Subsequent Event Risk in Individuals With Established Coronary Heart Disease:

Design and Rationale of the GENIUS-CHD Consortium

A full list of authors and affiliations appears at the end of the article.

Abstract

BACKGROUND: The Genetics of Subsequent Coronary Heart Disease (GENIUS-CHD) consortium was established to facilitate discovery and validation of genetic variants and biomarkers for risk of subsequent CHD events, in individuals with established CHD.

METHODS: The consortium currently includes 57 studies from 18 countries, recruiting 185614 participants with either acute coronary syndrome, stable CHD, or a mixture of both at baseline. All studies collected biological samples and followed-up study participants prospectively for subsequent events.

RESULTS: Enrollment into the individual studies took place between 1985 to present day with a duration of follow-up ranging from 9 months to 15 years. Within each study, participants with CHD are predominantly of self-reported European descent (38%–100%), mostly male (44%–91%) with mean ages at recruitment ranging from 40 to 75 years. Initial feasibility analyses, using a federated analysis approach, yielded expected associations between age (hazard ratio, 1.15; 95% CI, 1.14–1.16) per 5-year increase, male sex (hazard ratio, 1.17; 95% CI, 1.13–1.21) and smoking (hazard ratio, 1.43; 95% CI, 1.35–1.51) with risk of subsequent CHD death or myocardial infarction and differing associations with other individual and composite cardiovascular endpoints.

CONCLUSIONS: GENIUS-CHD is a global collaboration seeking to elucidate genetic and nongenetic determinants of subsequent event risk in individuals with established CHD, to improve residual risk prediction and identify novel drug targets for secondary prevention. Initial analyses demonstrate the feasibility and reliability of a federated analysis approach. The consortium now plans to initiate and test novel hypotheses as well as supporting replication and validation analyses for other investigators.

Keywords

coronary artery disease; genetics; myocardial infarction; prognosis; secondary prevention

---

Major public health initiatives and policy changes, along with advances in drug and interventional therapies have significantly reduced cardiovascular morbidity and mortality in

Correspondence Riyaz S. Patel, Institute of Cardiovascular Sciences, University College London, 222 Euston Rd, London NW1 2DA, United Kingdom, riyaz.patel@ucl.ac.uk or Folkert W. Asselbergs, Division of Heart and Lungs, Department of Cardiology, University Medical Center Utrecht, 3508GA Utrecht, the Netherlands, f.w.asselbergs@umcutrecht.nl.

*Drs Patel, Tragante, and Schmidt are joint first authors.

†Drs Samani, Hingorani, and Asselbergs are joint senior authors.

most high-in-come countries.[1–3] However, the improved survival rates following an initial presentation with coronary heart disease (CHD) has, paradoxically, led to a growing number of patients living with established CHD (eg, 16M in the United States and 3M in the United Kingdom)[4,5] who remain at substantially high risk of subsequent cardiovascular events. These include myocardial infarction (MI), repeated revascularizations but also heart failure, stroke, and sudden death.[4]

Despite a large body of knowledge on the patho-physiology of first CHD events in general populations,[6,7] little is known about factors that influence disease progression or subsequent events in patients with established CHD, beyond those consequent to the acute index event in the short-term (such as biomarkers of myocardial dysfunction or necrosis, left ventricular function, or arrhythmia).[8] As a result, although guidelines and treatment thresholds have progressively evolved over the past 2 decades, the targeted risk factors per se have remained largely unaltered.[9] Novel therapies beyond lipid lowering, antiplatelet agents, and drugs recommended for high blood pressure and heart failure have been slow to emerge. Importantly, multiple novel and existing agents (eg, darapladib, varespladib, and folic acid) have failed in very late stage clinical development despite promising observational data.[10–13] In contrast, some traditional risk factors, such as obesity, which show robust associations with initial CHD onset,[14] continue to show inverse or null associations with subsequent events once CHD has developed.[15]

Ultimately, the high (residual) risk in individuals with existing CHD despite optimal contemporary therapy emphasizes the need for studying risk of subsequent events and their related causal pathways. For example, in the intervention arm of the IMPROVE-IT study (Vytorin Efficacy International Trial), despite simvastatin and ezetimibe treatment following an acute coronary syndrome, at 7 years, almost a third of participants experienced the primary end point (a composite of cardiovascular death, major coronary event, coronary revascularization, or nonfatal stroke).[16] Similarly, in the FOURIER trial (Further Cardiovascular Outcomes Research with PCSK9 [proprotein convertase subtilisin-kexin type 9] Inhibition in Subjects with Elevated Risk), almost 10% of patients with established but stable CVD, experienced an event at 2.2 years despite high-intensity statin and PCSK9 inhibition, with achieved median LDL-C (low-density lipoprotein cholesterol) levels of 30 mg/dL.[17] These data point to the existence of risk factors beyond traditional ones such as LDL-C, and the need to elucidate their related causal pathways.[18] By studying those with established CHD at high risk of subsequent events, we plan to gain novel insights into other drivers of atherosclerosis or features that identify patients who may benefit most from novel therapies.[9] Genetic and biomarker studies in these individuals may help identify novel molecular pathways and future drug targets with the goal of advancing precision medicine.

In the absence of a single-large resource to study the determinants of coronary heart disease prognosis, we have established the Genetics of Subsequent CHD (GENIUS-CHD) consortium.[19] Assembling studies from across the globe that have recruited patients with different types of CHD at baseline, have acquired prospective follow-up, and have stored biological specimens, or genetic data, the consortium aims to: (1) investigate genetic and nongenetic determinants of risk for subsequent CHD, systematically and at scale and (2)

facilitate access to data and expertise, as a platform to foster collaboration among investigators working in the field.

Here, we describe the design of the consortium, including details of participating studies, available data, and samples, as well as the governance procedures and the consortium's approach to data sharing and collaboration to further advance the stated scientific aims. In addition, we present some early findings from an investigation of the association of patient characteristics and certain routinely recorded measures on the risk of subsequent events among patients with different types of CHD at baseline.

METHODS

In accordance with Transparency and Openness Promotion Guidelines, the data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedures. Participating studies received local institutional review board approval and included patients who had provided informed consent at the time of enrollment. The central analysis sites also received waivers from their local institutional review board for collating and analyzing summary-level data from these individual studies. Full details on the eligibility criteria, definitions of terminology, management of the consortium, and planned projects are provided in Materials in the Data Supplement.

RESULTS

The design and structure of the GENIUS-CHD consortium are presented in Figure 1. Studies meeting the main eligibility criteria were identified and invited to participate (Methods in the Data Supplement). In brief, studies are eligible to join the GENIUS-CHD consortium if they meet 3 inclusion criteria: (1) included individuals with established CHD (defined as the presence of or confirmed history of acute coronary syndrome at baseline, or of coronary artery disease as evidenced by any revascularization procedure (percutaneous coronary intervention or bypass surgery) or demonstrable plaque in any epicardial vessel on direct coronary imaging); (2) acquired prospective follow-up of participants with ascertainment of one or more subsequent cardiovascular disease events as well as all-cause mortality; and (3) had stored blood samples, which are viable and suitable for DNA and biomarker analysis or previously collected such data before sample depletion.

At the time of writing, 57 studies from 18 countries are participating in the consortium and are listed in Table 1. Please refer to www.genius-chd.org for an updated list. Brief narrative descriptions of each study are provided in Methods in the Data Supplement.

The majority of studies are either investigator-led clinical cohorts (n=42), but clinical trials (n=10) and nested case-cohort (inception-study design) studies (n=5) are also included. Of the total, 23 studies have included participants at the time of an acute coronary syndrome, while the remainder recruited those with stable CHD or a mixture of the 2 (eg, from cardiac catheterization labs). Collectively, 185 614 participants have been enrolled with CHD at baseline (including 812 803 person-years of follow-up); of which 170 343 are of self-reported European descent. Recruitment times varied between studies, ranging from the

earliest recruitment in 1985 to studies that remain actively recruiting to the present day. All studies enrolled patients >18 years of age, although one study exclusively recruited only those with premature CHD (MI <45 years), while another recruited only older subjects (>70 years). The overall mean age within each study reflects this heterogeneity, ranging from 40 to 75 years of age, and proportion of male sex ranging from 44% to 91% (Table 1).

Available Data

Core Phenotypes—All studies collected data on age, sex, and ethnicity. Risk factor data are available for diabetes mellitus, obesity, and smoking status in almost all participating studies (96%), while data on concentrations of routine blood lipids (total cholesterol, LDL-C, HDL-C [high-density lipoprotein cholesterol], and triglycerides; 84%), and blood pressure values at enrollment (82%) were collected by the majority of studies. Data on statin use at baseline are available in 90% of all participating studies (Table 2).

Additional Phenotypes—A list of selected additional phenotypes available by study is presented in Table I in the Data Supplement. Of note, 79% have available data on plasma CRP (C-reactive protein), while coronary disease burden information, from invasive angiography is available in 52% of studies. Finally, over a third of studies have also collected data on physical activity (38%) and socioeconomic status (37%).

Samples—Stored samples are available in most studies for future assay testing and stored frozen. The majority have stored plasma (75%), while others also have serum, blood EDTA, RNA, and urine (Table II in the Data Supplement).

DNA and Genotyping—More than two-thirds of the studies have DNA still available, either preextracted or as whole blood collected in EDTA and stored for future genotyping. All studies within the consortium have performed genotyping in some capacity, with genome-wide data available in a subset of studies (Table III in the Data Supplement).

Subsequent Events and Follow-Up—The most commonly collected end point was all-cause death, collected by all but 2 studies. CHD death during follow-up was collected in 70% of studies, while incident MI was reported by 82% of studies. Studies ascertained end points through different means, including telephone contact, in-person patient interviews, clinical chart reviews, and linkage to national mortality registers and hospital records (Table IV in the Data Supplement).

Power Calculations

Empirical power was estimated based on a conservative sample size of 150 000 subjects with an event rate of 10% (across the entire follow-up period with a mean of about 5 years); Figure 2. Given that the GENIUS-CHD consortium is designed to answer multiple questions, power was estimated for a range of genetic single nucleotide polymorphisms (SNPs) and nongenetic (biomarkers and clinical risk factors) effects.

Minor allele frequencies of 0.01, 0.05, 0.10, and 0.25 were examined, representing rare to common SNPs. For each minor allele frequency, power was calculated for a range of

plausible SNP effects on biomarkers (mean difference [μ] 0.01, 0.03, and 0.05) and clinical end points (odds ratios of 1.02, 1.05, and 1.10). For the association of SNPs with biomarkers, power was 80% (α=0.05) or more unless the SNP was rare (minor allele frequency of 0.01) or the effect size was small (eg, 0.01 per allele). For the association of SNPs with clinical end points, power was close to 80% when the effect size was large (odds ratio 1.10) or the minor allele frequency was 0.10.

Power of observational (ie, nongenetic) analysis was >99% for both continuous and binary exposures unless the odds ratio was close to 1. In addition to continuous and binary outcome data, GENIUS-CHD also collects time-to-event data. Given the similarity (in most empirical settings) between odds ratio and hazard ratios,[20] similar power is to be expected for time-to-event analysis.

Initial Analysis

To examine the feasibility of the federated analysis approach, we sought to collect data on participant characteristics, cardiovascular and mortality outcomes and association analyses with common clinical exposures. A standardized dataset was developed, with a federated analysis conducted using standardized statistical scripts. The summary-level outputs generated were then shared with the coordinating centers for aggregating and metaanalysis (Methods in the Data Supplement).

Participant Characteristics

Detailed characteristics of participants by study are presented in Table 2. Prevalence of risk factors varied by study, with diabetes mellitus ranging from 4% to 76%; smoking from 8% to 79%. Mean total cholesterol by study ranged from 166.3 to 239.8 mg/dL, mean body mass index ranged from 24.8 to 30.2 kg/m^2 and mean systolic blood pressure from 117 to 153 mm Hg. The proportion of participants with prior revascularization or MI was high in most studies reflecting the inclusion criteria for the consortium (Table 2).

Review of returned outputs from the federated analysis revealed good quality data with estimates falling within expected ranges for age, sex, and other variables, such as body mass index (Figure I in the Data Supplement).

