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Common variants associated with plasma triglycerides and risk for coronary artery disease*A full list of authors and affiliations appears at the end of the article.***Abstract**

Triglycerides are transported in plasma by specific triglyceride-rich lipoproteins; in epidemiologic studies, increased triglyceride levels correlate with higher risk for coronary artery disease (CAD). However, it is unclear whether this association reflects causal processes. We used 185 common variants recently mapped for plasma lipids ($P < 5 \times 10^{-8}$ for each) to examine the role of triglycerides on risk for CAD. First, we highlight loci associated with both low-density lipoprotein cholesterol (LDL-C) and triglycerides, and show that the direction and magnitude of both are factors in determining CAD risk. Second, we consider loci with only a strong magnitude of association with triglycerides and show that these loci are also associated with CAD. Finally, in a model accounting for effects on LDL-C and/or high-density lipoprotein cholesterol, a polymorphism's strength of effect on triglycerides is correlated with the magnitude of its effect on CAD risk. These results suggest that triglyceride-rich lipoproteins causally influence risk for CAD.

Coronary artery disease (CAD) is one of the leading causes of death and infirmity worldwide¹. Plasma lipids such as cholesterol and triglycerides are associated with risk for CAD. Cholesterol is mostly carried in either low-density lipoproteins (LDL) or high-density lipoproteins (HDL) whereas triglycerides are mostly transported in very low-density lipoproteins (VLDL), chylomicrons, and remnants of their metabolism.

In observational epidemiologic studies, plasma concentrations of increased triglycerides, increased LDL cholesterol (LDL-C), and decreased HDL cholesterol (HDL-C) are associated with increased risk for CAD^{2,3}. However, it is difficult to establish causal inference from observational epidemiology⁴, especially given the correlations among triglycerides, LDL-C, and HDL-C³.

Single nucleotide polymorphisms (SNPs) can be used as instruments to test whether a biomarker causally relates to disease risk^{5,6}. Because genotypes are randomly assigned at meiosis and fixed throughout lifetime, a genetic association may overcome some limitations of observational epidemiology such as confounding and reverse causation^{7,8}. Using gene variants that exclusively affect a biomarker of interest (i.e., no pleiotropic effects on other

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†Correspondence to: Sekar Kathiresan, M.D. skathiresan@partners.org or Benjamin M. Neale, Ph.D. bneale@broadinstitute.org or Mark J. Daly, Ph.D. mjdaly@atgu.mgh.harvard.edu.

*Denotes equal contribution

factors), investigators have confirmed LDL-C as a causal risk factor for CAD⁹ and have cast doubt on whether HDL-C directly influences risk for CAD¹⁰⁻¹⁵.

However, to date, it has been challenging to utilize a similar approach to define if plasma triglycerides reflect processes causal for CAD. In contrast to LDL-C and HDL-C, nearly all SNPs identified to date for plasma triglycerides have additional effects on either plasma LDL-C or HDL-C¹⁶⁻¹⁸, violating the “no pleiotropy” assumption of instrumental variable analysis^{8,19}.

Here, we utilize common variants and develop a statistical framework to dissect causal influences among a set of correlated biomarkers. As this approach requires a large set of SNPs where precise measurements of effect on triglycerides, LDL-C, HDL-C, and CAD risk are simultaneously available, we leveraged: 1) 185 common SNPs all representing independent loci that are associated with at least one lipid trait at genome-wide levels of significance; 2) estimates of effect of each SNP on plasma triglycerides, LDL-C, and HDL-C in a sample exceeding 180,000 individuals; and 3) estimates of effect of each SNP on CAD in a sample exceeding 86,000 individuals (22,233 cases and 64,762 controls).

We studied 185 SNPs at 157 one megabase pair intervals with association $P < 5 \times 10^{-8}$ for triglycerides, LDL-C, or HDL-C in a meta-analysis involving 188,578 genotyped individuals (see companion manuscript²⁰). For each SNP, we obtained effect estimates for triglycerides ($\beta_{\text{TRIGLYCERIDES}}$), LDL-C ($\beta_{\text{LDL-C}}$), and HDL-C ($\beta_{\text{HDL-C}}$) (in standard deviation units and estimated using inverse normal transformed residuals of lipid levels after adjusting for covariates; see Supplementary Figure 1 for study design). We also estimated the effect of each SNP on CAD (β_{CAD}) from a recently published genome-wide association study (GWAS) involving 86,995 individuals (the CARDIoGRAM study)²¹. For the 185 SNPs, effect sizes (β) and P -values for triglycerides, LDL-C, HDL-C, and CAD are shown in Supplementary Table 1.

We considered several analytic approaches to investigate whether plasma triglycerides reflect processes causal for CAD. First, we evaluated the direction and magnitude of $\beta_{\text{LDL-C}}$ and $\beta_{\text{TRIGLYCERIDES}}$ in combination, and then compared these to β_{CAD} (Figure 1 and Supplementary Figure 2). Second, to isolate the effect of triglycerides, from the 185 SNPs, we restricted analysis to loci that have moderate to strong effect on triglycerides (large $\beta_{\text{TRIGLYCERIDES}}$) but minimal effect on LDL-C (small $\beta_{\text{LDL-C}}$). Finally, across the 185 SNPs, we formally developed and applied a statistical framework to test if the effect size of a SNP on triglycerides is linearly related to its effect size on CAD, before and after accounting for the same SNP's potential effect on plasma LDL-C and/or HDL-C.

For each of the 185 independent lipid SNPs, we evaluated joint patterns of associations for triglycerides and LDL-C by examining SNPs that have strong association to both triglycerides and LDL-C ($P < 5 \times 10^{-8}$ for each). Among these, we examined SNPs with the same direction and a similar magnitude of association for both lipid traits (within a factor of 5). We observed 11 loci with this pattern of association. Five loci confer risk for CAD ($P < 0.05$) and ten of the eleven loci show a direction of effect consistent between the lipid traits and CAD (Table 1). For example, the A allele at rs2954022 in the *TRIB1* gene was

associated strongly with lower triglycerides ($\beta_{\text{TRIGLYCERIDES}}=-0.078$, $P=2\times 10^{-124}$) and lower LDL-C ($\beta_{\text{LDL-C}}=-0.055$, $P=4\times 10^{-51}$) and showed the expected association with lower CAD risk ($\beta_{\text{CAD}}=-0.056$, $P=6\times 10^{-5}$).

Next, we identified SNPs that had strong association with both triglycerides and LDL-C ($P<5\times 10^{-8}$ for each) but had opposite directions for $\beta_{\text{TRIGLYCERIDES}}$ and $\beta_{\text{LDL-C}}$ (within a factor of 5, Table 2). Four SNPs displayed this pattern and none showed significant association with CAD (all $P>0.05$). For example, the A allele at rs2255141 in the *GPAM* gene was associated with lower triglycerides ($\beta_{\text{TRIGLYCERIDES}}=-0.021$, $P=1\times 10^{-8}$) and higher LDL-C ($\beta_{\text{LDL-C}}=0.030$, $P=7\times 10^{-14}$) but had no discernible effect on CAD risk ($\beta_{\text{CAD}}=-0.0076$, $P=0.63$).

Secondly, we considered a subset of the 185 SNPs that have moderate to strong effects on triglycerides but minimal effect on LDL-C [$n=44$ SNPs, all SNPs have large $\beta_{\text{TRIGLYCERIDES}}$ (>0.01 or <-0.01) but small $\beta_{\text{LDL-C}}$ (between -0.01 and 0.01)]. In regression analysis, we confirmed that $\beta_{\text{LDL-C}}$ was not associated with β_{CAD} for this set of SNPs ($P=0.68$; see Supplementary Table 2). However, we observed a significant association of $\beta_{\text{TRIGLYCERIDES}}$ and β_{CAD} ($P=3\times 10^{-5}$; see Supplementary Table 3). These observations suggest that the direction and magnitude of effect of a SNP on both triglycerides and LDL-C impact risk for CAD.

