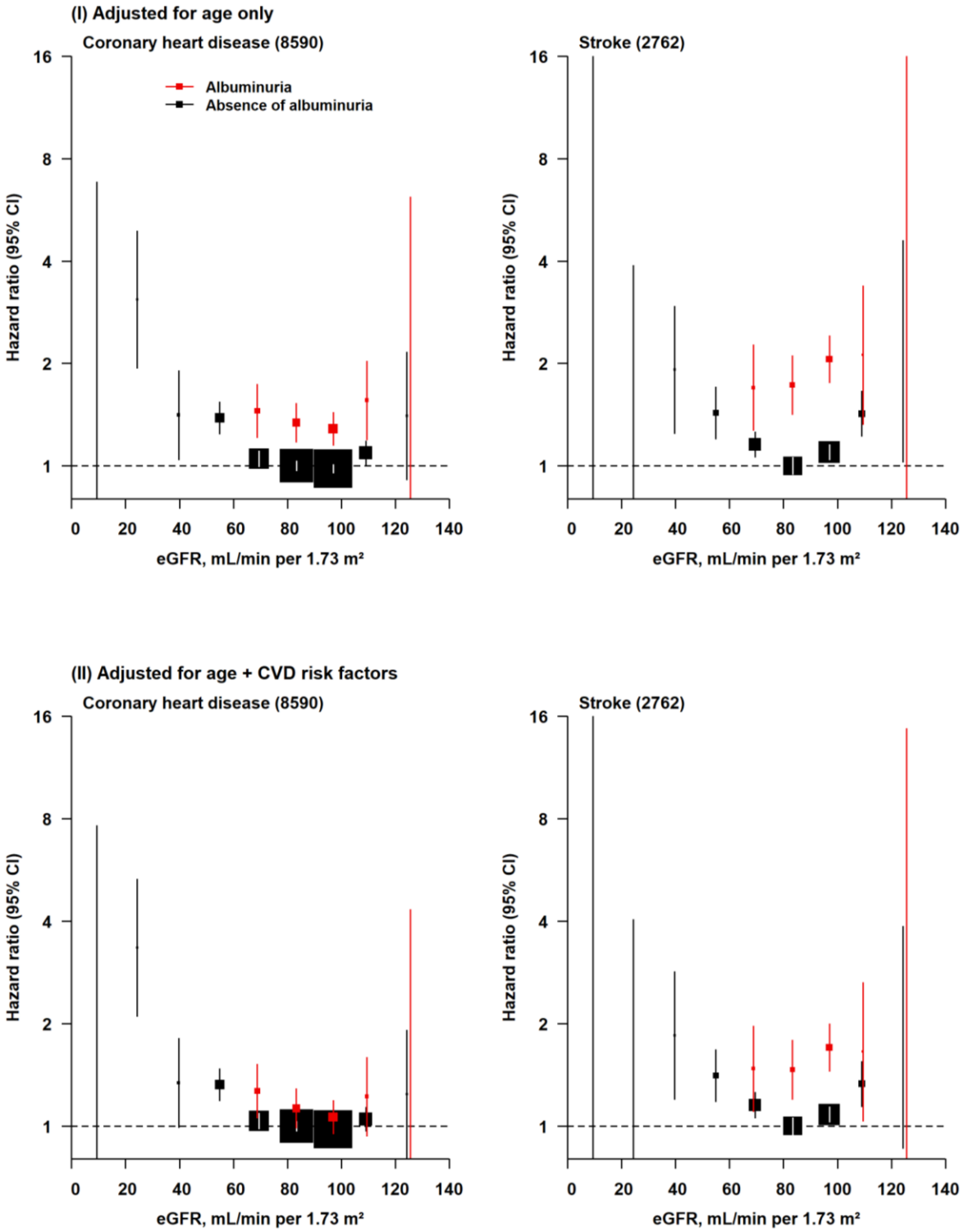
Participants with missing information on age, sex, systolic blood pressure, total and high-density lipoprotein cholesterol, body-mass index, smoking status were excluded from the analysis. Hazards ratios were estimated using Cox regression, adjusted for age, and systolic blood pressure, total and high-density lipoprotein cholesterol, body-mass index, and smoking status, and stratified by sex and study center. The reference point is 90 mL/min/1.73 m^2. Shaded regions indicate 95% confidence intervals.

Figure S9: Observational associations of urinary albumin and urinary albumin-creatinine ratio with risk of coronary heart disease and stroke in UK Biobank



Participants with missing information on age, sex, systolic blood pressure, total and high-density lipoprotein cholesterol, body-mass index, smoking status were excluded from the analysis. Participants were divided into deciles based on their detectable urinary albumin value (i.e., ≥6.7 mmol/L), with an extra category grouping those with urinary albumin below the detection limit (indicated as no albumin). The group with no albumin measurements was the reference category. Hazards ratios were estimated using Cox regression, and plotted against the mean levels of the urinary marker in each category. Sizes of the boxes are proportional to the inverse of the variance of the log risk within that specific group. Vertical lines represent 95% confidence intervals. Dashed lines above and below 1 indicated the 95% confidence interval for the reference category calculated using the method of floating absolute risk.