End Points

The primary end point preselected for the study was a composite of coronary death or MI (CHD death/MI). Mean follow-up was estimated in each study and ranged between 9 months and 15 years. In total, we estimated over 748 000 person-years of follow-up were available for the primary end point analysis.

Information was collected on 10 subsequent event end points in the initial feasibility analysis. Across all studies, the most frequently occurring event during prospective follow-up was the composite of all cardiovascular events (27%); followed by revascularization (21.8%); all-cause mortality (15%); coronary death or MI (14.2%); MI (10.7%); cardiovascular death (8.3%); coronary death (8%); heart failure (6.3%); all stroke (3.6%); and ischemic stroke (3.4%).

Association Analyses

As a feasibility analysis, we examined associations between age, male sex, and smoking with the primary end point CHD death/MI as well as with the 9 other secondary end points, to investigate any differential associations across discrete subsequent events.

In analyses unrestricted by race or type of CHD at baseline, but adjusted for sex, there was a strong association between each 5-year increment in age with subsequent risk of the primary end point of CHD death/MI (hazard ratio [HR] 1.15; 95% CI, 1.14–1.16). The largest observed HRs were for all-cause mortality (HR, 1.36; 95% CI, 1.35–1.37), cardiovascular death (HR, 1.36; 95% CI, 1.35–1.38), and heart failure (HR, 1.25; 95% CI, 1.24–1.27), while a smaller risk increase was observed for MI (HR, 1.06; 95% CI, 1.05–1.07). The risk of future revascularization, however, showed a modest inverse association with increasing age (HR, 0.98; 95% CI, 0.98–0.99; Figure 3).

Male sex was a risk factor for CHD death/MI (HR, 1.17; 95% CI, 1.13–1.21) and other coronary and mortality end points (Figure 4) after adjustment for age. In particular, the largest observed HR was for risk of revascularization, which was considerably higher in males (HR, 1.24; 95% CI, 1.20–1.27). In contrast, there was no strong evidence for an association between male sex and risk of stroke (ischemic or any stroke; Figure 4).

Finally, in analyses adjusted for age and sex, current smoking (compared to prior or never smoking) at the time of enrollment showed a strong association with risk of future CHD death/MI (HR, 1.43; 95% CI, 1.35–1.51). Similarly, smoking was associated with an increased risk of all-cause mortality (HR, 1.53; 95% CI, 1.47–1.58) and an increased risk of all other end points, although there was no strong evidence for an association with incident revascularization (HR, 1.02; 95% CI, 0.99–1.05; Figure 5).

When stratified by type of CHD at enrollment, that is, among those presenting with an acute event, those with stable CAD without ever having had an MI and those with stable CAD and a prior MI, the findings were similar and directionally concordant to nonstratified analyses described above, for all end points (data not shown).

DISCUSSION

The GENIUS-CHD Consortium is a global collaborative effort engaging 57 studies, including almost 185 000 patients with established CHD, for whom genetic and prospective follow-up data are available. It brings together over 170 domain experts, including clinicians, data scientists, geneticists, and epidemiologists, all engaged in improving our understanding of the determinants of subsequent event risk in these patients. With an agreed governance structure and a proven federated analysis approach, we anticipate that this consortium will be a valuable long-term resource for genetic and nongenetic research in this field.

Genetic association studies for CHD disease progression, recurrence, and adverse events after a CHD event may have particular utility for identifying novel causal pathways and therapeutic targets that may be different than those for first events, a concept recently

supported by research in other disease areas.[21] However, information on the determinants of subsequent CHD event risk is scarce, in contrast to the extensive knowledge about risk factors for a first CHD event. This disparity is due, in part, to the relatively small sample sizes of individual studies in the secondary prevention setting. While larger registry and electronic health care records efforts will result in higher numbers, they typically suffer from the lack of necessary depth of phenotyping, accuracy, and availability of biospecimens to infer further biological insights.[22,23] In contrast, large population studies with detailed phenotyping have relatively small numbers of mostly stable CHD patients, who have survived many years after their index event.[24,25] By bringing together multiple investigator-led studies, the GENIUS-CHD consortium aims to address and overcome this major limitation to subsequent CHD risk research.

Importantly, the scale and depth of the GENIUS-CHD consortium offer greater scope to tackle key challenges within subsequent CHD risk-related research. First, CHD is a heterogeneous phenotype, consisting of stable, unstable, and pathologically distinct subtypes, which have often been combined for individual studies to satisfy the need for statistical power. With the sample size available in GENIUS-CHD, we anticipate being able to disaggregate CHD into more precise subphenotypes such as acute versus stable CHD at baseline, or those with versus without prior MI, which may help uncover relevant biological differences.[26] Additional stratification on variables such as sex, time period of recruitment, duration of follow-up, country of study, LV function and treatment (such as statin, blood pressure lowering, and antiplatelet agent use) will also be possible, providing greater insights into the modifying influences of these variables on outcome.

A major strength of the consortium is the use of a federated analysis approach that permits individual level analysis without the need for sharing either samples or the individual datasets themselves, thereby overcoming major privacy and governance hurdles. The effort has been successful because (1) participation is entirely voluntary, with studies only participating in those analyses they feel are of value, or to which they have the capacity to contribute; (2) ownership of all data and samples remain with the principal investigator and are not shared nor stored centrally; and (3) there are open and transparent governance procedures. Our feasibility analysis has demonstrated that this federated approach works well and yields results that are consistent and suitable for high-quality meta-analysis.

Indeed, supported by this initial feasibility analysis, our findings demonstrate the validity of the data collected by confirming the anticipated associations of increasing age, male sex, and current smoking with higher risks of subsequent CHD death/MI during follow-up. Furthermore, by exploring multiple individual and composite end points, we can begin to unravel associations not discoverable in smaller studies. For example, we find that the risk of incident revascularization is lower with advancing age but higher for male sex and neutral for smoking. Plausible explanations may exist for each of these findings (eg, an association induced by clinical practice, with fewer older people being offered invasive treatments), but importantly they highlight the value of exploring multiple end points at an appropriate scale. This is especially relevant when exploring novel biomarkers or drug targets as these may, in turn, be used to inform clinical testing strategies and choice of end points to study in trials.

By virtue of the expertise it has assembled, the consortium is also well placed to address important methodological issues surrounding prognosis research in general. For example, selection bias is a key concern, whereby it is conceivable that those at highest risk may die early and not enter any of the member studies for evaluation (survival bias), or selection on an indexing event itself may distort patient characteristics and impact association findings (index event bias).[27] In addition, treatment effects may alter the trajectory of disease by stabilizing or regressing plaque burden or altering baseline risk, such as with high-dose statin or PCSK9 inhibitor use.[17,28] To address these and other issues, the consortium has established working groups of relevant national and international experts to explore the extent and impact of such biases/effects and if needed, to develop approaches to address these.[29]

There are inherent challenges to overcome when working with diverse multiple studies, including variations in definitions and processes for data collection and curation across different studies in different centers and different countries. The consortium members have attempted to standardize common data elements, for example, the measurement units for quantitative traits. Variability between studies will persist, but we anticipate that the overall size of the effort will help reduce the impact of such study level heterogeneity on any findings, which will also be explored through subgroup analyses where possible (eg, country, study size, and year of first recruitment). Analytical challenges will additionally include dealing with variability in length of follow-up across studies, handling multiple subsequent events along with competing risks, as well as confounding by treatment and selection biases as described above. The collective experience of the consortium members will be leveraged to address these as carefully as possible within each future analysis. Finally, factors influencing enrollment into genetic studies of CHD may limit the generalizability of findings. Men are over represented in participating CHD studies, partly reflecting sex-differential prevalence of disease but also underpinning a wider concern about underinvestigation of women, who may be inadvertently excluded given that entry criteria for most studies relies on documented presence of CHD. Similarly, many studies in the consortium have recruited mostly Europeans, limiting the opportunity to explore hypotheses in other ethnic groups. The steering committee is conscious of these imbalances and is actively seeking studies enriched for women and non-European participants to join the collaboration. In summary, the GENIUS-CHD consortium is a global collaboration among investigators who have recruited patients with CHD into multiple individual studies, seeking to gain a better understanding of subsequent CHD event risk and enhance secondary prevention. It seeks to be an open, collegiate, and transparent effort and we invite investigators with suitable studies to join and collectively enhance research efforts in this domain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Authors

Riyaz S. Patel, MD[*], Vinicius Tragante, PhD[*], Amand F. Schmidt, PhD[*], Raymond O. McCubrey, MS, Michael V. Holmes, MD, PhD, Laurence J. Howe, PhD, Kenan Direk, PhD, Axel Åkerblom, MD, PhD, Karin Leander, PhD, Salim S. Virani, MD, PhD, Karol A. Kaminski, MD, PhD, Jochen D. Muehlschlegel, MD, MMSc, Hooman Allayee, PhD, Peter Almgren, MSc, Maris Alver, MSc, Ekaterina V. Baranova, MSc, Hassan Behloui, PhD, Bram Boeckx, PhD, Peter S. Braund, PhD, Lutz P. Breitling, MD, Graciela Delgado, MSc, Nubia E. Duarte, PhD, Marie-Pierre Dubé, PhD, Line Dufresne, MSc, Niclas Eriksson, PhD, Luisa Foco, PhD, Markus Scholz, PhD, Crystel M. Gijsberts, MD, PhD, Charlotte Glinge, MD, Yan Gong, PhD, Jaana Hartiala, PhD, Mahyar Heydarpour, PhD, Jaroslav A. Hubacek, DSc, Marcus Kleber, PhD, Daniel Kofink, PhD, Salma Kotti, PharmD, PhD, Pekka Kuukasjärvi, PhD, Vei-Vei Lee, MS, Andreas Leiherer, PhD, Petra A. Lenzini, MS, Daniel Levin, PhD, Leo-Pekka Lyytikäinen, MD, Nicola Martinelli, MD, PhD, Ute Mons, PhD, Christopher P. Nelson, PhD, Kjell Nikus, PhD, Anna P. Pilbrow, PhD, Rafal Ploski, MD, PhD, Yan V. Sun, PhD, Michael W.T. Tanck, PhD, W.H. Wilson Tang, MD, Stella Trompet, PhD, Sander W. van der Laan, PhD, Jessica Van Setten, PhD, Ragnar O. Vilmundarson, MSc, Chiara Viviani Anselmi, PhD, Efthymia Vlachopoulou, PhD, Lawien Al Ali, MD, Eric Boerwinkle, PhD, Carlo Briguori, MD, PhD, John F. Carlquist, PhD, Kathryn F. Carruthers, MPhil, Gavino Casu, MD, John Deanfield, MD, Panos Deloukas, PhD, Frank Dudbridge, PhD, Thomas Engstrøm, MD, PhD, Natalie Fitzpatrick, MSc, Kim Fox, MD, PhD, Bruna Gigante, PhD, Stefan James, MD, PhD, Marja-Liisa Lokki, PhD, Paulo A. Lotufo, MD, PhD, Nicola Marziliano, PhD, Ify R. Mordi, MD, Joseph B. Muhlestein, MD, Christopher Newton-Cheh, MD, Jan Pitha, PhD, Christoph H. Saely, MD, Ayman Samman-Tahhan, MD, Pratik B. Sandesara, MD, Andrej Teren, MD, Adam Timmis, MD, Frans Van de Werf, PhD, Els Wauters, PhD, Arthur A.M. Wilde, MD,PhD, Ian Ford, MD, PhD, David J. Stott, MD, Ale Algra, MD, Maria G. Andreassi, PhD, Diego Ardissino, MD, Benoit J. Arsenault, PhD, Christie M. Ballantyne, MD, Thomas O. Bergmeijer, MD, Connie R. Bezzina, PhD, Simon C. Body, MBChB, MPH, Eric H. Boersma, MD, PhD, Peter Bogaty, MD, Michiel L. Bots, MD, Hermann Brenner, MD, PhD, Jasper J. Brugts, MD, PhD, Ralph Burkhardt, MD, Clara Carpeggiani, MD, Gianluigi Condorelli, MD, PhD, Rhonda M. Cooper-DeHoff, PharmD, Sharon Cresci, MD, Nicolas Danchin, MD, PhD, Ulf de Faire, PhD, Robert N. Doughty, MD, Heinz Drexel, MD, James C. Engert, PhD, Keith A.A. Fox, MD, PhD, Domenico Girelli, MD, PhD, Diederick E. Grobbee, MD, PhD, Emil Hagström, MD, PhD, Stanley L. Hazen, MD, PhD, Claes Held, MD, PhD, Harry Hemingway, MD, PhD, Imo E. Hoefer, MD, PhD, G. Kees Hovingh, MD, PhD, Reza Jabbari, MD, PhD, Julie A. Johnson, PharmD, J. Wouter Jukema, MD, PhD, Marcin P. Kaczor, MD, PhD, Mika Kähönen, PhD, Jiri Kettner, PhD, Marek Kiliszek, MD, PhD, Olaf H. Klungel, PharmD, PhD, Bo Lagerqvist, MD, PhD, Diether Lambrechts, PhD, Jari O. Laurikka, PhD, Terho Lehtimäki, PhD, Daniel Lindholm, MD, PhD, B. K. Mahmoodi, MD, PhD, Anke H. Maitland-van der Zee, PharmD, PhD, Ruth McPherson, MD, PhD, Olle Melander, MD, PhD, Andres Metspalu, MD, PhD, Anna Niemcunowicz-Janica, MD, PhD, Oliviero Olivieri, MD, Grzegorz Opolski, MD, PhD, Colin N.