To formally investigate whether the strength of a SNP's association with triglycerides predicts CAD risk, we devised a statistical framework that controls for pleiotropic effects on secondary lipid traits. This approach is particularly important because SNP association signals with triglycerides, LDL-C, and/or HDL-C ($\beta_{\text{TRIGLYCERIDES}}$, $\beta_{\text{LDL-C}}$, and $\beta_{\text{HDL-C}}$) are correlated (Supplementary Figure 3 and Supplementary Table 4).

We tested the role of triglycerides on CAD by first calculating residuals of β_{CAD} after including as covariates $\beta_{\text{LDL-C}}$ and $\beta_{\text{HDL-C}}$ in our regression model (Supplementary Figure 1). We then tested the association of $\beta_{\text{TRIGLYCERIDES}}$ with β_{CAD} residuals. Similar models were created to assess the independent roles of LDL-C and HDL-C.

We observed that across the 185 SNPs, $\beta_{\text{LDL-C}}$ was strongly associated with β_{CAD} , after adjusting for either $\beta_{\text{TRIGLYCERIDES}}$ individually, $\beta_{\text{HDL-C}}$ individually, or both $\beta_{\text{TRIGLYCERIDES}}$ and $\beta_{\text{HDL-C}}$ (all $P < 1\times 10^{-18}$, Table 3). The pattern for $\beta_{\text{HDL-C}}$ was different. Across the 185 SNPs, $\beta_{\text{HDL-C}}$ was associated with β_{CAD} , after adjusting for $\beta_{\text{LDL-C}}$ ($P=0.005$); however, this association was greatly attenuated after adjusting for $\beta_{\text{TRIGLYCERIDES}}$ individually ($P=0.057$) and rendered non-significant after accounting for both $\beta_{\text{TRIGLYCERIDES}}$ and $\beta_{\text{LDL-C}}$ ($P=0.35$, Table 3).

The results for triglycerides were similar to those observed for LDL-C. Across the 185 SNPs, $\beta_{\text{TRIGLYCERIDES}}$ was strongly associated with β_{CAD} , after adjusting for both $\beta_{\text{LDL-C}}$ and $\beta_{\text{HDL-C}}$ ($P=1\times 10^{-9}$, Table 3).

As an alternative to this approach using residuals, we also tested a single model with the outcome variable of β_{CAD} and predictor variables of $\beta_{\text{TRIGLYCERIDES}}$, $\beta_{\text{LDL-C}}$ and $\beta_{\text{HDL-C}}$ considered jointly (Supplementary Table 5). Results were similar with $\beta_{\text{TRIGLYCERIDES}}$ and

$\beta_{\text{LDL-C}}$ showing association with β_{CAD} ($P=2\times 10^{-10}$ and $P=1\times 10^{-22}$, respectively) but $\beta_{\text{HDL-C}}$ failing to show association ($P=0.32$).

In summary, we have demonstrated that: 1) SNPs with the same direction and a similar magnitude of association for both triglycerides and LDL-C tend to associate with CAD risk; 2) loci that have an exclusive effect on triglycerides are also associated with CAD; and 3) the strength of a SNP's effect on triglycerides is correlated with the magnitude of its effect on CAD risk, even after accounting for the same SNP's effect on LDL-C and/or HDL-C.

Using an analytical approach that accounts for the potential pleiotropic effects of a SNP on triglycerides, LDL-C, and/or HDL-C, we provide evidence that plasma triglycerides likely reflects processes causal for CAD. This finding based on 185 common SNPs is in line with recent reports of specific genes predominantly related to triglycerides also affecting risk for CAD. A promoter SNP in the *APOA5* gene²², a common SNP upstream of the *TRIB1* gene²³, and a nonsense polymorphism at the *APOC3* gene²⁴ all predominantly associate with plasma triglycerides and each SNP has been convincingly related to clinical CAD^{11,25} or subclinical atherosclerosis²⁴.

Our results raise several questions. First, if plasma triglycerides reflect causal processes, what are the specific mechanistic direct links to atherosclerosis? Triglycerides are carried in plasma mostly in VLDL, chylomicrons and remnants of their metabolism and as such, triglycerides capture several physiologic processes that may promote atherosclerosis. One potential link is post-prandial cholesterol metabolism. Plasma triglycerides are highly correlated with the amount of cholesterol in remnant lipoproteins (i.e., VLDL and chylomicron particles after interaction with lipoprotein lipase) and a variety of evidence ranging from the human Mendelian disorder of Type III hyperlipoproteinemia to experimental evidence in cell culture and animal models suggests that cholesterol-rich remnant particles have pro-atherogenic properties similar to LDL (reviewed in ²⁶). Another process reflected by plasma triglycerides is the activity of lipoprotein lipase, a key enzyme that hydrolyzes triglycerides within triglyceride-rich lipoproteins. Higher enzymatic activity of lipoprotein lipase in the circulation leads to lower plasma triglycerides; a gain-of-function nonsense polymorphism in the *LPL* gene has been shown to not only reduce plasma triglyceride levels but also lower risk for CAD²⁷.

Second, why are plasma triglycerides not significantly associated with CAD in observational epidemiologic studies when multiple risk factors are considered jointly to predict risk for future CAD²? Multivariable models have known limitations for assessing the etiological relevance for a given exposure. For example, an exposure may be rendered non-significant after multivariable adjustment because of less precise measurement or greater biologic variability when compared with other factors. Plasma triglyceride measurements are more variable than other plasma lipids such as HDL-C²⁶. Alternatively, downstream effects of an exposure may more completely capture the risk conferred. For example, body mass index does not predict CAD risk in the Framingham model after accounting for blood pressure and type 2 diabetes despite the accepted causal influence of weight on blood pressure and type 2 diabetes²⁸. Our approach using SNPs as proxies overcomes these limitations of observational epidemiology.

Finally, what are the implications of these data for the development of drugs aimed at lowering plasma triglycerides with the hope of reducing CAD risk? Several recent randomized controlled trials have tested whether the lowering of plasma triglycerides with fish oils²⁹ or with fibrates³⁰⁻³² will decrease risk for CAD and in many cases, treatment did not reduce risk^{29,31,32}. Possible explanations for failed trials are wrong study population, wrong mechanism of lowering triglycerides, insufficient degree of triglyceride-lowering, and limited statistical power.

Our study has several limitations. SNPs associated with triglycerides also relate to other lipid traits and thus, are not ideal instruments for Mendelian randomization analysis. Given that the plasma triglycerides measured in the blood is the end product of several metabolic processes, it is not surprising that triglyceride-related SNPs affect at least one other lipid trait. We have attempted to address this complexity through our statistical approach.

We are unable to distinguish if only specific mechanisms of altering triglycerides affect risk for CAD. Of note, there is strong evidence that at least three mechanisms that robustly influence triglycerides – loss of APOA5 function, loss of TRIB1 function, and gain of APOC3 function – increase risk for CAD.

In summary, we utilize common polymorphisms and employ a statistical framework to dissect causal influences among a set of correlated biomarkers. By applying this framework to a correlated set of plasma lipid measures and CAD risk, we suggest a causal role of triglyceride-rich lipoproteins in the development of CAD.