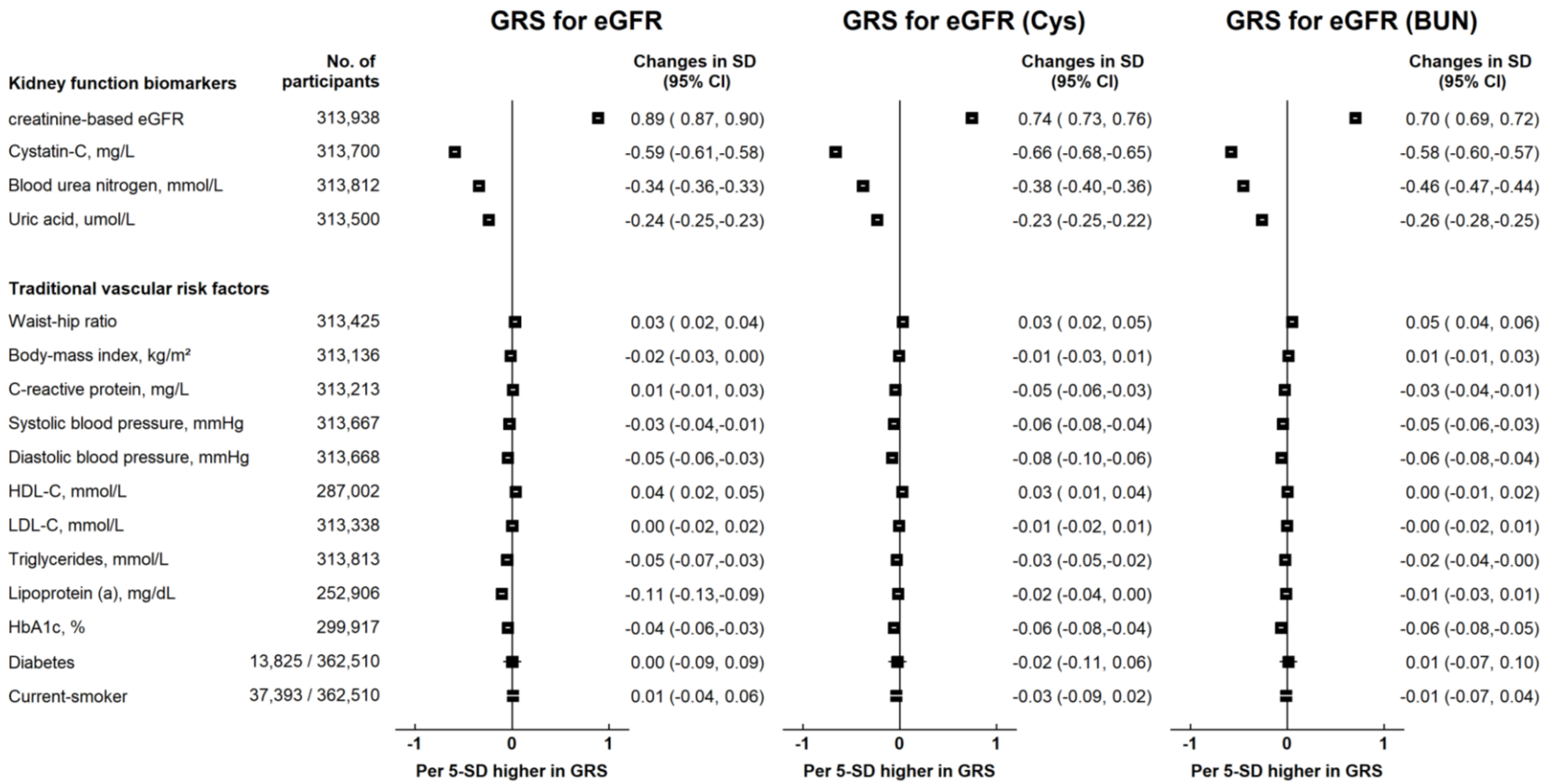
Figure S10: Observational association of creatinine-based eGFR with risk of coronary heart disease and stroke in UK Biobank, by presence of urinary microalbumin



Participants with missing information on age, sex, systolic blood pressure, total and high-density lipoprotein cholesterol, body-mass index, smoking status were excluded from the analysis. Hazards ratios were estimated using Cox regression, adjusted for age, and stratified by sex. Full adjustment included further adjustment for systolic blood pressure, body-mass index, total cholesterol, HDL cholesterol, smoking, and use of lipid-lowering treatments. eGFR was estimated using creatinine-based CKD-EPI formula. The categories of eGFR are <15, 15-<30, 30-<45. 45-<60, 60-<75, 75-<90, 90-<105, 105-<120, and ≥120 mL/min/1.73 m^2. The reference category is 75-<90 mL/min.1.73 m^2 with

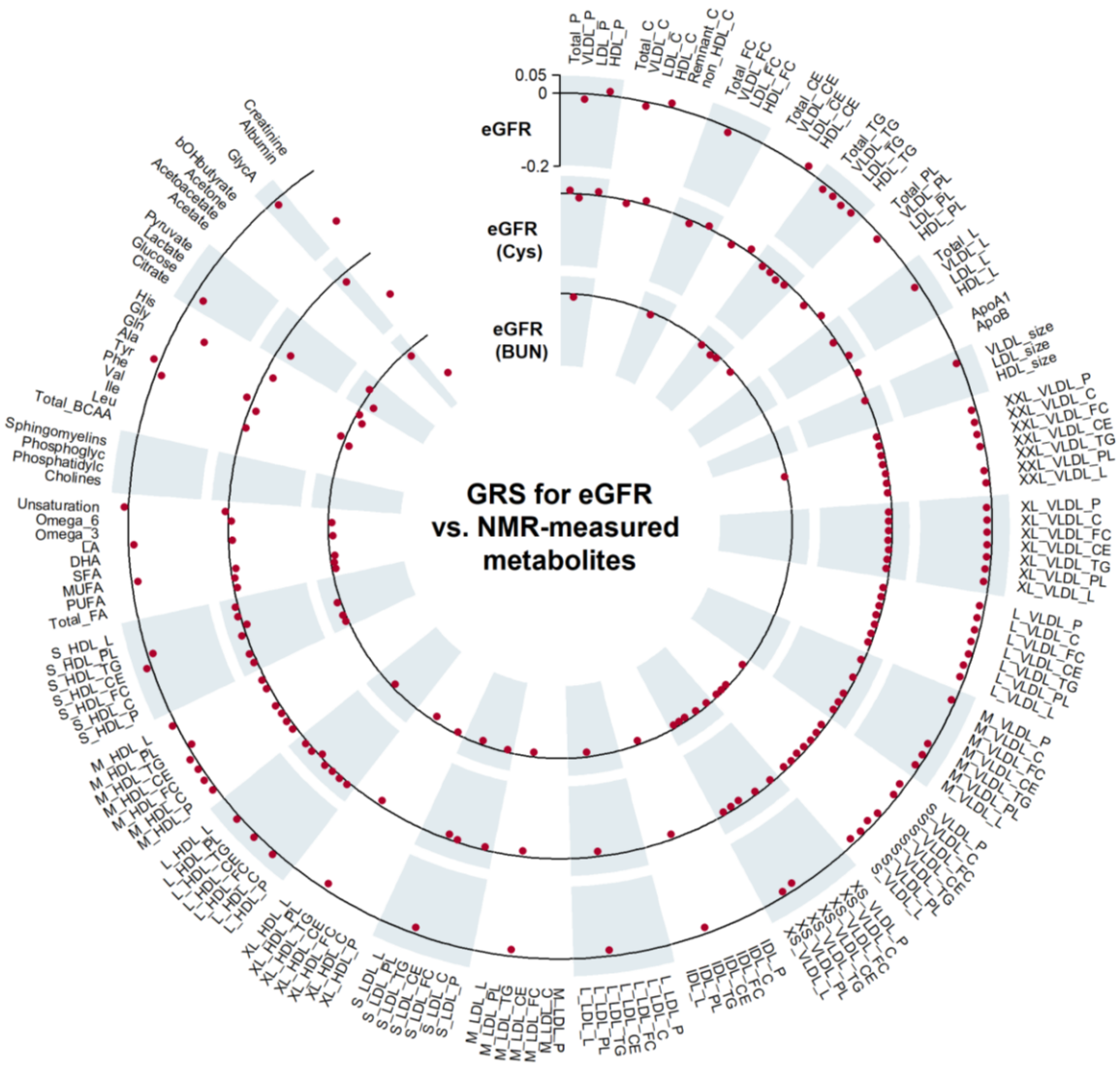
no urinary microalbumin. Hazards ratios are plotted against the mean eGFR within that category, and vertical lines represent 95% confidence interval.