Palmer, PhD, Gerard Pasterkamp, MD, PhD, Carl J. Pepine, MD, Alexandre C. Pereira, MD, PhD, Louise Pilote, MD, Arshed A. Quyyumi, MD, A. Mark Richards, MD, PhD, Marek Sanak, MD, PhD, Agneta Siegbahn, MD, PhD, Tabassome Simon, MD, PhD, Juha Sinisalo, MD, PhD, J. Gustav Smith, MD, PhD, John A. Spertus, MD, MPH, Steen Stender, MD, DSc, Alexandre F.R. Stewart, PhD, Wojciech Szczeklik, MD, PhD, Anna Szpakowicz, MD, PhD, Jean-Claude Tardif, MD, Jurriën M. ten Berg, MD, PhD, Jacob Tfelt-Hansen, MD, DMSc, George Thanassoulis, MD, Joachim Thiery, MD, Christian Torp-Pedersen, MD, DSc, Yolanda van der Graaf, MD, Frank L.J. Visseren, MD, Johannes Waltenberger, MD, Peter E. Weeke, MD, PhD, Pim Van der Harst, MD, PhD, Chim C. Lang, MD, Naveed Sattar, PhD, Vicky A. Cameron, PhD, Jeffrey L. Anderson, MD, James M. Brophy, MD, Guillaume Pare, MD, Benjamin D. Horne, PhD, MPH, Winfried März, MD, Lars Wallentin, MD, PhD, Nilesh J. Samani, MD, PhD[†], Aroon D. Hingorani, MD, PhD[†], Folkert W. Asselbergs, MD, PhD[†]

Affiliations

Institute of Cardiovascular Science (R.S.P., A.F.S., L.J.H., K.D., J.D., A.D.H., F.W.A) and Institute of Health Informatics (N.F., A. Timmis, H.H., F.W.A.), Faculty of Population Health Science, University College London, United Kingdom. Bart´s Heart Centre, St Bartholomew´s Hospital, London (R.S.P., J.D., A. Timmis). Division of Heart and Lungs, Department of Cardiology (V.T., A.F.S.,D.K.,F.W.A.), Laboratory of Experimental Cardiology (C.M.G.), Department of Clinical Chemistry and Hematology (I.E.H.), and Department of Clinical Chemistry (G.P.), UMC Utrecht, the Netherlands. Intermountain Heart Institute, Intermountain Medical Center, Salt Lake City, UT (R.O.M., J.F.C., J.B.M., J.L.A., B.D.H). Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, Medical Research Council Population Health Research Unit, University of Oxford, United Kingdom (M.V.H). National Institute for Health Research Oxford Biomedical Research Centre, Oxford University Hospital, United Kingdom (M.V.H.). Uppsala Clinical Research Center, Sweden (A. Åkerblom, N.E., S.J., C.H., B.L., D. Lindholm, A. Siegbahn, L.W.). Division of Cardiology, Department of Medical Sciences (A. Åkerblom, C.H., D. Lindholm, S.J., B.L., L.W.) and Division of Clinical Chemistry, Department of Medical Sciences (A. Siegbahn), Uppsala University, Sweden. Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden (K.L., B.G., U.d.F.). Section of Cardiology, Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX (S.S.V.). Section of Cardiovascular Research, Department of Medicine, Baylor College of Medicine, Houston, TX (S.S.V., C.M.B.). Department of Population Medicine and Civilization Disease Prevention (K.A.K.) and Department of Cardiology (K.A.K., A. Sz-pakowicz), Medical University of Bialystok, Poland. Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Boston, MA (J.D.M., M.H.). Harvard Medical School, Boston, MA (J.D.M., M.H., S.C.B). Departments of Preventive Medicine and Biochemistry and Molecular Medicine (H.A., J.H.) and Institute for Genetic Medicine (J.H.), Keck School of Medicine of USC, Los Angeles, CA. Department of Clinical Sciences, Lund University, Malmö, Sweden (P.A., O.M.). Estonian Genome Centre,

Department of Biotechnology, Institute of Genomics, Institute of Molecular and Cell Biology, University of Tartu, Estonia (M.A., A.M.). Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, the Netherlands (E.V.B., O.H.K., A.H.M.-v.d.Z.). Centre for Outcomes Research and Evaluation, Research Institute of the McGill University Health Centre, Montreal, QC, Canada (H.B., L.D., L.P., G.T., J.M.B.). Research Institute of the McGill University Health Centre, Montreal, QC, Canada (J.C.E.). Laboratory for Translational Genetics, Department of Human Genetics (B.B., D. Lambrechts) and Department of Cardiovascular Sciences (F.V.d.W.), Katholieke Universiteit Leuven, Belgium. Laboratory for Translational Genetics, VIB Center for Cancer Biology, Belgium (B.B., D. Lambrechts). Department of Cardiovascular Sciences, BHF Cardiovascular Research Centre, University of Leicester, United Kingdom (PS.B., C.P.N., N.J.S.). NIHR Leicester Biomedical Research Centre, Glenfield Hospital, United Kingdom (PS.B., C.P.N., N.J.S.). Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg (L.P.B., U.M.). Fifth Department of Medicine, Medical Faculty Mannheim, Heidelberg University, Germany (G.D., M. Kleber, W.M.). Heart Institute, University of Sao Paulo, Brazil (N.E.D., A.C.P.). Montreal Heart Institute, OC, Canada (M.-PD., J.-C.T.). Faculty of Medicine, Université de Montréal, QC, Canada (M.-PD., J.-C.T.). Preventive and Genomic Cardiology, McGill University Health Centre, Montreal, QC, Canada (L.D., J.C.E., G.T.). Institute for Biomedicine, Eurac Research, Affiliated Institute of the University of Lübeck, Bolzano, Italy (L.F.). Institute for Medical Informatics, Statistics, and Epidemiology (M.S.) and LIFE Research Centre for Civilization Diseases (M.S., A. Teren, R.B., J.T.), University of Leipzig, Germany. Department of Cardiology, The Heart Centre, Copenhagen University Hospital, Rigshospitalet (C.G., T.E., R.J.). Amsterdam UMC, University of Amsterdam, Clinical and Experimental Cardiology, Amsterdam Cardiovascular Sciences, AMC Heart Center, the Netherlands (C.G., A.A.M.W., C.R.B.). Department of Pharmacotherapy and Translational Research, Centre for Pharmacogenomics (Y.G., R.M.C.-D., J.A.J.) and Division of Cardiovascular Medicine, College of Medicine (R.M.C.-D., J.A.J., C.J.P.), University of Florida, Gainesville. Centre for Experimental Medicine, Institute for Clinical and Experimental Medicine, Prague, Czech Republic (J.A.H., J.P.). Assistance Publique-Hôpitaux de Paris (AP-HP), Department of Clinical Pharmacology, Platform of Clinical Research of East Paris (URCEST-CRCEST-CRB HUEP-UPMC), France (S.K.). Department of Cardio-Thoracic Surgery (P.K.), Department of Clinical Chemistry (L.-P.L., T.L.), Department of Cardiology (K.N.), Department of Clinical Physiology (M. Kähönen), and Department of Cardio-Thoracic Surgery, Finnish Cardiovascular Research Center, Faculty of Medicine & Life Sciences (J.O.L.), University of Tampere, Finland. Department of Biostatistics and Epidemiology, Texas Heart Institute, Houston (V.-V.L.). Vorarlberg Institute for Vascular Investigation and Treatment (VIVIT), Feldkirch, Austria (A. Leiherer, C.H.S., H.D.). Private University of the Principality of Liechtenstein, Triesen (A. Leiherer, C.H.S., H.D.). Medical Central Laboratories, Feldkirch, Austria (A. Leiherer). Statistical Genomics Division, Department of Genetics (P.A. Lenzini, S.C.) and Cardiovascular Division, Department of Medicine (S.C.), Washington University School of Medicine, Saint

Louis, MO. Division of Molecular and Clinical Medicine, School of Medicine, University of Dundee, Scotland, United Kingdom (D. Levin, I.R.M., C.C.L.). Department of Clinical Chemistry, Fimlab Laboratories, Tampere, Finland (L.-PL., T.L.). Department of Medicine, University of Verona, Italy (N.M., D.G., O.O.). Department of Cardiology, Heart Center (K.N.), Department of Clinical Physiology (M. Kähönen), and Department of Cardio-Thoracic Surgery, Heart Centre (J.O.L.), Tampere University Hospital, Finland. The Christchurch Heart Institute, University of Otago Christchurch, New Zealand (A.P.P., A.M.R., V.A.C.). Department of Medical Genetics (R. Ploski) and first Chair and Department of Cardiology (G.O.), Medical University of Warsaw, Poland. Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, GA (Y.V.S.). Amsterdam UMC, University of Amsterdam, Clinical Epidemiology and Biostatistics, The Netherlands (M.W.T.T.). Department of Biomedical Informatics (Y.V.S.) and Division of Cardiology, Department of Medicine (A.S.-T, P.B.S., A.A.Q.), Emory Clinical Cardiovascular Research Institute, Emory University School of Medicine, Atlanta, GA. Department of Cellular and Molecular Medicine, Lerner Research Institute, Cleveland Clinic, OH (W.H.W.T., S.L.H.). Department of Cardiovascular Medicine, Heart and Vascular Institute, and Centre for Clinical Genomics, Cleveland Clinic, OH (W.H.W.T.). Department of Cardiovascular Medicine, Centre for Microbiome and Human Health, Heart and Vascular Institute, Cleveland Clinic, OH (S.L.H.). Section of Gerontology and Geriatrics, Department of Internal Medicine (S.T.) and Department of Cardiology (S.T., J.W.J.), Leiden University Medical Centre, the Netherlands. Division Heart and Lungs, Department of Cardiology, UMC Utrecht, University of Utrecht, the Netherlands (J.V.S.). Ruddy Canadian Cardiovascular Genetics Centre, University of Ottawa Heart Institute, ON, Canada (R.O.V., R.M., A.F.R.S.). Department of Biochemistry, Microbiology and Immunology (R.O.V, A.F.R.S.) and Departments of Medicine and Biochemistry, Microbiology and Immunology(R.M.), University of Ottawa, ON, Canada. Department of Cardiovascular Medicine, Humanitas Clinical and Research Centre, Milan, Italy (C.V.A., G.C.). Transplantation Laboratory (E.V., M.-L.L.) and Heart and Lung Centre (J.S.), Helsinki University Hospital and University of Helsinki, Finland. University Medical Centre, University of Groningen, the Netherlands (L.A.A., P.V.d.H.). University of Texas School of Public Health, Houston(E.B.). Clinica Mediterranea, Naples, Italy (C.B.). Cardiology Division, Department of Internal Medicine (J.F.C., J.B.M., J.L.A.) and Department of Biomedical Informatics (B.D.H.), University of Utah, Salt Lake City. QMRI, Cardiovascular Sciences, University of Edinburgh, United Kingdom (K.F.C.). The University of Edinburgh, United Kingdom (K.A.A.F). ATS Sardegna, ASSL Nuoro—Ospedale San Francesco, Nuoro, Italy (G.C.). William Harvey Research Institute, Barts and the London Medical School (P.D) and Centre for Genomic Health (P.D.), Queen Mary University of London,United Kingdom. Department of Health Sciences, University of Leicester, United Kingdom (F.D.). Department of Cardiology, University of Lund, Sweden (T.E.). National Heart and Lung Institute, Imperial College and Institute of Cardiovascular Medicine and Science, Royal Brompton Hospital, London, United Kingdom (K.F.); Centro de Pesquisa Clinica, Hospital Universitario, Universidade de Sao Paulo, São Paulo, Brazil (P.A. Lotufo,). ATS Sardegna, ASL 3