Online Methods

For the association of a given SNP with a plasma lipid trait, we obtained estimates of the effect size ($\beta_{\text{TRIGLYCERIDES}}$, $\beta_{\text{LDL-C}}$ and $\beta_{\text{HDL-C}}$) and strength of association (P -value) from a meta-analysis of association results from genome-wide and custom-array genotyping – the Global Lipids Genetics Consortium (GLGC) Metabochip study (described in companion manuscript, Willer et al.²⁰). All effect sizes are in standard deviation units from inverse normal transformed residuals of lipids after adjusting for covariates. This analysis included up to 188,578 individuals from 60 studies. For the association of a given SNP with coronary artery disease (CAD), we obtained estimates of the effect size (β_{CAD}) and strength of association (P -value) from a published GWAS study for CAD, the CARDIoGRAM study²¹. This study included 22,233 cases and 63,762 controls.

We selected independent SNPs associated with plasma lipids using the following criteria. First, we restricted to SNPs with association with at least one of the three lipid traits (triglycerides, LDL-C or HDL-C) at a genome-wide significance level of $P < 5 \times 10^{-8}$. For each lipid locus – defined as a region of the genome that has a cluster of associated SNPs within one megabase from each other – we selected the strongest associated SNP ('lead' SNP). For loci with multiple associated SNPs, we calculated pairwise linkage disequilibrium (LD) estimates (r^2) of these SNPs using whole genome sequencing data from 85 Utah residents with ancestry from northern and western Europe (CEU) samples from the 1000 Genomes project³³, and selected a second SNP if there was very low LD ($r^2 < 0.05$) with the lead SNP. In total, we selected 185 SNPs that met these criteria. These criteria yield a

conservative estimate of the number of independent lipid SNPs. A list of effect sizes and *P*-values for triglycerides, LDL-C, HDL-C and CAD for the 185 selected SNPs is shown in Supplementary Table 1.

To formally investigate whether the strength of a SNP's association with triglycerides predicts CAD risk, we performed linear regression on the effect sizes of each SNP for triglycerides ($\beta_{\text{TRIGLYCERIDES}}$), LDL-C ($\beta_{\text{LDL-C}}$), HDL-C ($\beta_{\text{HDL-C}}$) as predictor variables, and the effect sizes of CAD (β_{CAD}) as the outcome variable. To control for pleiotropic effects, we first calculated the residuals of β_{CAD} after adjusting for covariates of $\beta_{\text{TRIGLYCERIDES}}$, $\beta_{\text{LDL-C}}$ and/or $\beta_{\text{HDL-C}}$. We then performed linear regression analysis in a second model on the effect size of the primary lipid trait ($\beta_{\text{TRIGLYCERIDES}}$, $\beta_{\text{LDL-C}}$ or $\beta_{\text{HDL-C}}$) with the residuals of β_{CAD} . For example, to test for the role of LDL-C on CAD, we first calculated residuals of β_{CAD} after including as covariates $\beta_{\text{TRIGLYCERIDES}}$ and $\beta_{\text{HDL-C}}$ in our regression model. In a second regression model, we then performed association of residual β_{CAD} with $\beta_{\text{LDL-C}}$. All possible combinations of linear regression analysis was performed between $\beta_{\text{TRIGLYCERIDES}}$, $\beta_{\text{LDL-C}}$ or $\beta_{\text{HDL-C}}$ on β_{CAD} (see Table 3).

As an alternative to this residuals approach, we also tested a single model where the outcome variable of β_{CAD} was tested with the predictor variables of $\beta_{\text{TRIGLYCERIDES}}$, $\beta_{\text{LDL-C}}$ and $\beta_{\text{HDL-C}}$ jointly considered (Supplementary Table 5). We also performed several sensitivity analyses to test for the effect of using different thresholds on $\beta_{\text{TRIGLYCERIDES}}$ and $\beta_{\text{LDL-C}}$ when highlighting loci with associations for both triglycerides and LDL-C (Supplementary Table 6, 7 and 8). We used thresholds that yielded the highest number of SNPs for each statistical analysis (factor threshold of 5 in Table 1 and Table 2, and β cutoff value of 0.01 in Supplementary Table 2 and 3). Furthermore, we assessed the effect of extreme influential outliers using Cook's D statistic³⁴ (Supplementary Figure 4 and Supplementary Table 9) on our conditional regression models (Table 3). A list of the number of SNPs included in each of the different analyses are shown in Supplementary Table 10.

Supplementary Material

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Authors

Ron Do^{1,2,3,4}, Cristen J. Willer^{5,6,7,8}, Ellen M. Schmidt⁶, Sebanti Sengupta⁸, Chi Gao^{1,2,4}, Gina M. Peloso^{2,4,9}, Stefan Gustafsson^{10,11}, Stavroula Kanoni¹², Andrea Ganna^{10,11,13}, Jin Chen⁸, Martin L. Buchkovich¹⁴, Samia Mora^{15,16}, Jacques S. Beckmann^{17,18}, Jennifer L. Bragg-Gresham⁸, Hsing-Yi Chang¹⁹, Ay e Demirkan²⁰, Heleen M. Den Hertog²¹, Louise A. Donnelly²², Georg B. Ehret^{23,24}, Tõnu Esko^{4,25,26}, Mary F. Feitosa²⁷, Teresa Ferreira²⁸, Krista Fischer²⁵, Pierre Fontanillas⁴, Ross M. Fraser²⁹, Daniel F. Freitag³⁰, Deepti Gurdasani^{12,30}, Kauko Heikkilä³¹, Elina Hyppönen³², Aaron Isaacs^{20,33}, Anne U. Jackson⁸, Åsa Johansson^{34,35}, Toby Johnson^{36,37}, Marika Kaakinen^{38,39}, Johannes Kettunen^{40,41}, Marcus E. Kleber^{42,43}, Xiaohui Li⁴⁴, Jian'an Luan⁴⁵, Leo-Pekka Lytykäinen^{46,47},