Figure S11: Associations of the genetic risk scores for eGFR with kidney function biomarkers and traditional vascular risk factors



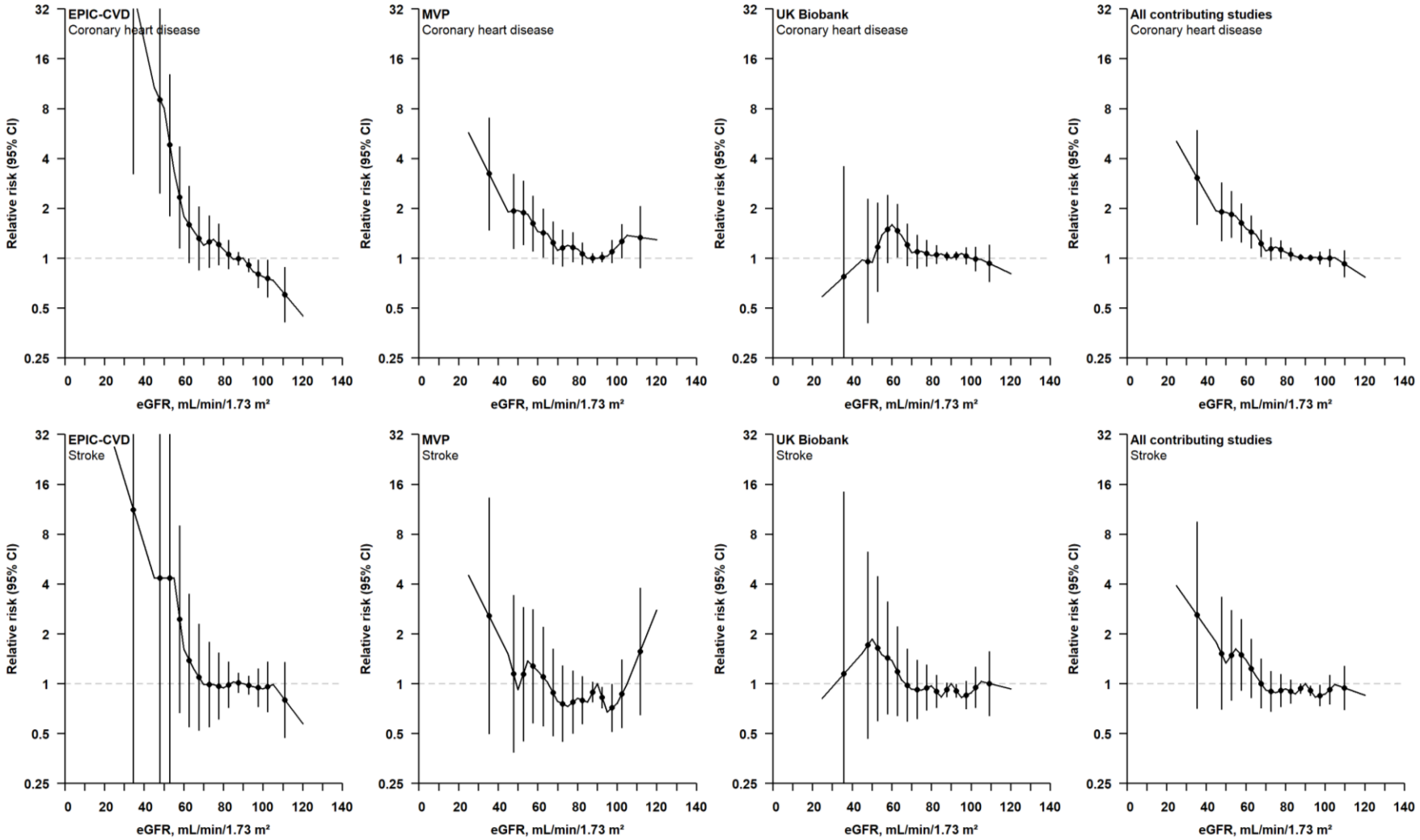
GRS was constructed using 218 eGFR (creatinine-based) associated genetic variants reported in CKDGen (n=567,460). GRS (Cys) included 127 genetic variants (out of the 218 genetic variants included in the GRS for eGFR) that were additionally associated ($P<5x10^{-8}$) with cystatin-C-based eGFR (n=460,826). GRS (BUN) included 121 genetic variants (out of the 218 genetic variants included in the GRS for eGFR) that were additionally associated ($P<5x10^{-8}$) with blood urine nitrogen (n=416,178). The analyses were conducted in UKB and restricted to participants of European ancestry, not on lipid-lowering treatment, without prior history of cardiovascular diseases or diabetes at baseline, where appropriate. Analyses were adjusted for age, age-squared, sex, study centre, the first ten principal components. For continuous traits, general linear regression was used to estimate SD differences in all traits (after rank inverse normal transformation) per 1 SD. higher GRS. For binary traits, logistic regression was used to estimate log odds ratio differences per 1 SD. higher GRS. Results were shown for each per 5-SD higher in GRS. SD= standard derivation. GRS= genetic risk score.