Nuoro, Nuoro, Italy (N. Marziliano). Cardiovascular Research Center, Center for Human Genetic Research, Massachusetts General Hospital, Boston (C.N.-C.). Program in Medical and Population Genetics, Broad Institute, Cambridge, MA (C.N.-C.). Department of Medicine and Cardiology, Academic Teaching Hospital Feldkirch, Austria (C.H.S.). Heart Centre Leipzig, Germany (A. Teren). Respiratory Oncology Unit, Department of Respiratory Medicine, University Hospitals KU Leuven, Belgium (E.W.). Princess Al-Jawhara Al-Brahim Centre of Excellence in Research of Hereditary Disorders, Jeddah, Saudi Arabia (A.A.M.W.). Robertson Centre for Biostatistics, University of Glasgow, United Kingdom (I.F.). Institute of Cardiovascular and Medical Sciences, University of Glasgow, United Kingdom (D.J.S., N.S.). Division Laboratories, Pharmacy, and Biomedical Genetics, Laboratory of Clinical Chemistry and Hematology (S.W.v.d.L.), Department of Neurology and Neurosurgery, Brain Centre Rudolf Magnus and Julius Centre for Health Sciences and Primary Care (A. Algra), Julius Center for Health Sciences and Primary Care (M.B., D.E.G., Y.v.d.G.) and Department of Vascular Medicine (F.L.J.V), UMC Utrecht, Utrecht University, the Netherlands. CNR Institute of Clinical Physiology, Pisa (M.G.A, C.C). Cardiology Department, Parma University Hospital, Italy (D.A.). Centre de recherche de l'Institut Universitaire de cardiologie et de pneumologie de Québec, Canada (B.J.A.). Department of Medicine, Faculty of Medicine, Université Laval, QC, Canada (B.J.A.); St Antonius Hospital, Department Cardiology, Nieuwegein, the Netherlands (T.O.B., B.K.M., J.M.t.B.). Department of Anesthesia, Critical Care & Pain Medicine, Beth Israel Deaconess Medical Center, Boston, MA (S.B.). Department of Cardiology, Erasmus MC, Thoraxcenter (E.H.B., J.J.B.). Cardiovascular Research School, Erasmus Medical Center (COEUR), Rotterdam, the Netherlands(E.H.B.). Laval University, Institute universitaire de cardiologie et de pneumologie de Québec, Canada (PB.). Network Aging Research (NAR), University of Heidelberg (H.B.). Institute of Clinical Chemistry and Laboratory Medicine, University Hospital Regensburg, Germany (R.B.). Department of Biomedical Sciences, Humanitas University, Milan, Italy (G.C.). Assistance Publique-Hôpitaux de Paris (AP-HP), Department of Cardiology, Hôpital Européen Georges Pompidou & FACT (French Alliance For Cardiovascular Trials), Université Paris Descartes, France (N.D.). Université Paris-Descartes, France (N.D.). Heart Health Research Group, University of Auckland, New Zealand (R.N.D.). Drexel University College of Medicine, Philadelphia PA (H.D.). Division of Cardiology, Department of Medicine, Royal Victoria Hospital, McGill Univ Health Centre, Montreal, QC, Canada (J.C.E., G.T.). Department of Cardiology, Uppsala Clinical Research Centre, Uppsala University, Sweden (E.H.). Department of Vascular Medicine, Academic Medical Centre, Amsterdam (G.K.H.). Einthoven Laboratory for Experimental Vascular Medicine, LUMC, Leiden (J.W.J.). Interuniversity Cardiology Institute of the Netherlands, Utrecht (J.W.J.). Department of Internal Medicine, Jagiellonian University Medical College, Krakow, Poland (M.P.K., M.S., W.S). Cardiology Centre, Institute for Clinical and Experimental Medicine, Prague, Czech Republic (J.K.). Department of Cardiology and Internal Diseases, Military Institute of Medicine, Warsaw, Poland (M. Kiliszek). Department of Respiratory Medicine, Academic Medical Centre, University of Amsterdam (A.H.M.-v.d.Z.). Department of

Internal Medicine, Skåne University Hospital, Malmö, Sweden (O.M.). Department of Forensic Medicine; Medical University of Bialystok (A.N.-J.). Pat Macpherson Centre for Pharmacogenetics and Pharmacogenomics, Division of Molecular and Clinical Medicine, Ninewells Hospital and Medical School, Dundee (C.N.P.). Department of Medicine, McGill University Health Centre, Montreal, QC, Canada (L.P, J.M.B.). Cardiovascular Research Institute, National University of Singapore (A.M.R.). Assistance Publique-Hôpitaux de Paris (AP-HP), Department of Clinical Pharmacology, Platform of Clinical Research of East Paris (URCEST-CRCEST-CRB HUEP-UPMC), FACT (French Alliance for Cardiovascular Trials), Sorbonne Université (T.S.). Paris-Sorbonne University, UPMC-Site St Antoine, France (T.S.). Department of Cardiology, Clinical Sciences, Lund University, Skåne University Hospital (J.G.S.). Wallenberg Centre for Molecular Medicine, Lund University Diabetes Centre, Lund University, Sweden (J.G.S.). Program in Medical and Population Genetics, Broad Institute, Cambridge, MA (J.G.S.). Saint Luke's Mid America Heart Institute, University of Missouri-Kansas City (J.A.S.). Saint Lukés Mid America Heart Insti Kansas City, MO (J.A.S.). Department of Clinical Biochemistry, Copenhagen University Hospital, Gentofte (S.S.). Department of Cardiology, The Heart Centre, Copenhagen University Hospital, Rigshospitalet (J.T.-H.). Department of Forensic Medicine, Faculty of Medical Sciences, University of Copenhagen, Denmark (J.T.-Hansen). Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics, University Hospital, Leipzig, Germany (J.T.). Unit of Epidemiology and Biostatistics, Department of Health Science and Technology, Aalborg University Hospital, Denmark (C.T.-Pedersen). Department of Cardiovascular Medicine, University of Münster, Germany (J.W.). Department of Cardiology, Herlev and Gentofte Hospital, Hellerup, Denmark (P.E.W.). Department of Pathology and Molecular Medicine, McMaster University (G.P.). Population Health Research Institute, Hamilton, ON, Canada (G.P.). Synlab Academy, Syn-lab Holding Deutschland GmbH, Mannheim, Germany (W.M.). Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Austria (W.M.). Durrer Centre of Cardiogenetic Research, ICIN-Netherlands Heart Institute, Utrecht (F.W.A.).

Acknowledgments

Disclosures

Dr Patel has received speaker fees and honoraria from Amgen, Sanofi, and Bayer and research funding from Regeneron; Dr Holmes has collaborated with Boehringer Ingelheim in research, and in accordance with the policy of the The Clinical Trial Service Unit and Epidemiological Studies Unit (University of Oxford), did not accept any personal payment; Dr Akerblom has received institutional research grant and speakers fee from AstraZeneca, institutional research grant from Roche Diagnostics; Dr James has received grants from AstraZeneca, The Medicines Company, Swedish heart and lung foundation, Swedish research council, Janssen; personal fees from Bayer; Dr Hagstrom declares being an expert committee member, lecture fees, and institutional research grant from Sanofi, and Amgen; institutional research grants from AstraZeneca, and GlaxoSmithKline; expert committee member and lecture fees NovoNordisk and Behringer; Dr Held declares institutional research grant, advisory board member and speaker's bureau from AstraZeneca; institutional research grants from Bristol-Myers Squibb Merck & Co, GlaxoSmithKline, Roche Diagnostics. Advisory board for Bayer and Boehringer Ingelheim; Dr Lindholm has received institutional research grants from AstraZeneca, and GlaxoSmithKline; Speaker fees from AstraZeneca, Speaker fees from AstraZeneca; Dr Siegbahn has received institutional research grants from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Roche Diagnostics, GlaxoSmithKline; Dr ten Berg reports receiving fees for board membership from AstraZeneca, consulting fees from AstraZeneca, Eli Lilly, and Merck, and lecture fees from Daiichi Sankyo and Eli Lilly, AstraZeneca, Sanofi and Accumetrics; Dr Wallentin reports institutional research grants, consultancy fees, lecture fees, and travel support from Bristol-Myers Squibb/Pfizer, AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim; institutional research grants from Merck & Co, Roche Diagnostics; consultancy fees from Abbott; and holds a patent EP2047275B1 licensed to Roche Diagnostics, and a patent US8951742B2 licensed to Roche Diagnostics; Dr Asselbergs has received research funding from Regeneron, Pfizer, Sanofi.

REFERENCES

1. Ford ES, et al. Proportion of the decline in cardiovascular mortality disease due to prevention versus treatment: public health versus clinical care. Annu Rev Public Health. 2011;32:5–22. doi: 10.1146/annurev-publhealth-031210-101211 [PubMed: 21417752]

2. Sidney S, et al. Recent trends in cardiovascular mortality in the united states and public health goals. JAMA Cardiol. 2016;1:594–599. doi: 10.1001/jamacardio.2016.1326 [PubMed: 27438477]

3. Ford ES, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980–2000. N Engl J Med. 2007;356:2388–2398. doi: 10.1056/NEJMsa053935 [PubMed: 17554120]

4. Benjamin EJ, et al.; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2017 Update: a report from the American Heart Association. Circulation. 2017;135:e146–e603. doi: 10.1161/CIR.0000000000000485 [PubMed: 28122885]

5. Scarborough PBP, et al. Coronary Heart Disease Statistics 2010 Edition. London: British Heart Foundation; 2010.

6. Yusuf S, et al.; Interheart Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364:937–952. doi: 10.1016/S0140-6736(04)17018-9 [PubMed: 15364185]

7. Deloukas P, et al. Large-scale association analysis identifies new risk loci for coronary artery disease. Nat Genet. 2013;45:25–33. [PubMed: 23202125]

8. Fox KA, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ. 2006;333:1091. doi: 10.1136/bmj.38985.646481.55 [PubMed: 17032691]

9. Schiele F, et al. Coronary artery disease: risk stratification and patient selection for more aggressive secondary prevention. Eur J Prev Cardiol. 2017;24(3_suppl):88–100. doi: 10.1177/2047487317706586 [PubMed: 28618915]

10. Schwartz GG, et al.; dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. N Engl J Med. 2012;367:2089–2099. doi: 10.1056/NEJMoa1206797 [PubMed: 23126252]

11. White HD, et al. Darapladib for preventing ischemic events in stable coronary heart disease. N Engl J Med. 2014;370:1702–1711. [PubMed: 24678955]

12. Boden WE, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011;365:2255–2267. [PubMed: 22085343]

13. Armitage JM, et al. Effects of homocysteine-lowering with folic acid plus vitamin B12 vs placebo on mortality and major morbidity in myocardial infarction survivors: a randomized trial. JAMA. 2010;303: 2486–2494. [PubMed: 20571015]

14. Global BMIMC, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet. 2016;388:776–786. [PubMed: 27423262]

15. Wang ZJ, et al. Association of body mass index with mortality and cardiovascular events for patients with coronary artery disease: a systematic review and meta-analysis. Heart. 2015;101:1631–1638. doi: 10.1136/heartjnl-2014-3071 [PubMed: 26025084]

16. Cannon CP, et al.; Improve-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387–2397. doi: 10.1056/NEJMoa1410489 [PubMed: 26039521]

17. Sabatine MS, et al.; Fourier Steering Committee and Investigators. Evo-locumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376:1713–1722. doi: 10.1056/NEJMoa1615664 [PubMed: 28304224]

18. Ridker PM, et al.; Cantos Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med. 2017;377:1119–1131. doi: 10.1056/NEJMoa1707914 [PubMed: 28845751]