Patrik K.E. Magnusson¹³, Massimo Mangino⁴⁸, Evelin Mihailov^{25,26}, May E. Montasser⁴⁹, Martina Müller-Nurasyid^{50,51,52}, Ilja M. Nolte⁵³, Jeffrey R. O'Connell⁴⁹, Cameron D. Palmer^{4,54,55}, Markus Perola^{25,40,41}, Ann-Kristin Petersen⁵⁰, Serena Sanna⁵⁶, Richa Saxena², Susan K. Service⁵⁷, Sonia Shah⁵⁸, Dmitry Shungin^{59,60,61}, Carlo Sidore^{8,56,62}, Ci Song^{10,11,13}, Rona J. Strawbridge^{63,64}, Ida Surakka^{40,41}, Toshiko Tanaka⁶⁵, Tanya M. Teslovich⁸, Gudmar Thorleifsson⁶⁶, Evita G. Van den Herik²¹, Benjamin F. Voight^{67,68}, Kelly A. Volcik⁶⁹, Lindsay L. Waite⁷⁰, Andrew Wong⁷¹, Ying Wu¹⁴, Weihua Zhang^{72,73}, Devin Absher⁷⁰, Gershon Asiki⁷⁴, Inês Barroso^{12,75}, Latonya F. Been⁷⁶, Jennifer L. Bolton²⁹, Lori L Bonnycastle⁷⁷, Paolo Brambilla⁷⁸, Mary S. Burnett⁷⁹, Giancarlo Cesana⁸⁰, Maria Dimitriou⁸¹, Alex S.F. Doney²², Angela Döring^{82,83}, Paul Elliott^{39,72,84}, Stephen E. Epstein⁷⁹, Gudmundur Ingi Eyjolfsson⁸⁵, Bruna Gigante⁸⁶, Mark O. Goodarzi⁸⁷, Harald Grallert⁸⁸, Martha L. Gravitto⁷⁶, Christopher J. Groves⁸⁹, Göran Hallmans⁹⁰, Anna-Liisa Hartikainen⁹¹, Caroline Hayward⁹², Dena Hernandez⁹³, Andrew A. Hicks⁹⁴, Hilma Holm⁶⁶, Yi-Jen Hung⁹⁵, Thomas Illig^{88,96}, Michelle R. Jones⁸⁷, Pontiano Kaleebu⁷⁴, John J.P. Kastelein⁹⁷, Kay-Tee Khaw⁹⁸, Eric Kim⁴⁴, Norman Klopp^{88,96}, Pirjo Komulainen⁹⁹, Meena Kumari⁵⁸, Claudia Langenberg⁴⁵, Terho Lehtimäki^{46,47}, Shih-Yi Lin¹⁰⁰, Jaana Lindström¹⁰¹, Ruth J.F. Loos^{45,102,103,104}, François Mach²³, Wendy L McArdle¹⁰⁵, Christa Meisinger⁸², Braxton D. Mitchell⁴⁹, Gabrielle Müller¹⁰⁶, Ramaiah Nagaraja¹⁰⁷, Narisu Narisu⁷⁷, Tuomo V.M. Nieminen^{108,109,110}, Rebecca N. Nsubuga⁷⁴, Isleifur Olafsson¹¹¹, Ken K. Ong^{45,71}, Aarno Palotie^{40,112,113}, Theodore Papamarkou^{12,30,114}, Cristina Pomilla^{12,30}, Anneli Pouta^{91,115}, Daniel J. Rader^{116,117}, Muredach P. Reilly^{116,117}, Paul M. Ridker^{15,16}, Fernando Rivadeneira^{118,119,120}, Igor Rudan²⁹, Aimo Ruukonen¹²¹, Nilesh Samani^{122,123}, Hubert Scharnagl¹²⁴, Janet Seeley^{74,125}, Kaisa Silander^{40,41}, Alena Stan áková¹²⁶, Kathleen Stirrups¹², Amy J. Swift⁷⁷, Laurence Tiret¹²⁷, Andre G. Uitterlinden^{118,119,120}, L. Joost van Pelt^{128,129}, Sailaja Vedantam^{4,54,55}, Nicholas Wainwright^{12,30}, Cisca Wijmenga^{129,130}, Sarah H. Wild²⁹, Gonneke Willemsen¹³¹, Tom Wilsgaard¹³², James F. Wilson²⁹, Elizabeth H. Young^{12,30}, Jing Hua Zhao⁴⁵, Linda S. Adair¹³³, Dominique Arveiler¹³⁴, Themistocles L. Assimes¹³⁵, Stefania Bandinelli¹³⁶, Franklyn Bennett¹³⁷, Murielle Bochud¹³⁸, Bernhard O. Boehm^{139,140}, Dorret I. Boomsma¹³¹, Ingrid B. Borecki²⁷, Stefan R. Bornstein¹⁴¹, Pascal Bovet^{138,142}, Michel Burnier¹⁴³, Harry Campbell²⁹, Aravinda Chakravarti²⁴, John C. Chambers^{72,73,144}, Yii-Der Ida Chen^{145,146}, Francis S. Collins⁷⁷, Richard S. Cooper¹⁴⁷, John Danesh³⁰, George Dedoussis⁸¹, Ulf de Faire⁸⁶, Alan B. Feranil¹⁴⁸, Jean Ferrières¹⁴⁹, Luigi Ferrucci⁶⁵, Nelson B. Freimer^{57,150}, Christian Gieger⁵⁰, Leif C. Groop^{151,152}, Vilmundur Gudnason¹⁵³, Ulf Gyllensten³⁴, Anders Hamsten^{63,64,154}, Tamara B. Harris¹⁵⁵, Aroon Hingorani⁵⁸, Joel N. Hirschhorn^{4,54,55}, Albert Hofman^{118,120}, G. Kees Hovingh⁹⁷, Chao Agnes Hsiung¹⁵⁶, Steve E. Humphries¹⁵⁷, Steven C. Hunt¹⁵⁸, Kristian Hveem¹⁵⁹, Carlos Iribarren¹⁶⁰, Marjo-Riitta Jarvelin^{38,39,72,84,115,161}, Antti Jula¹⁶², Mika Kähönen¹⁶³, Jaakko Kaprio^{31,40,164}, Antero Kesäniemi¹⁶⁵, Mika Kivimäki⁵⁸, Jaspal S. Kooner^{73,144,166}, Peter J. Koudstaal²¹, Ronald M. Krauss¹⁶⁷, Diana Kuh⁷¹, Johanna Kuusisto¹⁶⁸, Kirsten O. Kyvik^{169,170}, Markku Laakso¹⁶⁸, Timo A. Lakka^{99,171}, Lars Lind¹⁷², Cecilia M. Lindgren²⁸, Nicholas G. Martin¹⁷³, Winfried März^{43,124,174}, Mark

I. McCarthy^{28,89}, Colin A. McKenzie¹⁷⁵, Pierre Meneton¹⁷⁶, Andres Metspalu^{25,26}, Leena Moilanen¹⁷⁷, Andrew D. Morris²², Patricia B. Munroe^{36,37}, Inger Njølstad¹³², Nancy L. Pedersen¹³, Chris Power³², Peter P. Pramstaller^{94,178,179}, Jackie F. Price²⁹, Bruce M. Psaty^{180,181}, Thomas Quertermous¹³⁵, Rainer Rauramaa^{99,182}, Danish Saleheen^{30,183,184}, Veikko Salomaa¹⁸⁵, Dharambir K. Sanghera⁷⁶, Jouko Saramies¹⁸⁶, Peter E.H. Schwarz^{141,187}, Wayne H-H Sheu¹⁸⁸, Alan R. Shuldiner^{49,189}, Agneta Siegbahn^{10,35,172}, Tim D. Spector⁴⁸, Kari Stefansson^{66,190}, David P. Strachan¹⁹¹, Bamidele O. Tayo¹⁴⁷, Elena Tremoli¹⁹², Jaakko Tuomilehto^{101,193,194,195}, Matti Uusitupa^{196,197}, Cornelia M. van Duijn^{20,33}, Peter Vollenweider¹⁹⁸, Lars Wallentin^{35,172}, Nicholas J. Wareham⁴⁵, John B. Whitfield¹⁷³, Bruce H.R. Wolffenbuttel^{129,199}, David Altshuler^{2,3,4}, Jose M. Ordovas^{200,201,202}, Eric Boerwinkle⁶⁹, Colin N.A. Palmer²², Unnur Thorsteinsdottir^{66,190}, Daniel I. Chasman^{15,16}, Jerome I. Rotter⁴⁴, Paul W. Franks^{59,61,203}, Samuli Ripatti^{12,40,41}, L. Adrienne Cupples^{9,204}, Manjinder S. Sandhu^{12,30}, Stephen S. Rich²⁰⁵, Michael Boehnke⁸, Panos Deloukas¹², Karen L. Mohlke¹⁴, Erik Ingelsson^{10,11,28}, Goncalo R. Abecasis⁸, Mark J. Daly^{2,4,206,*†}, Benjamin M. Neale^{2,4,206,*†}, and Sekar Kathiresan^{1,2,3,4,*†}