Figure S12: Associations of the GRSs for eGFR with 167 NMR-measured metabolites



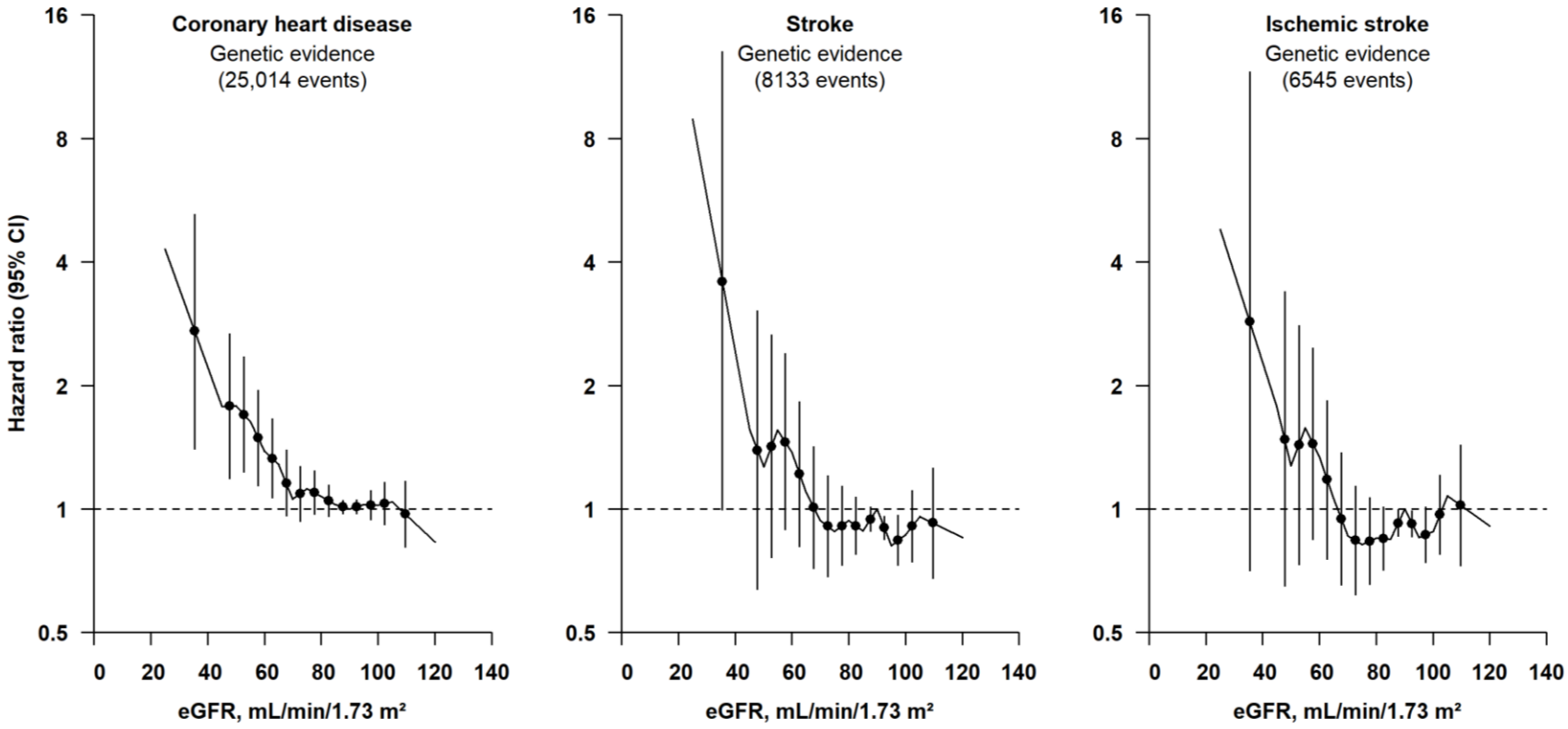
GRS was constructed using 218 eGFR (creatinine-based) associated genetic variants (n=567,460). GRS (Cys) included 127 genetic variants (out of the 218 genetic variants included in the GRS for eGFR) that were additionally associated with cystatin-C-based eGFR (n=460,826). GRS (BUN) included 121 genetic variants (out of the 218 genetic variants included in the GRS for eGFR) that were additionally associated with blood urine nitrogen (n=416,178). The analyses were conducted in a subset of UK Biobank study (n=79,413), with European ancestry, not on lipid-lowering treatments, and had no prior history of diabetes or vascular disease at baseline. Estimates were adjusted for age, age-squared, sex, study center, the first ten principal components. Points shown represent estimates for each metabolite per SD higher GRSs that fell below Bonferroni-corrected significant ($P<3.0x10^{-4}$). XXL= chylomicrons and extremely large. XL= extra large. L= large. M= medium. S= small. XS= very small. VLDL= very low-density lipoprotein. LDL= low-density lipoprotein. HDL= high-density lipoprotein. TG= triglycerides. P= particle concentrations. C= cholesterol. FC= free cholesterol. EC= esterified cholesterol. PL= phospholipids. L= total lipids. D= particle size. FA= fatty acids. LA= linoleic acid. PUFA= polyunsaturated fatty acids. MUFA= monounsaturated fatty acids.

Figure S13: Mendelian randomization estimates of genetically-predicted eGFR with risk of coronary heart disease and stroke (n=413,718)