19. Patel RS, et al. The Genius-CHD consortium. Eur Heart J. 2015;36:2674–2676. [PubMed: 26788565]

20. Rothman KJ, Greenland S. Modern epidemiology. 2nd ed. Philadelphia: Lippincott-Raven, 1998.

21. Lee JC, et al.; UK IBD Genetics Consortium. Genome-wide association study identifies distinct genetic contributions to prognosis and susceptibility in Crohn's disease. Nat Genet. 2017;49:262–268. doi: 10.1038/ng.3755 [PubMed: 28067912]

22. Ohman EM, et al.; Reach Registry Investigators. The Reduction of Athero-thrombosis for Continued Health (REACH) registry: an international, prospective, observational investigation in subjects at risk for atherothrom-botic events-study design. Am Heart J. 2006;151:786.e1–786.e10. doi: 10.1016/j.ahj.2005.11.004 [PubMed: 16569533]

23. Psaty BM, et al. The Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium as a model of collaborative science. Epidemiology. 2013;24:346–348. doi: 10.1097/EDE.0b013e31828b2cbb [PubMed: 23549178]

24. Collins R, et al. What makes UK Biobank special? Lancet. 2012;379:1173–1174. doi: 10.1016/S0140-6736(12)60404-8 [PubMed: 22463865]

25. Chen Z, et al.; China Kadoorie Biobank (CKB) collaborative group. China Kadoorie Biobank of 0.5 million people: survey methods, baseline characteristics and long-term follow-up. Int J Epidemiol. 2011;40:1652–1666. doi: 10.1093/ije/dyr120 [PubMed: 22158673]

26. Reilly MP, et al.; Myocardial Infarction Genetics Consortium; Well-come Trust Case Control Consortium. Identification of ADAMTS7 as a novel locus for coronary atherosclerosis and association of ABO with myocardial infarction in the presence of coronary atherosclerosis: two genome-wide association studies. Lancet. 2011;377:383–392. doi: 10.1016/S0140-6736(10)61996-4 [PubMed: 21239051]

27. Dahabreh IJ, et al. Index event bias as an explanation for the paradoxes of recurrence risk research. JAMA. 2011; 305:822–823. doi: 10.1001/jama.2011.163 [PubMed: 21343582]

28. Nicholls SJ, et al. Effect of evolocumab on progression of coronary disease in statin-treated patients: the glagov randomized clinical trial. JAMA. 2016;316:2373–2384. doi: 10.1001/jama.2016.16951 [PubMed: 27846344]

29. Hu YJ, et al. Impact of selection bias on estimation of subsequent event risk. Circ Cardiovasc Genet. 2017;10:001616
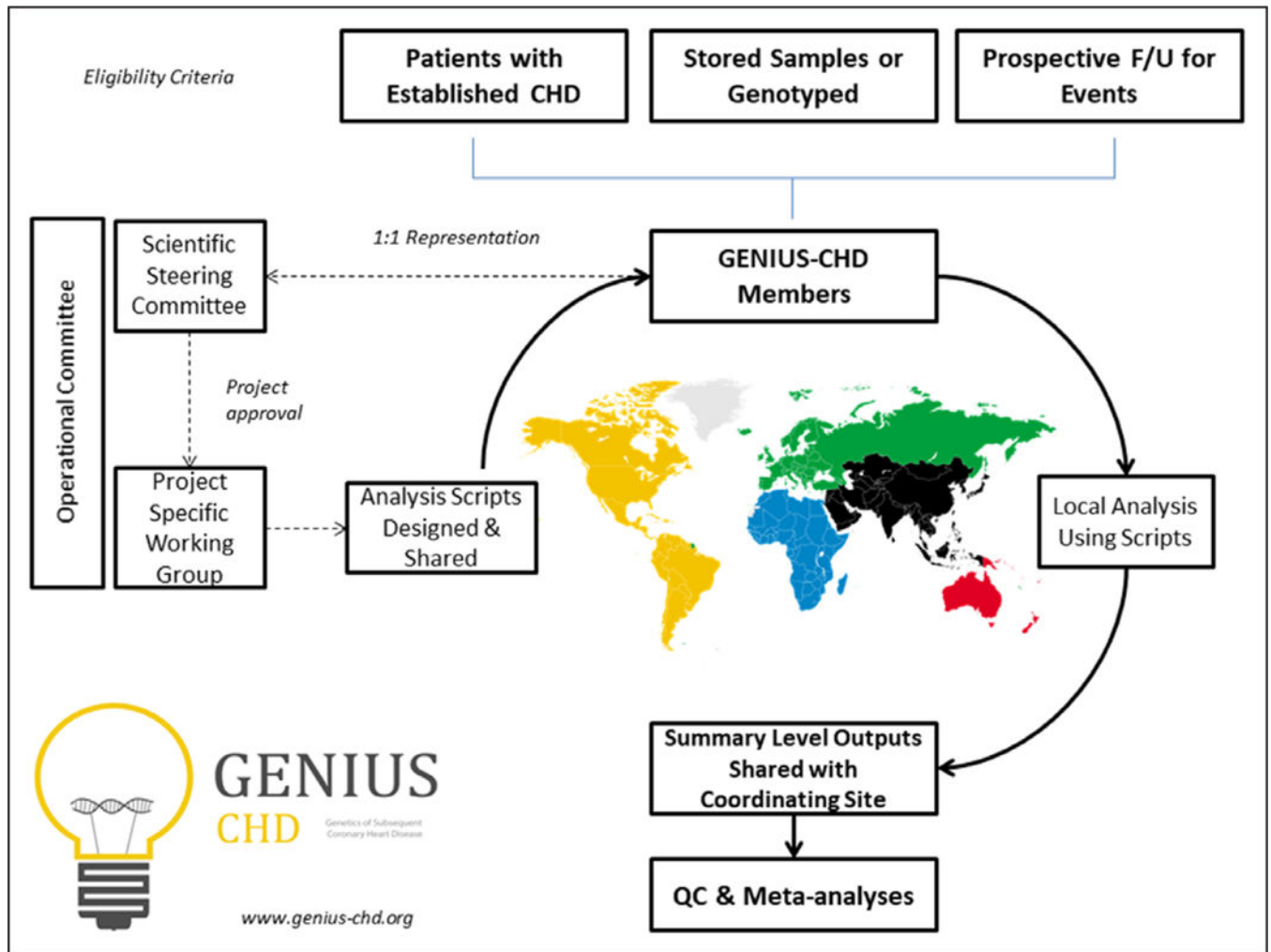
Figure 1. Overview of the Genetics of Subsequent Coronary Heart Disease (GENIUS-CHD) consortium, illustrating inclusion criteria and governance structure.

Following project approval by the steering committee, analyses scripts are prepared and distributed to all members, with sharing of summary-level outputs before meta-analysis at the coordinating centers. Further details can be found at www.genius-chd.org. QC indicates quality control.
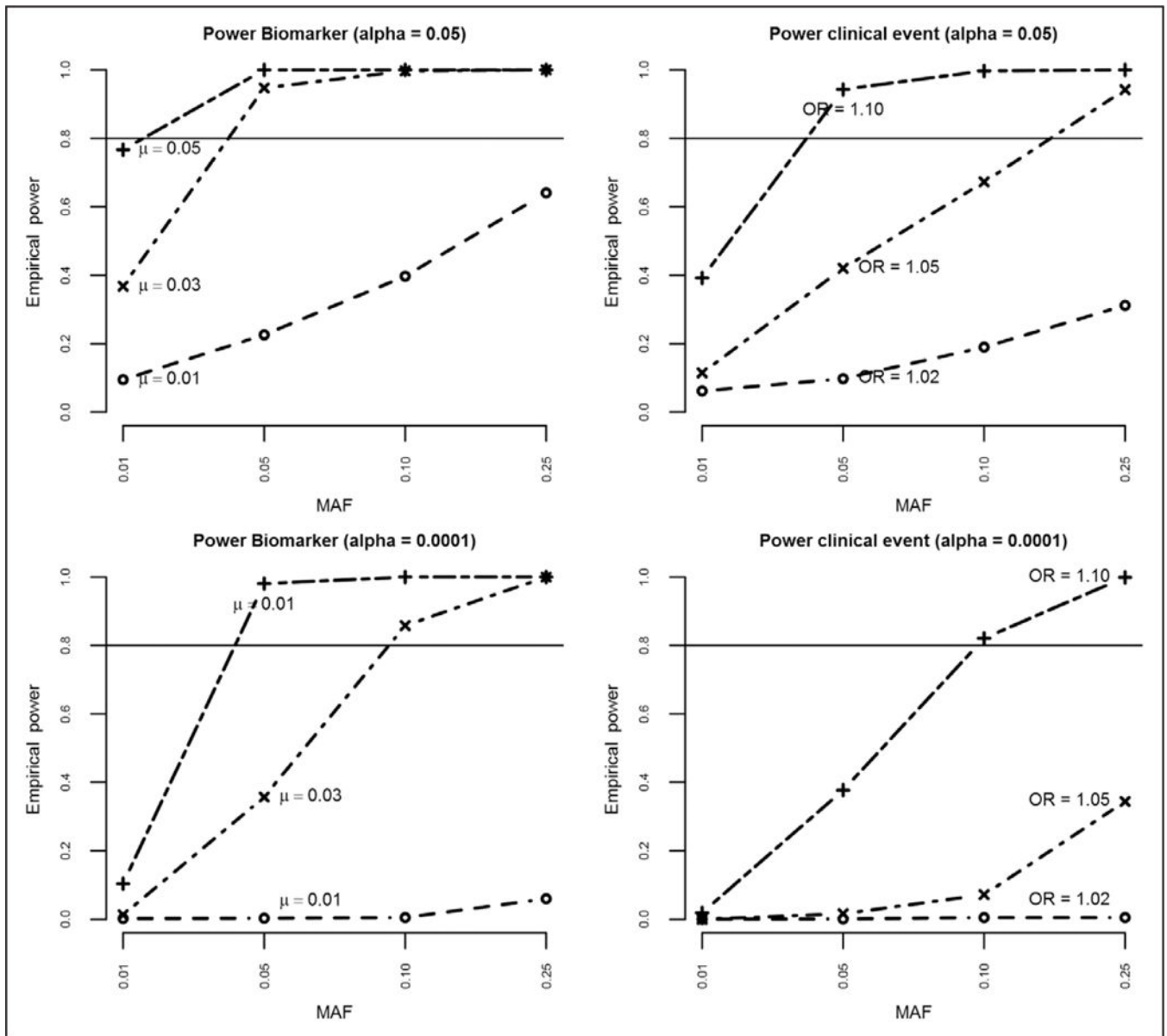
Figure 2. Figure illustrating empirical power for detecting different effect sizes for biomarker variance and clinical events for both α 0.05 and 0.0001, by varying minor allele frequencies, for a conservative total number of 150 000 with an event rate of 10%.
MAF indicates minor allele frequency; and OR, odds ratio.
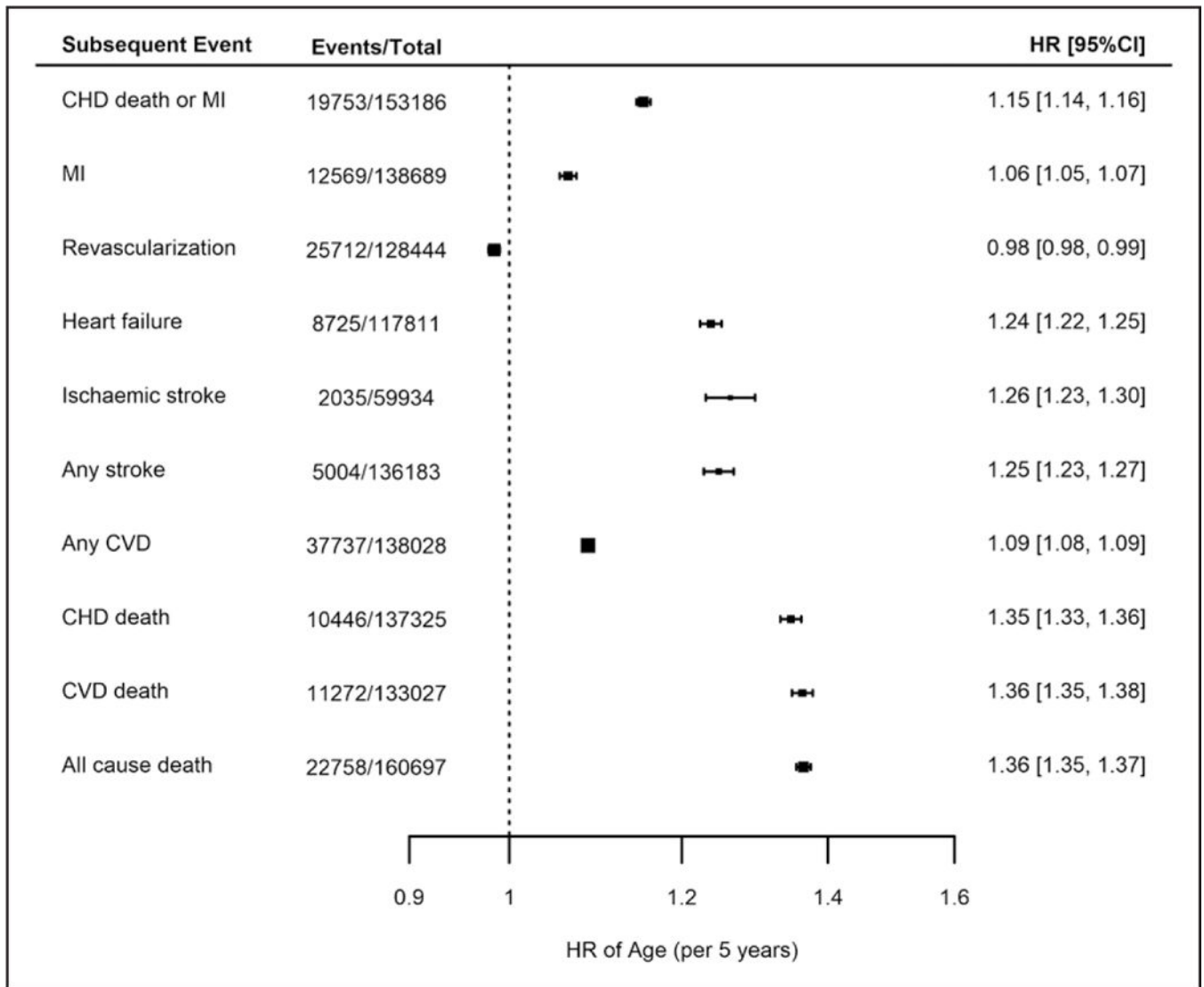
Figure 3. Meta-analyses of the associations between age (per 5-year intervals) and different end points, adjusted for sex.