Affiliations

¹Cardiovascular Research Center, Massachusetts General Hospital, Boston, Massachusetts 02114, USA ²Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts 02114, USA ³Department of Medicine, Harvard Medical School, Boston, Massachusetts 02115, USA ⁴Program in Medical and Population Genetics, Broad Institute, 7 Cambridge Center, Cambridge, MA 02142, USA ⁵Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, Michigan 48109, USA ⁶Department of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, Michigan 48109, USA ⁷Department of Human Genetics, University of Michigan, Ann Arbor, Michigan 48109, USA ⁸Center for Statistical Genetics, Department of Biostatistics, University of Michigan, Ann Arbor, Michigan 48109, USA ⁹Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts 02118, USA ¹⁰Department of Medical Sciences, Molecular Epidemiology, Uppsala University, Uppsala, Sweden ¹¹Science for Life Laboratory, Uppsala University, Uppsala, Sweden ¹²Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, CB10 1SA, Hinxton, United Kingdom ¹³Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden ¹⁴Department of Genetics, University of North Carolina, Chapel Hill, NC 27599 USA ¹⁵Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Ave., Boston MA 02215, USA ¹⁶Harvard Medical School, Boston MA 02115, USA ¹⁷Service of Medical Genetics, Lausanne University Hospital, Lausanne, Switzerland ¹⁸Department of Medical Genetics, University of Lausanne, Lausanne, Switzerland ¹⁹Division of Preventive Medicine and Health Services Research, Institute of Population Health Sciences, National Health Research Institutes, Zhunan, Taiwan ²⁰Genetic Epidemiology Unit, Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands

²¹Department of Neurology, Erasmus Medical Center, Rotterdam, The Netherlands
²²Medical Research Institute, University of Dundee, Ninewells Hospital and Medical School, Dundee, DD1 9SY, United Kingdom ²³Cardiology, Department of Specialities of Medicine, Geneva University Hospital, Rue Gabrielle-Perret-Gentil 4, 1211 Geneva 14, Switzerland ²⁴Center for Complex Disease Genomics, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA ²⁵Estonian Genome Center of the University of Tartu, Tartu, Estonia ²⁶Institute of Molecular and Cell Biology, University of Tartu, Tartu, Estonia ²⁷Department of Genetics, Washington University School of Medicine, USA ²⁸Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, OX3 7BN, United Kingdom ²⁹Centre for Population Health Sciences, University of Edinburgh, Teviot Place, Edinburgh, EH8 9AG, Scotland, United Kingdom ³⁰Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom ³¹Hjelt Institute, Department of Public Health, University of Helsinki, Finland ³²Centre For Paediatric Epidemiology and Biostatistics/MRC Centre of Epidemiology for Child Health, University College of London Institute of Child Health, London, United Kingdom ³³Centre for Medical Systems Biology, Leiden, the Netherlands ³⁴Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden ³⁵Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden ³⁶Genome Centre, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK ³⁷Clinical Pharmacology, NIHR Cardiovascular Biomedical Research Unit, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry Queen Mary University of London, London, UK ³⁸Biocenter Oulu, University of Oulu, Oulu, Finland ³⁹Institute of Health Sciences, University of Oulu, Finland ⁴⁰Institute for Molecular Medicine Finland FIMM, University of Helsinki, Finland ⁴¹Public Health Genomics Unit, National Institute for Health and Welfare, Helsinki, Finland ⁴²Department of Internal Medicine II – Cardiology, University of Ulm Medical Centre, Ulm, Germany ⁴³Mannheim Institute of Public Health, Social and Preventive Medicine, Medical Faculty of Mannheim, University of Heidelberg, Ludolf-Krehl-Strasse 7-11, 68167 Mannheim, Germany ⁴⁴Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA ⁴⁵MRC Epidemiology Unit, Institute of Metabolic Science, Box 285, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 0QQ, United Kingdom ⁴⁶Department of Clinical Chemistry, Fimlab Laboratories, Tampere 33520, Finland ⁴⁷Department of Clinical Chemistry, University of Tampere School of Medicine, Tampere 33014, Finland ⁴⁸Department of Twin Research and Genetic Epidemiology, King's College London, London, United Kingdom ⁴⁹Division of Endocrinology, Diabetes, and Nutrition, Department of Medicine, University of Maryland, School of Medicine, Baltimore, Maryland ⁵⁰Institute of Genetic Epidemiology, Helmholtz Zentrum München, Neuherberg 85764, Germany ⁵¹Department of Medicine I, University Hospital Grosshadern, Ludwig-Maximilians University, Munich, Germany ⁵²Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-University of Munich, Munich, Germany ⁵³Department of Epidemiology, University of Groningen, University

Medical Center Groningen, The Netherlands ⁵⁴Division of Endocrinology, Children's Hospital Boston, Boston, Massachusetts 02115, USA ⁵⁵Division of Genetics, Program in Genomics, Children's Hospital Boston, Boston, Massachusetts 02115, USA ⁵⁶Istituto di Ricerca Genetica e Biomedica, Consiglio Nazionale delle Ricerche, Monserrato, 09042, Italy ⁵⁷Center for Neurobehavioral Genetics, The Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, USA ⁵⁸Genetic Epidemiology Group, Department of Epidemiology and Public Health, UCL, London WC1E 6BT, United Kingdom ⁵⁹Department of Clinical Sciences, Genetic & Molecular Epidemiology Unit, Lund University Diabetes Center, Scania University Hospital, Malmö, Sweden ⁶⁰Department of Odontology, Umeå University, Umeå, Sweden ⁶¹Department of Public Health and Primary Care, Unit of Medicine, Umeå University, Umeå, Sweden ⁶²Dipartimento di Scienze Biomediche, Università di Sassari, 07100 SS, Italy ⁶³Atherosclerosis Research Unit, Department of Medicine Solna, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden ⁶⁴Center for Molecular Medicine, Karolinska University Hospital, Stockholm, Sweden ⁶⁵Clinical Research Branch, National Institute Health, Baltimore, MD, USA ⁶⁶deCODE Genetics/Amgen, 101 Reykjavik, Iceland ⁶⁷Department of Genetics, University of Pennsylvania - School of Medicine, Philadelphia PA, 19104, USA ⁶⁸Department of Systems Pharmacology and Translational Therapeutics, University of Pennsylvania - School of Medicine, Philadelphia PA, 19104, USA ⁶⁹Human Genetics Center, University of Texas Health Science Center - School of Public Health, Houston, TX 77030, USA ⁷⁰HudsonAlpha Institute for Biotechnology, Huntsville, AL, USA ⁷¹MRC Unit for Lifelong Health and Ageing, 33 Bedford Place, London, WC1B 5JU, United Kingdom ⁷²Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, United Kingdom ⁷³Ealing Hospital, Southall, Middlesex UB1 3HW, United Kingdom ⁷⁴MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda ⁷⁵University of Cambridge Metabolic Research Laboratories and NIHR Cambridge Biomedical Research Centre, Level 4, Institute of Metabolic Science Box 289 Addenbrooke's Hospital Cambridge CB2 0QQ, UK ⁷⁶Department of Pediatrics, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA ⁷⁷Genome Technology Branch, National Human Genome Research Institute, NIH, Bethesda, MD 20892, USA ⁷⁸Department of Experimental Medicine, University of Milano Bicocca, Italy ⁷⁹MedStar Health Research Institute, 6525 Belcrest Road, Suite 700, Hyattsville, MD 20782, USA ⁸⁰Research Centre on Public Health, University of Milano Bicocca, Italy ⁸¹Department of Dietetics-Nutrition, Harokopio University, 70 El. Venizelou Str, Athens, Greece ⁸²Institute of Epidemiology I, Helmholtz Zentrum München, Neuherberg 85764, Germany ⁸³Institute of Epidemiology II, Helmholtz Zentrum München, Neuherberg 85764, Germany ⁸⁴MRC Health Protection Agency (HPA) Centre for Environment and Health, School of Public Health, Imperial College London, UK ⁸⁵The Laboratory in Mjodd, 108 Reykjavik, Iceland ⁸⁶Division of Cardiovascular Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden ⁸⁷Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, Cedars-Sinai