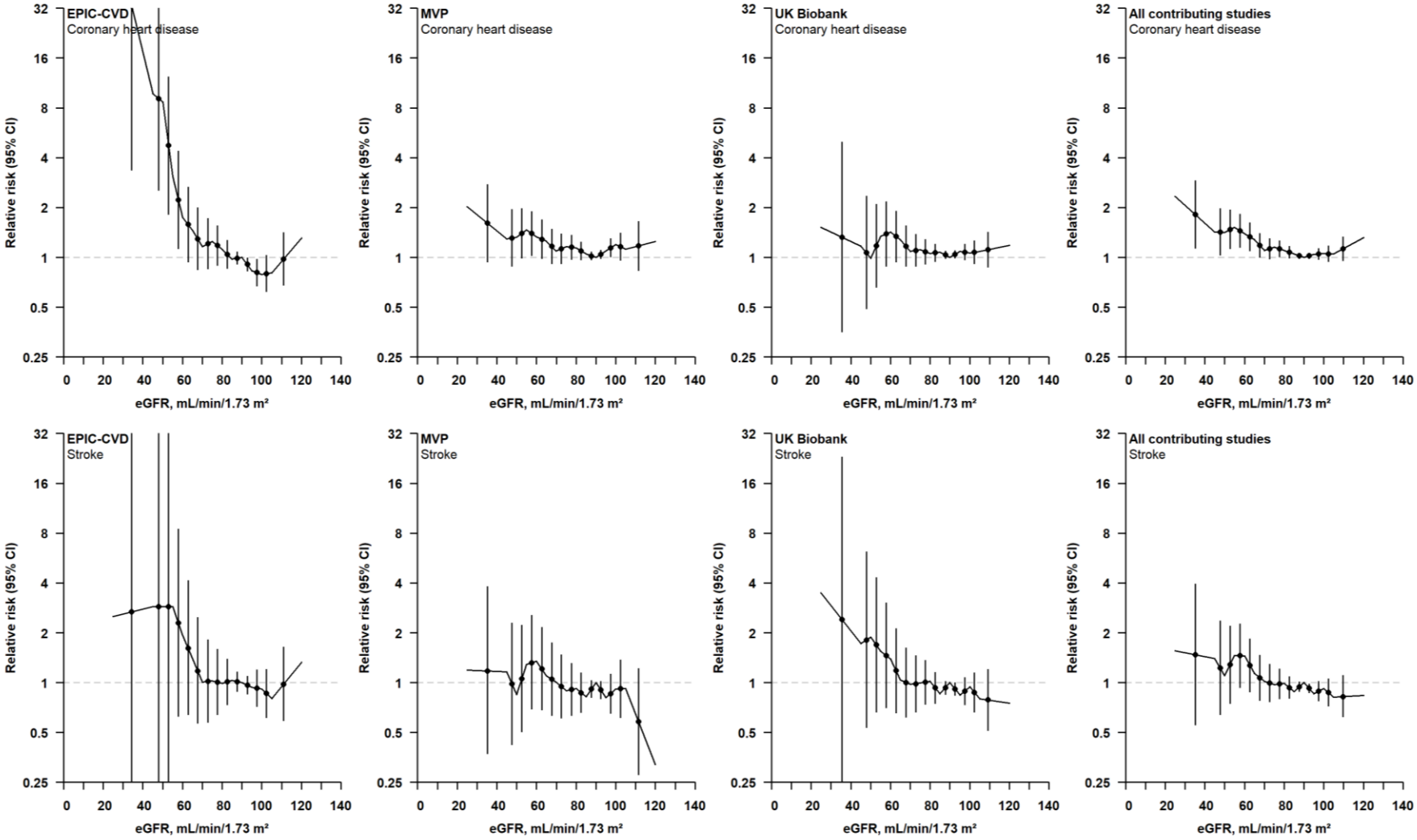
The reference point is 90 mL/min/1.73 m^2. Gradients at each point of the curve represent the localized average causal effect on coronary heart disease or stroke per 5 mL/min/1.73 m^2 change in genetically-predicted eGFR. Vertical lines represent 95% confidence intervals. Analyses were adjusted for age, age-squared, sex, study center, and the first ten principal components.

Figure S14: Mendelian randomization estimates of genetically-predicted eGFR with risk of coronary heart disease, stroke, and ischemic stroke, *adjusted for other factors* (n=408,021)



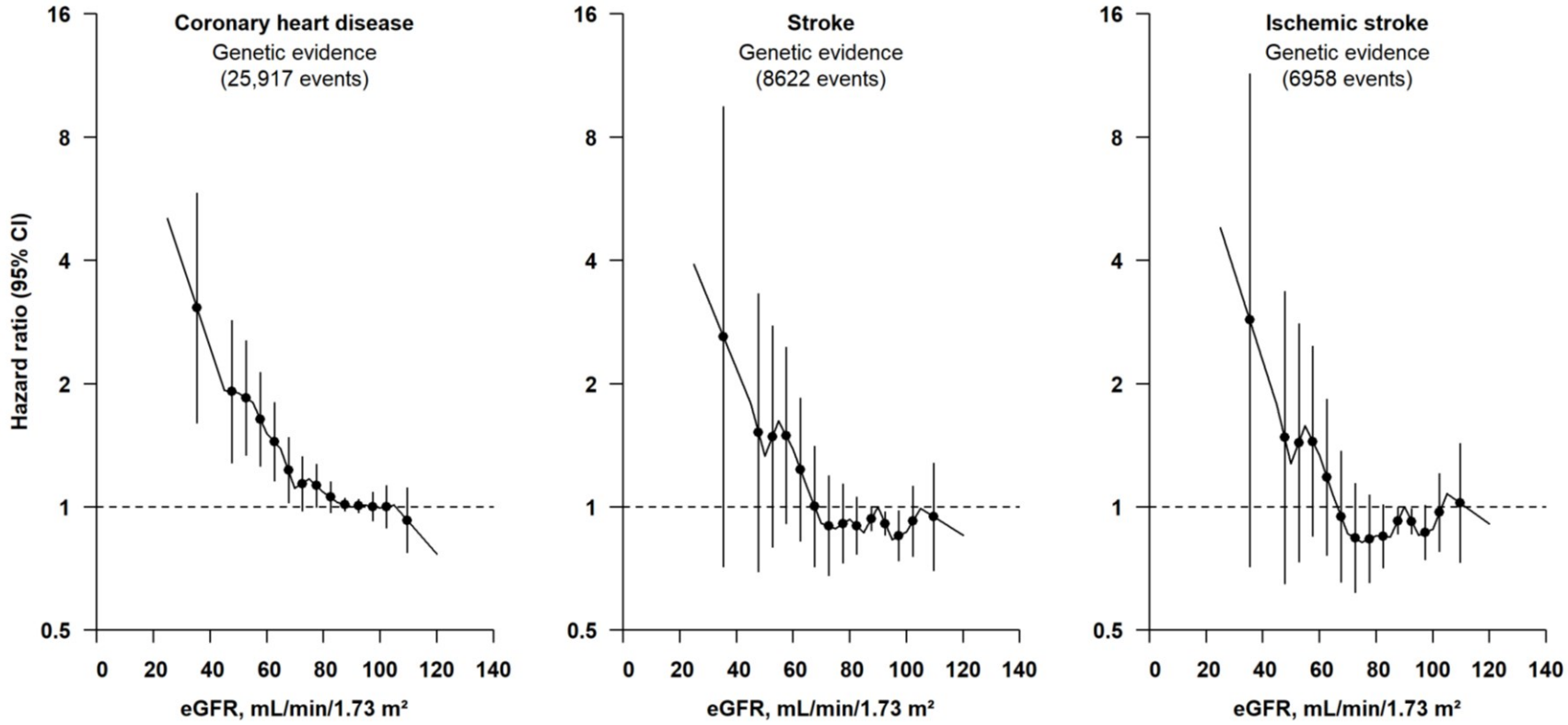
Stratum-specific localized average casual effect estimates were adjusted for age, age-squared, sex, study center, and the first ten principal components, with additional adjustment for vascular traits associated with the eGFR GRS, (systolic blood pressure, lipoprotein [a], hemoglobin A1c, and triglycerides). To maximize the number of participants with complete information on those vascular traits, we used genetically-predicted lipoprotein (a),[20] genetically-predicted hemoglobin A1c,[21] and genetically-predicted triglycerides,[22] instead of the measured levels. The reference point is 90 mL/min/1.73 m^2. Gradients at each point of the curve represent the localized average causal effect on coronary heart disease or stroke per 5 mL/min/1.73 m^2 change in genetically-predicted eGFR. Vertical lines represent 95% confidence intervals.