Estimates are presented as hazard ratios (HRs) with 95% CI. CHD indicates coronary heart disease; CVD, cardiovascular disease; and MI myocardial infarction.
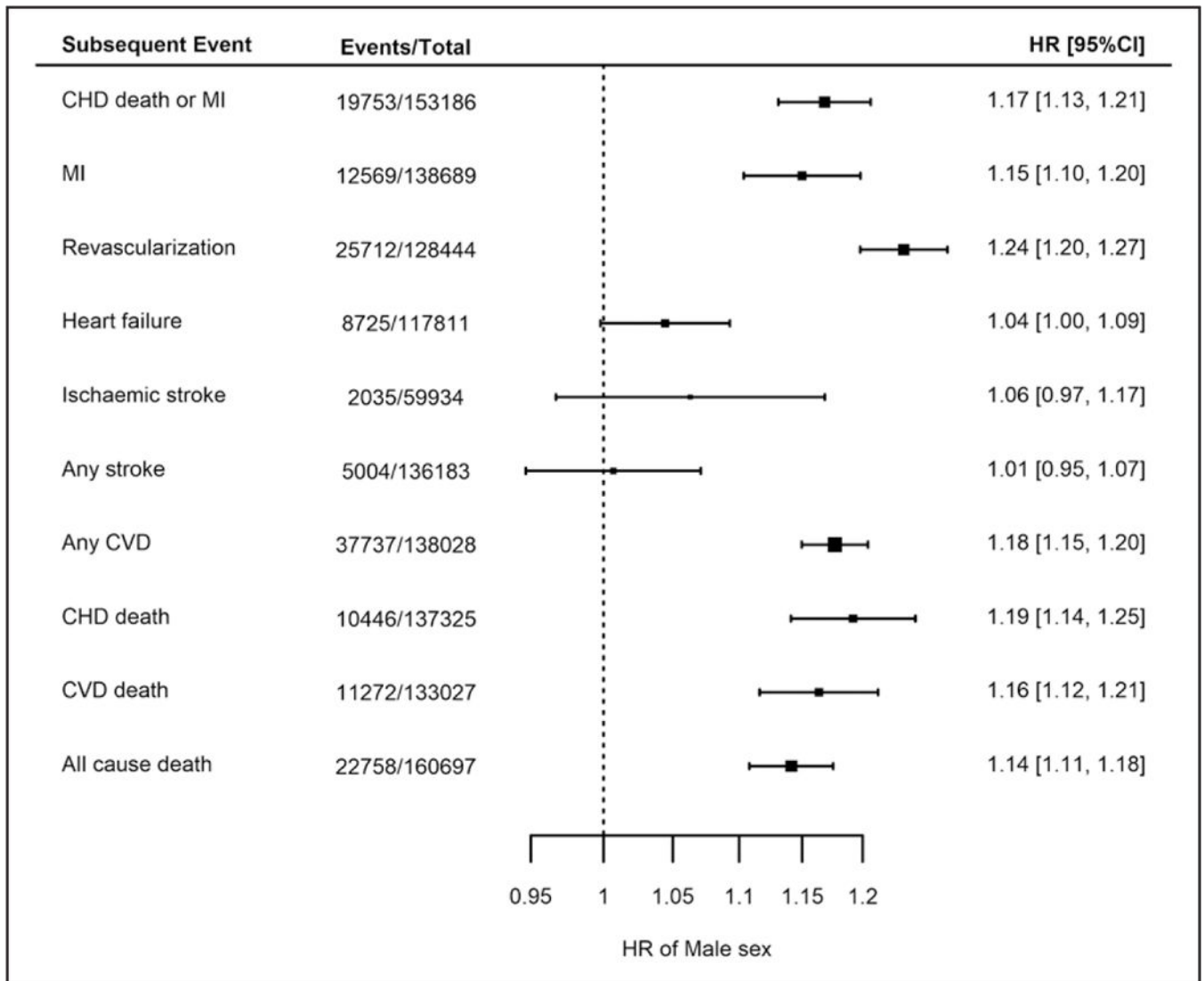
Figure 4. Meta-analyses of the associations between male sex and different end points, adjusted for age.

Estimates are presented as hazard ratios (HRs) with 95% CI. CHD indicates coronary heart disease; CVD, cardiovascular disease; and MI, myocardial infarction.
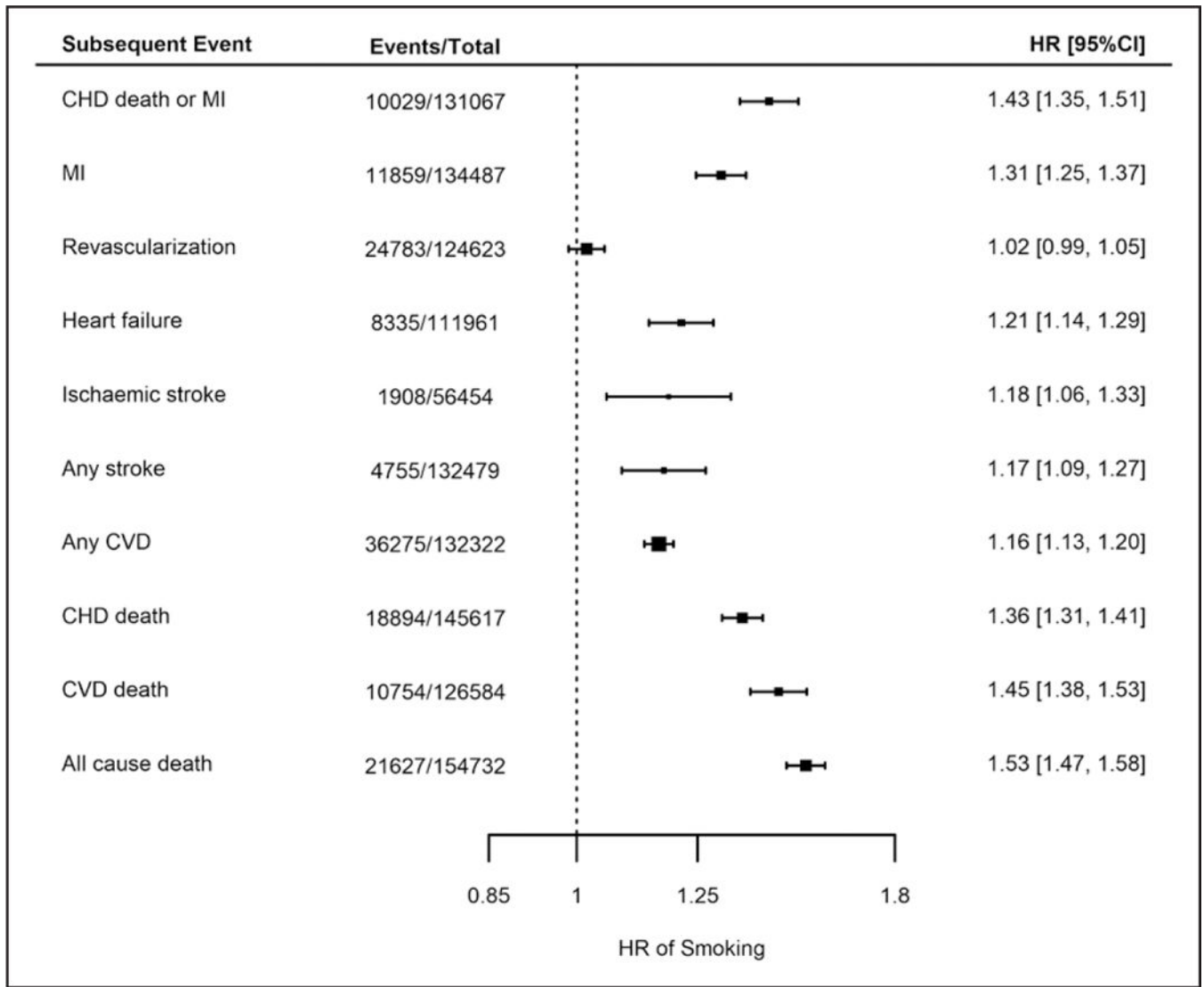
Figure 5. Meta-analyses for the associations between smoking at coronary heart disease (CHD) indexing event compared to not smoking and for different end points, adjusted for age and sex. Estimates are presented as hazard ratios (HRs) with 95% CI. CVD indicates cardiovascular disease; and MI, myocardial infarction.

Table 1.