Medical Center, Los Angeles, CA 90048, USA ⁸⁸Research Unit of Molecular Epidemiology, Helmholtz Zentrum München, Neuherberg 85764, Germany ⁸⁹Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, OX3 7LJ, United Kingdom ⁹⁰Department of Public Health and Clinical Medicine, Nutritional research, Umeå University, Umeå, Sweden ⁹¹Department of Clinical Sciences/ Obstetrics and Gynecology, Oulu University Hospital, Oulu, Finland ⁹²MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, Western General Hospital, Edinburgh, Scotland, United Kingdom ⁹³Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD 20892, USA ⁹⁴Center for Biomedicine, European Academy Bozen/Bolzano (EURAC), Bolzano, Italy - Affiliated Institute of the University of Lübeck, Lübeck, Germany ⁹⁵Division of Endocrinology & Metabolism, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan ⁹⁶Hannover Unified Biobank, Hannover Medical School, Hannover 30625, Germany ⁹⁷Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands ⁹⁸Clinical Gerontology Unit, University of Cambridge, Cambridge, United Kingdom ⁹⁹Kuopio Research Institute of Exercise Medicine, Kuopio, Finland ¹⁰⁰Division of Endocrine and Metabolism, Department of Internal Medicine, Taichung Veterans General Hospital, School of Medicine, National Yang-Ming University, Taipei, Taiwan ¹⁰¹Diabetes Prevention Unit, National Institute for Health and Welfare, 00271 Helsinki, Finland ¹⁰²The Genetics of Obesity and Related Metabolic Traits Program, The Icahn School of Medicine at Mount Sinai, New York, USA ¹⁰³The Charles Bronfman Institute for Personalized Medicine, The Icahn School of Medicine at Mount Sinai, New York, USA ¹⁰⁴The Mindich Child Health and Development Institute, The Icahn School of Medicine at Mount Sinai, New York ¹⁰⁵School of Social and Community Medicine, University of Bristol, Oakfield House, Oakfield Grove, Bristol BS8 2BN, United Kingdom ¹⁰⁶Institute for Medical Informatics and Biometrics, University of Dresden, Medical Faculty Carl Gustav Carus, Fetscherstrasse 74, 01307 Dresden, Germany ¹⁰⁷Laboratory of Genetics, National Institute on Aging, Baltimore, MD21224, USA ¹⁰⁸Department of Clinical Pharmacology, University of Tampere School of Medicine, Tampere 33014, Finland ¹⁰⁹Department of Internal Medicine, Päijät-Häme Central Hospital, Lahti, Finland ¹¹⁰Division of Cardiology, Helsinki University Central Hospital, Helsinki, Finland ¹¹¹Department of Clinical Biochemistry, Landspítali University Hospital, 101 Reykjavik, Iceland ¹¹²Department of Medical Genetics, Haartman Institute, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland ¹¹³Genetic Epidemiology Group, Wellcome Trust Sanger Institute, Hinxton, Cambridge, United Kingdom ¹¹⁴Department of Statistical Sciences, University College of London, London, United Kingdom ¹¹⁵National Institute for Health and Welfare, Oulu, Finland ¹¹⁶Cardiovascular Institute, Perelman School of Medicine at the University of Pennsylvania, 3400 Civic Center Blvd, Building 421, Translational Research Center, Philadelphia, PA 19104-5158, USA ¹¹⁷Division of Translational Medicine and Human Genetics, Perelman School of Medicine at the University of Pennsylvania, 3400 Civic Center Blvd, Building 421, Translational Research Center, Philadelphia, PA 19104-5158, USA ¹¹⁸Department of Epidemiology, Erasmus

University Medical Center, Rotterdam, the Netherlands ¹¹⁹Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands ¹²⁰Netherlands Genomics Initiative (NGI)-sponsored Netherlands Consortium for Healthy Aging (NCHA), Leiden, The Netherlands ¹²¹Department of Clinical Sciences/Clinical Chemistry, University of Oulu, Oulu, Finland ¹²²National Institute for Health Research Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital, Leicester LE3 9QP, UK ¹²³Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester, LE3 9QP, UK ¹²⁴Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Austria ¹²⁵School of International Development, University of East Anglia, Norwich NR4 7TJ, United Kingdom ¹²⁶University of Eastern Finland and Kuopio University Hospital, 70210 Kuopio, Finland ¹²⁷INSERM UMRS 937, Pierre and Marie Curie University, Paris, France ¹²⁸Department of Laboratory Medicine, University of Groningen, University Medical Center Groningen, The Netherlands ¹²⁹LifeLines Cohort Study, University of Groningen, University Medical Center Groningen, The Netherlands ¹³⁰Department of Genetics, University of Groningen, University Medical Center Groningen, The Netherlands ¹³¹Department of Biological Psychology, VU Univ, Amsterdam, The Netherlands ¹³²Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, Tromsø, Norway ¹³³Department of Nutrition, University of North Carolina, Chapel Hill, NC, USA ¹³⁴Department of Epidemiology and Public Health, EA 3430, University of Strasbourg, Faculty of Medicine, Strasbourg, France ¹³⁵Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA ¹³⁶Geriatric Unit, Azienda Sanitaria Firenze (ASF), Florence, Italy ¹³⁷Chemical Pathology, Department of Pathology, University of the West Indies, Mona, Kingston 7, Jamaica ¹³⁸Institute of Social and Preventive Medicine (IUMSP), Lausanne University Hospital, Route de la Corniche 10, 1010 Lausanne, Switzerland ¹³⁹Division of Endocrinology and Diabetes, Department of Internal Medicine, Ulm University Medical Centre, Ulm, Germany ¹⁴⁰Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore ¹⁴¹Department of Medicine III, University of Dresden, Medical Faculty Carl Gustav Carus, Fetscherstrasse 74, 01307 Dresden, Germany ¹⁴²Ministry of Health, Victoria, Republic of Seychelles ¹⁴³Service of Nephrology, Lausanne University Hospital, Lausanne, Switzerland ¹⁴⁴Imperial College Healthcare NHS Trust, London, United Kingdom ¹⁴⁵Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, Cedars-Sinai Medical Center, Los Angeles, California, USA ¹⁴⁶Department of Medicine, University of California Los Angeles, Los Angeles, California, USA ¹⁴⁷Department of Preventive Medicine and Epidemiology, Loyola University Medical School, Maywood, Illinois 60153, USA ¹⁴⁸Office of Population Studies Foundation, University of San Carlos, Talamban, Cebu City, Philippines ¹⁴⁹Department of Cardiology, Toulouse University School of Medicine, Rangueil Hospital, Toulouse, France ¹⁵⁰Department of Psychiatry, University of California, Los Angeles, USA ¹⁵¹Department of Clinical Sciences, Lund University, SE-20502, Malmö, Sweden ¹⁵²Department of Medicine, Helsinki University Hospital, FI-00029 Helsinki, Finland