Figure S15: Mendelian randomization estimates of genetically-predicted eGFR with risk of coronary heart disease and stroke, *irrespective of diabetes status at recruitment* (n=463,051)



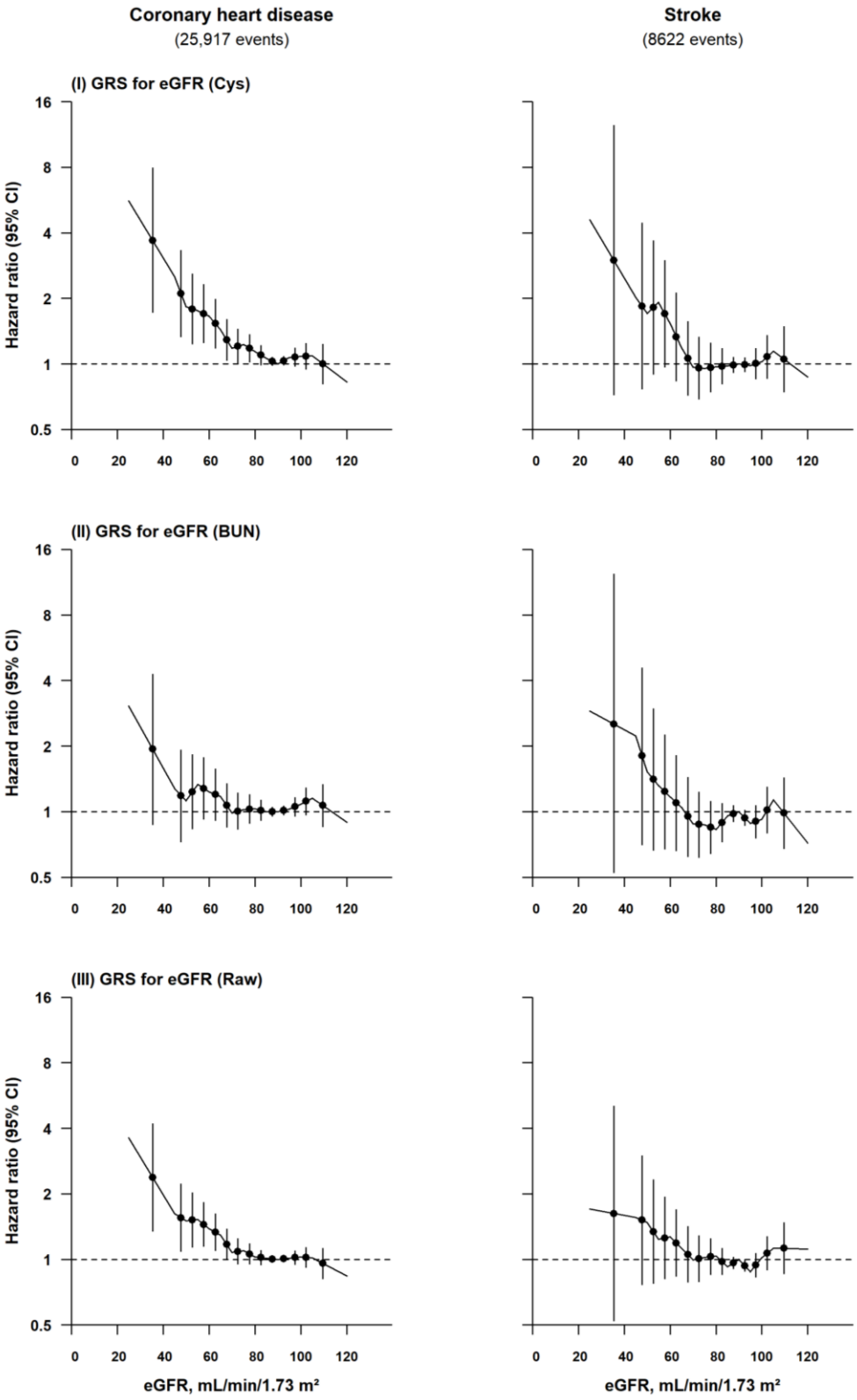
The reference point is 90 mL/min/1.73 m^2. Gradients at each point of the curve represent the localized average causal effect on coronary heart disease or stroke per 5 mL/min/1.73 m^2 change in genetically-predicted eGFR. Vertical lines represent 95% confidence intervals.

Figure S16: Mendelian randomization estimates of genetically-predicted eGFR with risk of coronary heart disease, stroke, and ischemic stroke (n=413,718)



The reference point is 90 mL/min/1.73 m^2. Gradients at each point of the curve represent the localized average causal effect on coronary heart disease or stroke per 5 mL/min/1.73 m^2 change in genetically-predicted eGFR. Vertical lines represent 95% confidence intervals.

Figure S17: Mendelian randomization estimates of genetically-predicted eGFR with risk of coronary heart disease, stroke, and ischemic stroke, by different GRSs



The reference point is 90 mL/min/1.73 m^2. Gradients at each point of the curve represent the localized average causal effect on coronary heart disease or stroke per 5 mL/min/1.73 m^2 changes in genetically-predicted eGFR. Vertical lines represent 95% confidence intervals.