Overview of Each Study Participating in the GENIUS-CHD Consortium

Alias	Cohort Name	Country	Study Design	Recruitment Period	CHD Type	Total Recruited With CHD	European Ancestry (%)	Europeans Recruited With CHD	Mean Follow-Up Time (SD)	Age (SD)	Male (%)	PubMED ID
4C	Clinical Cohorts in Coronary disease Collaboration	United Kingdom	Clinical Cohort	2009–2014	CAD	3345	54.8	1832	2.56 (0.95)	61.8(12.14)	61.5	NA
AGNES	Arrhythmia Genetics in The Netherlands	The Netherlands	Clinical Cohort	2001–2005	ACS	1459	100.0	1459	6.73 (4.75)	57.8(10.73)	79.2	20622880
ANGES	Angiography and Genes Study	Finland	Clinical Cohort	2002–2005	Mixed	588	100.0	588	8.20(4.47)	64.1 (9.59)	65.5	21640993
ATVB	Italian Atherosclerosis, Thrombosis and Vascular Biology Group	Italy	Clinical Cohort	1997–2006	ACS	1741	100.0	1741	10.47 (4.45)	40.0 (4.40)	90.8	21757122
CABGenomics	CABG Genomics	United States	Clinical Cohort	2001–2014	Mixed	2694	85.5	2303	6.9 (3.5)	64.4 (10.38)	79	25649697
CARDIOLINES	Cardiolines	The Netherlands	Clinical Cohort	2011	Mixed	1269	75.0	1692	1.3 (0.5)	63.5 (11.6)	72.8	NA
CDCS	Coronary Disease Cohort Study	New Zealand	Clinical Cohort	2002–2009	ACS	2139	91.4	1956	5.21 (2.15)	67.4 (12.01)	71.3	20400779
COGEN	The Copenhagen Cardiovascular Genetic study	Denmark	Clinical Cohort	2011–2017	Mixed	3709	95.0	3904	5.5(1.01)	70.1 (17.4)	67.5	In press
COROGENE	Corogene Study	Finland	Clinical Cohort	2006–2008	ACS	1489	100.0	1489	7.7 (0.5)	64.7 (11.88)	70.9	21642350
CTMM	Circulating Cells	The Netherlands	Clinical Cohort	2009–2011	Mixed	713	96.5	688	0.97 (0.37)	62.6 (10.08)	69	23975238
CURE	Cure-Genetics Study	Canada	RCT	1998–2000	ACS	12 434	82.1	10203	0.78 (0.28)	65.4(11.19)	61.4	11102254
EGCUT	Estonian Biobank	Estonia	Population	2002–2011	CAD	2783	100.0	2783	6.65 (2.93)	66.6 (10.99)	51.5	24518929
EMORY	Emory Cardiovascular Biobank	United States	Clinical Cohort	2004	Mixed	5873	72.0	4229	4.49 (3.15)	65.4 (11.74)	68.7	20729229
ERICO	Estratégia de Registro de Insuficiência Coronariana	Brazil	Clinical Cohort	2009–2014	ACS	738	61.0	450	2.85 (1.48)	63.8 (13.35)	56	23644870
FASTMI2005	The French Registry of Acute ST-elevation MI	France	Clinical Cohort	2005	ACS	3669	100.0	3669	1.72 (0.63)	67.3 (13.94)	68.5	17893635
FINCAVAS	Finnish Cardiovascular Study	Finland	Clinical Cohort	2001–2008	Mixed	1671	100.0	1671	8.57 (3.99)	60.9(11.04)	69.4	16515696
FRISCII	FRISCII Study	Sweden	RCT	1996–1998	ACS	3147	99.3	3125	7.46 (2.09)	66.3 (9.82)	69.5	10475181
GENDEMIP	Genetic Determination of Myocardial Infarction in Prague	Czech Republic	Clinical Cohort	2006–2009	ACS	1302	100.0	1302	1.13 (0.78)	56.5 (8.66)	74.4	23249639
GENEBANK	Cleveland Clinic Genebank Study	United States	Clinical Cohort	2001–2007	Mixed	2345	100.0	2345	3.00 (0.00)	61.5(11.06)	74.3	21475195

Alias	Cohort Name	Country	Study Design	Recruitment Period	CHD Type	Total Recruited With CHD	European Ancestry (%)	Europeans Recruited With CHD	Mean Follow-Up Time (SD)	Age (SD)	Male (%)	PubMED ID
GENESIS-PRAXY	Gender and Sex Determinants of Cardiovascular Disease: From Bench to Beyond-Premature Acute Coronary Syndrome	Canada	Clinical Cohort	2009–2013	ACS	784	99.4	779	1.00 (0.00)	48.3 (5.62)	69.1	22607849
GENOCOR	Genetic Mapping for Assessment of Cardiovascular Risk	Italy	Clinical Cohort	2007–2010	Mixed	497	100.0	497	5.68(1.20)	65.2 (8.47)	86.7	22717531
GEVAMI	The Genetic Causes to Ventricular Arrhythmia in Patients During First ST-Elevation Myocardial Infraction	Denmark	Clinical Cohort	2011	ACS	1033	100.0	1033	3.93 (1.40)	59.5 (10.37)	79.3	25559012
GoDARTS incident	Genetics of Diabetes Audit and Research in Tayside Scotland (I)	Scotland	Population	2004–2012	CAD	1261	99.8	1258	3.47 (2.95)	71.3(10.91)	61.1	29025058
GoDARTS prevalent	Genetics of Diabetes Audit and Research in Tayside Scotland (P)	Scotland	Population	2004–2012	CAD	2514	99.7	2507	6.48 (3.06)	69.1 (9.41)	65.9	29025058
GRACE_B	Global Registry of Acute Coronary Events - Belgium	Belgium	Clinical Cohort	1999–2010	ACS	734	100.0	734	4.25 (1.80)	65.9(11.91)	75.8	20231156
GRACE_UK	Global Registry of Acute Coronary Events - UK	United Kingdom	Clinical Cohort	2001–2010	ACS	1443	100.0	1443	9.54 (2.68)	64.3 (12.21)	69.6	20231156
IDEAL	Incremental Decrease in End Points Through Aggressive lipid Lowering (IDEAL)	Canada	RCT	1999–2005	ACS	8888	99.3	8823	4.63 (0.82)	61.8 (9.47)	80.8	16287954
INTERMOUNTAIN	Intermountain Heart Collaborative Study	United States	Clinical Cohort	1993–2009	Mixed	7556	89.5	6763	8.56(5.39)	61.2 (11.06)	66.7	20691829
INVEST	International Verapamil SR Trandolopril Study Genetic Substudy INVEST-GENES	United States/International	RCT	1997–2003	CAD	5979	38.0	2270	2.83 (0.82)	66.1 (9.70)	44	21372283, 17700361
JUMC	Krakow-GENIUS-CHD	Poland	Clinical Cohort	2010–2014	Mixed	747	100.0	747	0.84 (0.34)	68.3 (10.26)	71.6	28444280, 27481134
KAROLA	Karola Study	Germany	Clinical Cohort	1999–2000	Mixed	1206	100.0	1206	11.62 (3.01)	58.7 (8.15)	84.2	24829374
LIFE-Heart	Leipzig (LIFE) Heart Study	Germany	Clinical Cohort	2006–2014	Mixed	5564	100.0	5564	1.62 (2.03)	63.9 (11.09)	77.2	22216169
LURIC	The Ludwigshafen Risk and Cardiovascular Health Study	Germany	Clinical Cohort	1997–2000	Mixed	2320	100.00	2320	8.58(3.18)	63.8 (9.92)	76.6	11258203
MDCS	Malmo Diet and Cancer Study	Sweden	Population	1991–1996	CAD	4,546	100.00	4546	8.3 (8.0)	58.0(7.6)	60.2	19936945
NE_POLAND	North East Poland Myocardial Infarction Study	Poland	Clinical Cohort	2001–2005	ACS	646	100.0	646	7.20 (2.75)	62.3 (11.84)	75.4	26086777
NEAPOLIS	Neapolis Campania Italia	Italy	Clinical Cohort	2008–2012	Mixed	1394	100.0	1394	1.07 (0.54)	67.6 (10.50)	74.5	24262617

Alias	Cohort Name	Country	Study Design	Recruitment Period	CHD Type	Total Recruited With CHD	European Ancestry (%)	Europeans Recruited With CHD	Mean Follow-Up Time (SD)	Age (SD)	Male (%)	PubMED ID
OHGS	Ottawa Heart Genomics Study	Canada	Clinical Cohort	2010–2013	Mixed	546	100.0	546	1.77 (0.27)	65.6(11.11)	73.8	NA
PERGENE	Perindopril Genetic Association Study (EUROPA)	The Netherlands	RCT	1997–2000	CAD	8746	99.0	8656	4.20 (0.62)	59.9(9.27)	85.6	19082699
PLATO	The Study of Platelet Inhibition and Patient Outcomes	International	RCT	2006–2008	ACS	18624	98.3	18315	0.86 (0.24)	62.6 (10.96)	69.5	19332184
PMI	Post Myocardial Infarction Study	New Zealand	Clinical Cohort	1994–2001	ACS	1057	91.1	963	8.56 (3.58)	62.8 (10.56)	78	12771003
POPular	The Popular study	The Netherlands	Clinical Cohort	2005–2007	Mixed	1024	98.2	1006	1.00 (0)	63.8(10.39)	74.6	20179285
POPular Genetics	The Popular GENETICS Study	The Netherlands and Belgium	RCT	2011–2017	ACS	2481	94.3	2287	1.00 (0)	NA	74.9	24952855
PROSPER	Prospective Study of Pravastatin in the Elderly at Risk	The Netherlands	RCT	1997–1999	CAD	893	100.0	893	3.15 (0.71)	75.4(3.38)	70.3	10569329
RISCA	Recurrance and Inflammation in the Acute Coronary Syndromes Study	Canada	Clinical Cohort	2001–2002	ACS	1054	100.0	1054	1.22 (0.18)	61.8(11.45)	75.9	18549920
SHEEP	Stockholm Heart Epidemiology Program (SHEEP)	Sweden	Clinical Cohort	1992–1995	ACS	1150	100.0	1150	14.87 (5.91)	59.3 (7.21)	70.7	17667644
SMART	Second Manifestations of Arterial Disease	The Netherlands	Clinical Cohort	1999–2010	Mixed	3057	98.2	3001	6.77 (3.86)	60.5 (9.31)	81.7	10468526
STABILITY	Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy trial	International	RCT	2008–2010	CAD	10786	86.1	9287	3.60 (0.57)	64.7 (9.10)	82	24678955
THI	Texgen	United States	Clinical Cohort	2001–2008	ACS	3875	73.1	2834	5.50 (3.42)	63.6 (10.61)	74.9	21414601
TNT	Treating to New Targets	Canada	RCT	1998–1999	CAD	10 000	94.1	9409	4.36 (1.47)	61.1 (8.82)	81.6	15755765
TRIUMPH	Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patient's Health Status	United States	Clinical Cohort	2005–2008	ACS	2062	100.0	2062	0.97 (0.15)	59.8 (12.10)	72.2	21772003
UCORBIO	Utrecht Coronary Biobank	The Netherlands	Clinical Cohort	2011–2014	Mixed	1493	72.4	1081	1.6 (0.9)	65.4 (10.27)	75.6	NA
UCP	Utrecht Cardiovascular Pharacogenetics Study	The Netherlands	Clinical Cohort	1985–2010	Mixed	1508	100.0	1508	8.00 (4.16)	64.1 (9.97)	75.4	25652526
UKB	UK Biobank	United Kingdom	Population	2006–2010	CAD	12 045	94.2	11 342	6.39 (1.72)	69.9 (6.07)	80.6	1001779
VHS	Verona Heart Study	Italy	Clinical Cohort	1996-	CAD	939	100.0	939	5.62 (2.97)	61.3 (9.74)	81	10984565

Alias	Cohort Name	Country	Study Design	Recruitment Period	CHD Type	Total Recruited With CHD	European Ancestry (%)	Europeans Recruited With CHD	Mean Follow-Up Time (SD)	Age (SD)	Male (%)	PubMED ID
VIVIT	Vorarlberg Institute for Vascular Investigation and Treatment Study	Austria	Clinical Cohort	1999–2008	CAD	1447	99.8	1444	7.43 (2.91)	64.5 (10.45)	72	24265174
WARSAW ACS	Warsaw ACS Genetic Registry	Poland	Clinical Cohort	2008–2011	ACS	681	100.0	681	2.97 (1.16)	63.5 (11.84)	74.2	NA
WTCC	WTCCC CAD Study	United Kingdom	Clinical Cohort	1998–2003	Mixed	1926	100.0	1926	10.05 (2.81)	60.0 (8.13)	79.3	16380912, 17634449

Alias denotes the abbreviated name of study used in figures and analyses. PubMed IDs are provided for individual study descriptions; mean (SD) with proportions (%) are provided unless otherwise stated. ACS indicates acute coronary syndrome; CAD, coronary artery disease; GENIUS-CHD, Genetics of Subsequent Coronary Heart Disease; and RCT, randomized controlled trial.

Table 2.