¹⁵³Icelandic Heart Association, Kopavogur, Iceland ¹⁵⁴Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden ¹⁵⁵Laboratory of Epidemiology, Demography, and Biometry, National Institute on Ageing, Bethesda, MD, USA ¹⁵⁶Institute of Population Health Sciences, National Health Research Institutes, Zhunan, Taiwan ¹⁵⁷Cardiovascular Genetics, BHF Laboratories, Institute Cardiovascular Science, University College London, London, United Kingdom ¹⁵⁸Cardiovascular Genetics, University of Utah School of Medicine, Salt Lake City, UT, USA ¹⁵⁹HUNT Research Centre, Department of Public Health and General Practice, Norwegian University of Science and Technology, Levanger, Norway ¹⁶⁰Kaiser Permanente, Division of Research, Oakland, CA, USA ¹⁶¹Unit of Primary Care, Oulu University Hospital, Oulu, Finland ¹⁶²Department of Chronic Disease Prevention, National Institute for Health and Welfare, Turku, Finland ¹⁶³Department of Clinical Physiology, University of Tampere School of Medicine, Tampere 33014, Finland ¹⁶⁴Department of Mental Health and Substance Abuse Services, National Institute for Health and Welfare, Helsinki, Finland ¹⁶⁵Institute of Clinical Medicine, Department of Medicine, University of Oulu and Clinical Research Center, Oulu University Hospital, Oulu, Finland ¹⁶⁶National Heart & Lung Institute, Imperial College London, Hammersmith Hospital, London, United Kingdom ¹⁶⁷Children's Hospital Oakland Research Institute, 5700 Martin Luther King Junior Way, Oakland, CA 94609, USA ¹⁶⁸Department of Medicine, University of Eastern Finland and Kuopio University Hospital, 70210 Kuopio, Finland ¹⁶⁹Institute of Regional Health Services Research, University of Southern Denmark, Odense, Denmark ¹⁷⁰Odense Patient data Explorative Network (OPEN), Odense University Hospital, Odense, Denmark ¹⁷¹Institute of Biomedicine/Physiology, University of Eastern Finland, Kuopio Campus, Finland ¹⁷²Department of Medical Sciences, Uppsala University, Uppsala, Sweden ¹⁷³Queensland Institute of Medical Research, Locked Bag 2000, Royal Brisbane Hospital, Queensland 4029, Australia ¹⁷⁴Synlab Academy, Synlab Services GmbH, Gottlieb-Daimler-Straße 25, 68165 Mannheim, Germany ¹⁷⁵Tropical Metabolism Research Unit, Tropical Medicine Research Institute, University of the West Indies, Mona, Kingston 7, Jamaica ¹⁷⁶U872 Institut National de la Santé et de la Recherche Médicale, Centre de Recherche des Cordeliers, 75006 Paris, France ¹⁷⁷Department of Medicine, Kuopio University Hospital, Kuopio, Finland ¹⁷⁸Department of Neurology, General Central Hospital, Bolzano, Italy ¹⁷⁹Department of Neurology, University of Lübeck, Lübeck, Germany ¹⁸⁰Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology, and Health Services, University of Washington, Seattle, WA, USA ¹⁸¹Group Health Research Institute, Group Health Cooperative, Seattle, WA, USA ¹⁸²Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital, Kuopio, Finland ¹⁸³Center for Non-Communicable Diseases, Karachi, Pakistan ¹⁸⁴Department of Medicine, University of Pennsylvania, USA ¹⁸⁵Unit of Chronic Disease Epidemiology and Prevention, National Institute for Health and Welfare, Helsinki, Finland ¹⁸⁶South Karelia Central Hospital, Lappeenranta, Finland ¹⁸⁷Paul Langerhans Institute Dresden, German Center for Diabetes Research (DZD), Dresden, Germany ¹⁸⁸Division of Endocrine and Metabolism, Department of Internal

Medicine, Taichung Veterans General Hospital, Taichung, Taiwan ¹⁸⁹Geriatric Research and Education Clinical Center, Veterans Administration Medical Center, Baltimore, Maryland ¹⁹⁰Faculty of Medicine, University of Iceland, 101 Reykjavík, Iceland ¹⁹¹Division of Population Health Sciences and Education, St George's, University of London, Cranmer Terrace, London SW17 0RE, United Kingdom ¹⁹²Department of Pharmacological Sciences, University of Milan, Monzino Cardiology Center, IRCCS, Milan, Italy ¹⁹³Centre for Vascular Prevention, Danube-University Krems, 3500 Krems, Austria ¹⁹⁴King Abdulaziz University, Faculty of Medicine, Jeddah 21589, Saudi Arabia ¹⁹⁵Red RECAVA Grupo RD06/0014/0015, Hospital Universitario La Paz, 28046 ¹⁹⁶Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Finland ¹⁹⁷Research Unit, Kuopio University Hospital, Kuopio, Finland ¹⁹⁸Department of Medicine, Lausanne University Hospital, Switzerland ¹⁹⁹Department of Endocrinology, University of Groningen, University Medical Center Groningen, The Netherlands ²⁰⁰Department of Cardiovascular Epidemiology and Population Genetics, National Center for Cardiovascular Investigation, Madrid, Spain ²⁰¹IMDEA-Alimentacion, Madrid, Spain ²⁰²Nutrition and Genomics Laboratory, Jean Mayer-USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA, USA ²⁰³Department of Nutrition, Harvard School of Public Health, Boston, MA, USA ²⁰⁴Framingham Heart Study, Framingham, MA, USA ²⁰⁵Center for Public Health Genomics, University of Virginia, Charlottesville, VA 22908, USA ²⁰⁶Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA 02138, USA

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Disclosures

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S. Kathiresan serves on scientific advisory boards for Merck, Celera, American Genomics and Catabasis. He has received unrestricted research grants from Merck and Pfizer.

Author Contributions

R.D. carried out primary data analyses and prepared the supplementary information. R.D. and C.G. prepared figures and tables. C.W., E.M.S., S.Sebanti, G.R.A. contributed meta-analysis results. R.D., M.J.D, B.M.N., S.Kathiresan contributed to the design and conduct of the study. R.D., M.J.D, B.M.N., S.Kathiresan wrote the manuscript.

All authors contributed to the research and reviewed the manuscript.

Design, management and coordination of contributing cohorts

(ADVANCE) T.L.A.; (AGES Reykjavik study) T.B.H., V.G.; (AIDHS/SDS) D.K.S.; (AMC-PAS) P.D., G.K.H.; (Amish GLGC) A.R.S.; (ARIC) E.B.; (B58C-WTCCC & B58C-T1DGC) D.P.S.; (B58C-MetaboChip) C.M.L., C.Power, M.I.M.; (BLSA) L.F.; (BRIGHT) P.B.M.; (CHS) B.M.P., J.I.R.; (CLHNS) A.B.F., K.L.M., L.S.A.; (CoLaus) P.V.; (deCODE) K.Stefansson, U.T.; (DIAGEN) P.E.S., S.R.B.; (DILGOM) S.R.; (DPS) M.U.; (DR's EXTRA) R.R.; (EAS) J.F.P.; (EGCUT (Estonian Genome Center of University of Tartu)) A.M.; (ELY) N.W.; (EPIC) N.W., K.K.; (EPIC_N_OBSET GWAS) E.H.Young; (ERF) C.M.V.; (ESS (Erasmus Stroke Study)) P.J.K.; (Family Heart Study FHS) I.B.B.; (FBPP) A.C., R.S.C., S.C.H.; (FENLAND) R.L., N.W.; (FIN-D2D 2007) A.K., L.M.; (FINCAVAS) M.Kähönen; (Framingham) L.A.C., S.Kathiresan, J.M.O.; (FRISCII) A.Siegbahn, L.W.; (FUSION GWAS) K.L.M., M.Boehnke; (FUSION stage 2) F.S.C., J.T., J.Saramies; (GenomEUTwin) J.B.W., N.G.M., K.O.K., V.S., J.Kaprio, A.Jula, D.I.B., N.P., T.D.S.; (GLACIER) P.W.F.; (Go-DARTS) A.D.M., C.N.P.; (GxE/Spanish Town) B.O.T., C.A.M., F.B., J.N.H., R.S.C.; (HUNT2) K.Hveem; (IMPROVE) U.D., A.Hamsten, E.T., S.E.H.; (InCHIANTI) S.B.; (KORAF4) C.Gieger;(LifeLines) B.H.W.; (LOLIPOP) J.S.K., J.C.C.; (LURIC) B.O.B.; W.M.; (MDC) L.C.G., D. Altshuler, S.Kathiresan; (METSIM) J.Kuusisto, M.L.; (MICROS) P.P.P.; (MORGAM) D.Arveiler, J.F.; (MRC/UVRI GPC GWAS) P.Kaleebu, G.A., J.Seeley, E.H.Y.; (MRC National Survey of Health & Development) D.K.; (NFBC1986) M-R.J.; (NSPHS) U.G.; (ORCADES) H.Campbell; (PARC) Y.I.C., R.M.K., J.I.R.; (PIVUS) E.I., L.Lind; (PROMIS) J.D., P.D., D.Saleheen; (Rotterdam Study) A.Hofman, A.G.U.; (SardiNIA) G.R.A.; (SCARFSHEEP) A.Hamsten, U.D.; (SEYCHELLES) M.Burnier, M.Bochud; P.Bovet; (SUVIMAX) P.M.; (Swedish Twin Reg.) E.I., N.L.P.; (TAICHI) T.L.A., Y.I.C., C.A.H., T.Q., J.I.R., W.H.S.; (THISEAS) G.D., P.D.; (Tromsø) I.N.; (TWINGENE) U.D., E.I.; (ULSAM) E.I.; (Whitehall II) A.Hingorani, M.Kivimaki