ACKNOWLEDGEMENTS

VA Million Veteran Program

Core Acknowledgement for Publications

Updated December 2021

MVP Program Office

- Program Director - Sumitra Muralidhar, Ph.D.
  US Department of Veterans Affairs, 810 Vermont Avenue NW, Washington, DC 20420
- Associate Director, Scientific Programs - Jennifer Moser, Ph.D.
  US Department of Veterans Affairs, 810 Vermont Avenue NW, Washington, DC 20420
- Associate Director, Cohort Management & Public Relations - Jennifer E. Deen, B.S.
  US Department of Veterans Affairs, 810 Vermont Avenue NW, Washington, DC 20420

MVP Executive Committee

- Co-Chair: J. Michael Gaziano, M.D., M.P.H.
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- Co-Chair: Sumitra Muralidhar, Ph.D.
  US Department of Veterans Affairs, 810 Vermont Avenue NW, Washington, DC 20420
- Jean Beckham, Ph.D.
  Durham VA Medical Center, 508 Fulton Street, Durham, NC 27705
- Kyong-Mi Chang, M.D.
  Philadelphia VA Medical Center, 3900 Woodland Avenue, Philadelphia, PA 19104
- Philip S. Tsao, Ph.D.
  VA Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304
- Shiuh-Wen Luoh, M.D., Ph.D.
  VA Portland Health Care System, 3710 SW US Veterans Hospital Rd, Portland, OR 97239
  US Department of Veterans Affairs, 810 Vermont Avenue NW, Washington, DC 20420
- Juan P. Casas, M.D., Ph.D., Ex-Officio
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130

MVP Principal Investigators

- J. Michael Gaziano, M.D., M.P.H.
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- Philip S. Tsao, Ph.D.
  VA Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304

MVP Operations

- MVP Executive Director – Juan P. Casas, M.D., Ph.D.
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- Director of Regulatory Affairs – Lori Churby, B.S.
  VA Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304
- MVP Cohort Management Director – Stacey B. Whitbourne, Ph.D.
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- MVP Recruitment/Enrollment Director - Jessica V. Brewer, M.P.H.
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- Director, VA Central Biorepository, Boston – Mary T. Brophy M.D., M.P.H.
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- Executive Director for MVP Biorepositories - Luis E. Selva, Ph.D.
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- MVP Informatics, Boston – Shahpoor (Alex) Shayan, M.S.
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- Director, MVP Data Operations/Analytics, Boston – Kelly Cho, M.P.H., Ph.D.
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- Director, Center for Computational and Data Science (C-DACS) & Genomics Core – Saiju Pyarajan Ph.D.
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- Director, Molecular Data Core – Philip S. Tsao, Ph.D.
  VA Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304
- Director, Phenomics Data Core – Kelly Cho, M.P.H, Ph.D.
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- Director, VA Informatics and Computing Infrastructure (VINCI) – Scott L. DuVall, Ph.D.
  VA Salt Lake City Health Care System, 500 Foothill Drive, Salt Lake City, UT 84148
- MVP Coordinating Centers
  - Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque – Todd Connor, Pharm.D.; Dean P. Argyres, B.S., M.S.
    New Mexico VA Health Care System, 1501 San Pedro Drive SE, Albuquerque, NM 87108
  - Genomics Coordinating Center, Palo Alto – Philip S. Tsao, Ph.D.

VA Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304

- MVP Boston Coordinating Center, Boston - J. Michael Gaziano, M.D., M.P.H.
  VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- MVP Information Center, Canandaigua – Brady Stephens, M.S.
  Canandaigua VA Medical Center, 400 Fort Hill Avenue, Canandaigua, NY 14424

Current MVP Local Site Investigators

- Atlanta VA Medical Center (Peter Wilson, M.D.)
  1670 Clairmont Road, Decatur, GA 30033
- Bay Pines VA Healthcare System (Rachel McArdle, Ph.D.)
  10,000 Bay Pines Blvd Bay Pines, FL 33744
- Birmingham VA Medical Center (Louis Dellitalia, M.D.)
  700 S. 19th Street, Birmingham AL 35233
- Central Western Massachusetts Healthcare System (Kristin Mattocks, Ph.D., M.P.H.)
  421 North Main Street, Leeds, MA 01053
- Cincinnati VA Medical Center (John Harley, M.D., Ph.D.)
  3200 Vine Street, Cincinnati, OH 45220
- Clement J. Zablocki VA Medical Center (Jeffrey Whittle, M.D., M.P.H.)
  5000 West National Avenue, Milwaukee, WI 53295
- VA Northeast Ohio Healthcare System (Frank Jacono, M.D.)
  10701 East Boulevard, Cleveland, OH 44106
- Durham VA Medical Center (Jean Beckham, Ph.D.)
  508 Fulton Street, Durham, NC 27705
- Edith Nourse Rogers Memorial Veterans Hospital (John Wells., Ph.D.)
  200 Springs Road, Bedford, MA 01730
- Edward Hines, Jr. VA Medical Center (Salvador Gutierrez, M.D.)
  5000 South 5th Avenue, Hines, IL 60141
- Veterans Health Care System of the Ozarks (Kathrina Alexander, M.D.)
  1100 North College Avenue, Fayetteville, AR 72703
- Fargo VA Health Care System (Kimberly Hammer, Ph.D.)
  2101 N. Elm, Fargo, ND 58102
- VA Health Care Upstate New York (James Norton, Ph.D.)
  113 Holland Avenue, Albany, NY 12208
- New Mexico VA Health Care System (Gerardo Villareal, M.D.)
  1501 San Pedro Drive, S.E. Albuquerque, NM 87108
- VA Boston Healthcare System (Scott Kinlay, M.B.B.S., Ph.D.)
  150 S. Huntington Avenue, Boston, MA 02130
- VA Western New York Healthcare System (Junzhe Xu, M.D.)