Participant Characteristics of Each Study Contributing to GENIUS-CHD

Alias	BMI, kg/m² (SD)	Systolic BP (SD)	Diastolic BP (SD)	Diabetes mellitus (%)	Current Smoking (%)	Total cholesterol (SD), mmol/L	LDL-C (SD), mmol/L	HDL-C (SD), mmol/L	Creatinine (SD)	Statin use (%)	Prior Revascularization (%)	Prior MI (%)
4C	30.2 (5.7)	133.8 (23)	77.9 (12.2)	21.8	19.1	4.64(1.10)	NA	1.309 (0.42)	98.7 (81)	24.7	20.6	14.1
AGNES	26.6(3.9)	NA	NA	7.9	61.0	5.26(1.04)	3.25(1.01)	1.198 (0.45)	NA	10.0	0.0	0.0
ANGES	28.1 (4.4)	NA	NA	30.8	14.7	4.71 (0.84)	2.68 (0.77)	1.166 (0.33)	83.0 (37)	69.4	42.4	24.7
ATVB	26.8(4.0)	132.4(21)	83.5 (13.5)	8.2	79.5	5.83 (1.39)	NA	1.080 (0.33)	NA	55.4	NA	NA
CABGenomics	29.8(5.6)	NA	NA	9.0	10.3	4.32 (0.94)	2.13 (0.85)	1.085 (0.35)	NA	74.1	NA	37.0
CARDIOLINES	26.9(3.8)	134.4(23)	84.34 (14.6)	NA	0.6	5.43 (1.1)	3.84(1.0)	1.16 (0.3)	NA	NA	NA	NA
CDCS	27.3 (4.7)	129.1 (22)	74.6(11.7)	15.2	5.8	5.01 (1.09)	2.95 (1.03)	1.175 (0.34)	100.8 (41)	46.0	26.5	30.4
COGEN	NA	NA	NA	16.7	26.2	NA	NA	NA	NA	NA	NA	NA
COROGENE	27.6(4.8)	NA	NA	18.2	34.4	4.58 (0.99)	2.43 (0.88)	1.250 (0.37)	84.0 (46)	5.2	NA	NA
CTMM	27.6(4.4)	135.5 (19)	77.4(11.2)	21.0	20.9	4.54(1.06)	2.59 (0.98)	1.135 (0.32)	86.2 (40)	NA	NA	30.3
CURE	27.7 (4.5)	135.1 (22)	77.1 (13.6)	20.9	23.0	NA	NA	NA	93.1 (35)	NA	14.8	31.7
EGCUT	29.0(5.2)	135.7 (18)	80.4 (10.6)	18.9	19.8	5.70(1.17)	3.84(1.08)	1.340 (0.35)	NA	27.7	15.4	35.3
EMORY	29.8(6.7)	137.0 (22)	75.0 (15.0)	34.2	7.8	4.49(1.04)	2.42 (0.93)	1.090 (0.34)	100.2 (56)	74.2	59.6	26.8
ERICO	27.0(5.1)	134.8(32)	99.4 (38.0)	39.4	31.2	NA	NA	NA	NA	23.8	11.7	26.2
FASTMI2005	27.2 (4.8)	139.9(28)	80.0 (17.0)	35.9	29.1	5.03 (1.22)	3.03 (1.07)	1.239 (0.43)	103.4 (62)	74.1	NA	18.2
FINCAVAS	27.8(4.3)	140.2 (22)	82.2 (10.6)	18.4	24.3	4.70 (0.90)	2.62 (0.80)	1.300 (0.39)	90.8 (70)	57.3	32.6	39.0
FRISCII	26.8(3.9)	143.4(23)	82.0 (10.6)	12.8	27.0	5.81 (1.12)	3.72 (0.99)	1.151 (0.36)	90.6 (19)	12.3	12.1	27.2
GENDEMIP	28.6(4.7)	137.1 (21)	84.0 (10.8)	19.0	61.0	5.42(1.16)	3.58(1.09)	1.183 (0.33)	NA	16.7	30.2	40.8
GENEBANK	29.4(5.4)	132.7 (21)	75.0 (12.0)	11.8	16.8	4.38 (0.93)	2.51 (0.82)	0.903 (0.26)	NA	71.8	65.3	56.1
GENESIS-PRAXY	29.5 (6.5)	139.5 (27)	86.2 (17.2)	13.9	44.2	4.87(1.19)	2.89(1.13)	0.966 (0.30)	75.9 (20)	92.9	11.4	11.5
GENOCOR	NA	129.5 (20)	75.54(11.1)	13.3	64.4	4.82 (0.92)	3.10(0.83)	1.082 (0.28)	94.8 (27)	72.1	13.7	63.2
GEVAMI	27.2 (4.3)	124.8(18)	73.2 (11.1)	8.9	52.4	NA	NA	NA	NA	13.4	0.0	0.0
GoDARTSincident	29.8(5.6)	126.7 (17)	NA	70.9	NA	4.57 (1.02)	2.43 (0.91)	1.277 (0.41)	107.0 (65)	49.6	0.2	1.2
GoDARTSprevalent	30.2 (5.4)	136.0(20)	NA	75.8	14.5	4.37 (0.84)	2.04 (0.74)	1.320 (0.38)	101.0 (34)	66.3	30.2	46.8
GRACE_B	27.0(4.3)	138.3 (25)	78.7 (14.6)	81.1	49.3	5.19(1.20)	3.06(1.09)	1.343 (0.98)	102.6 (63)	79.4	NA	80.5
GRACE_UK	27.9(5.0)	137.9 (27)	76.4 (16.5)	13.9	69.2	5.20 (1.27)	3.07(1.14)	1.204 (0.49)	101.5 (38)	14.5	20.2	30.0

Alias	BMI, kg/m² (SD)	Systolic BP (SD)	Diastolic BP (SD)	Diabetes mellitus (%)	Current Smoking (%)	Total cholesterol (SD), mmol/L	LDL-C (SD), mmol/L	HDL-C (SD), mmol/L	Creatinine (SD)	Statin use (%)	Prior Revascularization (%)	Prior MI (%)
IDEAL	27.3 (3.8)	136.9(20)	80.4 (10.2)	11.9	20.7	5.09(1.00)	3.14(0.90)	1.192 (0.31)	100.6 (17)	75.5	40.9	100.0
INTERMOUNTAIN	29.5 (6.1)	141.8(24)	81.1 (13.3)	20.3	10.2	4.91 (1.12)	2.76(0.94)	1.048 (0.35)	99.6 (67)	38.7	NA	6.6
INVEST	29.4(5.6)	148.4(18)	82.4 (10.5)	24.3	13.3	NA	NA	NA	NA	52.7	48.1	23.3
JUMC	26.3 (4.5)	148.2 (25)	80.3 (12.4)	36.1	27.5	4.97(1.08)	3.11 (1.14)	1.232 (0.37)	91.3 (42)	87.5	49.8	39.9
KAROLA	26.9(3.3)	120.0(16)	73.1 (9.1)	18.6	31.8	4.44 (0.84)	2.61 (0.76)	1.030 (0.28)	82.7 (28)	77.0	42.8	22.4
LIFE-Heart	28.9(4.7)	139.0 (22)	80.0 (12.9)	33.9	27.8	5.16(1.19)	3.12 (1.05)	1.227 (0.35)	88.8 (34)	45.8	NA	13.3
LURIC	27.5 (4.0)	142.2 (24)	81.0(11.5)	44.1	24.6	4.94 (0.99)	2.98 (0.89)	0.965 (0.26)	88.7 (38)	58.9	48.3	57.8
MDCS	25.8(4.0)	141.1 (20)	85.6 (10.0)	4.4	26.6	6.17 (1.1)	4.16(1.0)	1.38 (0.4)	84.76 (16)	0.03	0.00	0.00
NE_POLAND	24.8(3.8)	138.7 (27)	88.1 (15.6)	22.3	48.5	5.12 (1.04)	3.31 (0.97)	1.126 (0.34)	92.0 (36)	81.2	1.7	11.2
NEAPOLIS	28.0(4.2)	129.4(14)	75.7(7.7)	42.7	26.9	4.49(1.03)	2.45 (0.99)	1.233 (0.66)	101.0 (68)	82.6	41.9	40.9
OHGS	28.5 (4.9)	132.2 (19)	72.1 (11.3)	5.5	19.3	5.57 (1.05)	3.46 (0.88)	1.222 (0.34)	89.1 (21)	91.6	27.8	23.3
PERGENE	27.5(3.5)	136.9(15)	81.8 (8.1)	12.7	14.7	5.41 (1.04)	NA	NA	86.5 (26)	55.3	54.6	65.4
PLATO	28.2 (4.5)	135.6 (22)	79.5 (12.9)	22.8	35.2	5.40 (1.23)	3.27(1.11)	1.279 (0.35)	85.6 (26)	79.7	15.1	20.6
PMI	26.5 (3.8)	116.5(16)	66.5 (9.6)	12.5	28.0	5.97(1.19)	3.98(1.07)	NA	88.0 (28)	44.6	NA	18.4
POPular	27.2 (4.1)	144.9(22)	81.4 (12.1)	19.0	27.6	4.56(0.94)	2.73(1.15)	1.260 (0.32)	92.7 (27)	80.7	32.9	43.6
POPular Genetics	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PROSPER	26.6(3.9)	150.0 (22)	81.1 (11.4)	10.4	17.3	5.55 (0.84)	3.74 (0.74)	1.174 (0.31)	109.2 (23)	0.0	26.5	86.9
RISCA	27.2 (4.4)	NA	NA	19.8	30.4	NA	NA	NA	100.6 (29)	46.6	28.3	27.8
SHEEP	26.8(4.0)	131.8(21)	79.6 (10.3)	18.2	50.1	6.20(1.16)	4.22 (1.01)	1.082 (0.31)	NA	0.0	0.0	0.0
SMART	27.4(3.7)	137.0(19)	80.1 (10.8)	17.1	24.2	4.66 (0.95)	2.64 (0.88)	1.231 (0.72)	92.3 (23)	77.5	100.0	44.5
STABILITY	29.9(5.0)	131.7 (16)	79.1 (10.0)	38.4	21.4	NA	2.25 (0.85)	1.216 (0.32)	NA	97.3	74.6	58.6
THI	29.6(5.6)	NA	NA	30.4	21.1	NA	NA	NA	NA	57.2	21.7	16.7
TNT	28.5 (4.5)	130.7 (17)	77.9 (9.4)	14.2	13.3	4.53 (0.61)	2.52 (0.45)	1.223 (0.28)	104.5 (17)	70.1	NA	58.2
TRIUMPH	29.6(6.0)	117.7(18)	68.1 (10.9)	29.1	37.4	NA	2.70 (1.02)	1.037 (0.33)	113.7 (81)	89.0	27.2	18.5
UCORBIO	27.2 (4.3)	NA	NA	21.4	23.1	4.80(1.18)	2.64(1.05)	1.205 (0.33)	92.0 (45)	63.9	NA	29.0
UCP	NA	153.4 (25)	87.1 (13.3)	NA	NA	5.66(1.10)	3.36(1.01)	1.244 (0.33)	94.7 (25)	27.0	NA	NA
UKB	29.4(4.9)	139.1 (20)	78.7 (10.9)	22.2	75.9	NA	NA	NA	NA	82.9	59.6	36.7
VHS	26.8(3.6)	NA	NA	18.4	69.1	5.51 (1.13)	3.69(1.00)	1.175 (0.30)	96.7 (32)	46.4	17.6	59.4
VIVIT	27.4(4.1)	137.4(19)	80.6 (10.9)	31.0	19.4	5.36(1.15)	3.33 (1.02)	1.348 (0.40)	89.9 (41)	49.9	20.6	30.4

Alias	BMI, kg/m^2 (SD)	Systolic BP (SD)	Diastolic BP (SD)	Diabetes mellitus (%)	Current Smoking (%)	Total cholesterol (SD), mmol/L	LDL-C (SD), mmol/L	HDL-C (SD), mmol/L	Creatinine (SD)	Statin use (%)	Prior Revascularization (%)	Prior MI (%)
WARSAW ACS	28.1 (4.7)	128.0 (23)	76.2 (13.2)	21.8	42.4	4.98(1.06)	2.99(1.02)	1.105 (0.33)	93.5 (44)	NA	NA	18.9
WTCC	27.6(4.2)	143.6 (22)	84.3 (12.3)	11.7	12.8	5.31 (0.98)	3.12 (0.90)	1.198 (0.38)	NA	71.6	67.2	72.0

Data were collected through a federated analysis. Alias denotes the abbreviated name of study used in figures and analyses. Mean (SD) and proportions (%) are provided unless otherwise stated. BMI indicates body mass index; BP, blood pressure; GENIUS-CHD, Genetics of Subsequent Coronary Heart Disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; and NA, not applicable.