3495 Bailey Avenue, Buffalo, NY 14215-1199
- Ralph H. Johnson VA Medical Center (Mark Hamner, M.D.)
  109 Bee Street, Mental Health Research, Charleston, SC 29401
- Columbia VA Health Care System (Roy Mathew, M.D.)
  6439 Garners Ferry Road, Columbia, SC 29209
- VA North Texas Health Care System (Sujata Bhushan, M.D.)
  4500 S. Lancaster Road, Dallas, TX 75216
- Hampton VA Medical Center (Pran Iruvanti, D.O., Ph.D.)
  100 Emancipation Drive, Hampton, VA 23667
- Richmond VA Medical Center (Michael Godschalk, M.D.)
  1201 Broad Rock Blvd., Richmond, VA 23249
- Iowa City VA Health Care System (Zuhair Ballas, M.D.)
  601 Highway 6 West, Iowa City, IA 52246-2208
- Eastern Oklahoma VA Health Care System (River Smith, Ph.D.)
  1011 Honor Heights Drive, Muskogee, OK 74401
- James A. Haley Veterans' Hospital (Stephen Mastorides, M.D.)
  13000 Bruce B. Downs Blvd, Tampa, FL 33612
- James H. Quillen VA Medical Center (Jonathan Moorman, M.D., Ph.D.)
  Corner of Lamont & Veterans Way, Mountain Home, TN 37684
- John D. Dingell VA Medical Center (Saib Gappy, M.D.)
  4646 John R Street, Detroit, MI 48201
- Louisville VA Medical Center (Jon Klein, M.D., Ph.D.)
  800 Zorn Avenue, Louisville, KY 40206
- Manchester VA Medical Center (Nora Ratcliffe, M.D.)
  718 Smyth Road, Manchester, NH 03104
- Miami VA Health Care System (Ana Palacio, M.D., M.P.H.)
  1201 NW 16th Street, 11 GRC, Miami FL 33125
- Michael E. DeBakey VA Medical Center (Olaoluwa Okusaga, M.D.)
  2002 Holcombe Blvd, Houston, TX 77030
- Minneapolis VA Health Care System (Maureen Murdoch, M.D., M.P.H.)
  One Veterans Drive, Minneapolis, MN 55417
- N. FL/S. GA Veterans Health System (Peruvemba Sriram, M.D.)
  1601 SW Archer Road, Gainesville, FL 32608
- Northport VA Medical Center (Shing Shing Yeh, Ph.D., M.D.)
  79 Middleville Road, Northport, NY 11768
- Overton Brooks VA Medical Center (Neeraj Tandon, M.D.)
  510 East Stoner Ave, Shreveport, LA 71101
- Philadelphia VA Medical Center (Darshana Jhala, M.D.)
  3900 Woodland Avenue, Philadelphia, PA 19104
- Phoenix VA Health Care System (Samuel Aguayo, M.D.)
  650 E. Indian School Road, Phoenix, AZ 85012
- Portland VA Medical Center (David Cohen, M.D.)
  3710 SW U.S. Veterans Hospital Road, Portland, OR 97239
- Providence VA Medical Center (Satish Sharma, M.D.)

830 Chalkstone Avenue, Providence, RI 02908
- Richard Roudebush VA Medical Center (Suthat Liangpunsakul, M.D., M.P.H.)
  1481 West 10th Street, Indianapolis, IN 46202
- Salem VA Medical Center (Kris Ann Oursler, M.D.)
  1970 Roanoke Blvd, Salem, VA 24153
- San Francisco VA Health Care System (Mary Whooley, M.D.)
  4150 Clement Street, San Francisco, CA 94121
- South Texas Veterans Health Care System (Sunil Ahuja, M.D.)
  7400 Merton Minter Boulevard, San Antonio, TX 78229
- Southeast Louisiana Veterans Health Care System (Joseph Constans, Ph.D.)
  2400 Canal Street, New Orleans, LA 70119
- Southern Arizona VA Health Care System (Paul Meyer, M.D., Ph.D.)
  3601 S 6th Avenue, Tucson, AZ 85723
- Sioux Falls VA Health Care System (Jennifer Greco, M.D.)
  2501 W 22nd Street, Sioux Falls, SD 57105
- St. Louis VA Health Care System (Michael Rauchman, M.D.)
  915 North Grand Blvd, St. Louis, MO 63106
- Syracuse VA Medical Center (Richard Servatius, Ph.D.)
  800 Irving Avenue, Syracuse, NY 13210
- VA Eastern Kansas Health Care System (Melinda Gaddy, Ph.D.)
  4101 S 4th Street Trafficway, Leavenworth, KS 66048
- VA Greater Los Angeles Health Care System (Agnes Wallbom, M.D., M.S.)
  11301 Wilshire Blvd, Los Angeles, CA 90073
- VA Long Beach Healthcare System (Timothy Morgan, M.D.)
  5901 East 7th Street Long Beach, CA 90822
- VA Maine Healthcare System (Todd Stapley, D.O.)
  1 VA Center, Augusta, ME 04330
- VA New York Harbor Healthcare System (Peter Liang, M.D., M.P.H.)
  423 East 23rd Street, New York, NY 10010
- VA Pacific Islands Health Care System (Daryl Fujii, Ph.D.)
  459 Patterson Rd, Honolulu, HI 96819
- VA Palo Alto Health Care System (Philip Tsao, Ph.D.)
  3801 Miranda Avenue, Palo Alto, CA 94304-1290
- VA Pittsburgh Health Care System (Patrick Strollo, Jr., M.D.)
  University Drive, Pittsburgh, PA 15240
- VA Puget Sound Health Care System (Edward Boyko, M.D.)
  1660 S. Columbian Way, Seattle, WA 98108-1597
- VA Salt Lake City Health Care System (Jessica Walsh, M.D.)
  500 Foothill Drive, Salt Lake City, UT 84148
- VA San Diego Healthcare System (Samir Gupta, M.D., M.S.C.S.)
  3350 La Jolla Village Drive, San Diego, CA 92161
- VA Sierra Nevada Health Care System (Mostaqul Huq, Pharm.D., Ph.D.)
  975 Kirman Avenue, Reno, NV 89502
- VA Southern Nevada Healthcare System (Joseph Fayad, M.D.)

6900 North Pecos Road, North Las Vegas, NV 89086

- VA Tennessee Valley Healthcare System (Adriana Hung, M.D., M.P.H.)
  1310 24th Avenue, South Nashville, TN 37212
- Washington DC VA Medical Center (Jack Lichy, M.D., Ph.D.)
  50 Irving St, Washington, D. C. 20422
- W.G. (Bill) Hefner VA Medical Center (Robin Hurley, M.D.)
  1601 Brenner Ave, Salisbury, NC 28144
- White River Junction VA Medical Center (Brooks Robey, M.D.)
  163 Veterans Drive, White River Junction, VT 05009
- William S. Middleton Memorial Veterans Hospital (Prakash Balasubramanian, M.D.)
  2500 Overlook Terrace, Madison, WI 53705