Genotyping of contributing cohorts

(ADVANCE) D.Absher; (AIDHS/SDS) L.F.B., M.L.G.; (AMC-PAS) P.D., G.K.H.; (B58C-WTCCC & B58C-T1DGC) W.L.M.; (B58C-MetaboChip) M.I.M.; (BLSA) D.H.; (BRIGHT) P.B.M.; (CHS) J.I.R.; (DIAGEN) N.N., G.M.; (DILGOM) A. Palotie; (DR's EXTRA) T.A.L.; (EAS) J.F.W.; (EGCUT (Estonian Genome Center of University of Tartu)) T.E.; (EPIC) P.D.; (EPIC_N_SUBCOH GWAS) I.B.; (ERF) C.M.V.; (ESS (Erasmus Stroke Study)) C.M.V.; (FBPP) A.C., G.B.E.; (FENLAND) M.S.S.; (FIN-D2D 2007) A.J.S.; (FINCAVAS) T.L.; (Framingham) J.M.O.; (FUSION stage 2) L.L.B.; (GLACIER) I.B.; (Go-DARTS) C.Groves, C.N.P., M.I.M.; (IMPROVE) A.Hamsten; (KORAF3) H.G., T.I.; (KORAF4) N.K.; (LifeLines) C.W.; (LOLIPOP) J.S.K., J.C.C.; (LURIC) M.E.K.; (MDC) B.F.V., R.D.; (MICROS) A.A.H.; (MORGAM) L.T., P.Brambilla; (MRC/UVRI GPC GWAS) M.S.S.; (MRC National Survey of Health & Development) A.W., D.K., K.K.O.; (NFBC1986) A-L.H., M.J, M.McCarthy, P.E., S.V.; (NSPHS and FRISCII) Å.J.; (ORCADES) H.Campbell; (PARC) M.O.G., M.R.J., J.I.R.; (PIVUS) E.I., L.Lind; (PROMIS) P.D., K.Stirrup; (Rotterdam Study) A.G.U., F.R.; (SardiNIA) R.N.;

(SCARFSHEEP) B.G., R.J.S.; (SEYCHELLES) F.M., G.B.E.; (Swedish Twin Reg.) E.I., N.L.P.; (TAICHI) D.Absher, T.L.A., E.K., T.Q., L.L.W.; (THISEAS) P.D.; (TWINGENE) A.Hamsten, E.I.; (ULSAM) E.I.; (WGHS) D.I.C., P.M.R.; (Whitehall II) A.Hingorani, C.L., M.Kumari, M.Kivimaki

Phenotype definition of contributing cohorts

(ADVANCE) C.I.; (AGES Reykjavik study) T.B.H., V.G.; (AIDHS/SDS) L.F.B.; (AMC-PAS) J.J.K.; (Amish GLGC) A.R.S., B.D.M.; (B58C-WTCCC & B58C-T1DGC) D.P.S.; (B58C-MetaboChip) C.Power; E.H.; (BRIGHT) P.B.M.; (CHS) B.M.P.; (CoLaus) P.V.; (deCODE) G.I.E., H.H., I.O.; (DIAGEN) G.M.; (DILGOM) K.Silander; (DPS) J.Lindström; (DR's EXTRA) P.Komulainen; (EAS) J.L.Bolton; (EGCUT (Estonian Genome Center of University of Tartu)) A.M.; (EGCUT (Estonian Genome Center of University of Tartu)) K.F.; (ERF and Rotterdam Study) A.Hofman; (ERF) C.M.V.; (ESS (Erasmus Stroke Study)) E.G.V., H.M.D., P.J.K.; (FBPP) A.C., R.S.C., S.C.H.; (FINCAVAS) T.V.N.; (Framingham) S.Kathiresan, J.M.O.; (GenomEUTwin: MZGWA) J.B.W.; (GenomEUTwin-FINRISK) V.S.; (GenomEUTwin-FINTWIN) J.Kaprio, K.Heikkilä; (GenomEUTwin-GENMETS) A.Jula; (GenomEUTwin-NLDTWIN) G.W.; (Go-DARTS) A.S.D., A.D.M., C.N.P., L.A.D.; (GxE/Spanish Town) C.A.M., F.B.; (IMPROVE) U.D.; A.Hamsten, E.T.; (KORAF3) C.M.; (KORAF4) A.Döring; (LifeLines) L.J.; (LOLIPOP) J.S.K., J.C.C.; (LURIC) H.S.; (MDC) L.C.G.; (METSIM) A.Stan áková; (MORGAM) G.C.; (MRC/UVRI GPC GWAS) R.N.N.; (MRC National Survey of Health & Development) D.K.; (NFBC1986) A.R., A-L.H., A.Pouta, M-R.J.; (NSPHS and FRISCI) Å.J.; (NSPHS) U.G.; (ORCADES) S.H.W.; (PARC) Y.I.C., R.M.K.; (PIVUS) E.I., L.Lind; (PROMIS) D.F.F.; (Rotterdam Study) A.Hofman; (SCARFSHEEP) U.D., B.G.; (SEYCHELLES) M.Burnier, M.Bochud, P.Bovet; (Swedish Twin Reg.) E.I., N.L.P.; (TAICHI) H.Chang, C.A.H., Y.H., E.K., S.L., W.H.S.; (THISEAS) G.D., M.D.; (Tromsø) T.W.; (TWINGENE) U.D., E.I.; (ULSAM) E.I.; (WGHS) P.M.R.; (Whitehall II) M.Kumari

Primary analysis from contributing cohorts

(ADVANCE) L.L.W.; (AIDHS/SDS) R.S.; (AMC-PAS) S.Kanoni; (Amish GLGC) J.R.O., M.E.M.; (ARIC) K.A.V.; (B58C-MetaboChip) C.M.L., E.H., T.F.; (B58C-WTCCC & B58C-T1DGC) D.P.S.; (BLSA) T.T.; (BRIGHT) T.J.; (CLHNS) Y.W.; (CoLaus) J.S.B.; (deCODE) G.T.; (DIAGEN) A.U.J.; (DILGOM) M.P.; (EAS) R.M.F.; (DPS) A.U.J.; (DR'S EXTRA) A.U.J.; (EGCUT (Estonian Genome Center of University of Tartu)) E.M., K.F., T.E.; (ELY) D.G.; (EPIC) K.Stirrup, D.G.; (EPIC_N_OBSET GWAS) E.Y., C.L.; (EPIC_N_SUBCOH GWAS) N.W.; (ERF) A.I.; (ESS (Erasmus Stroke Study)) C.M.V., E.G.V.; (EUROSPAN) A.Demirkan; (Family Heart Study FHS) I.B.B., M.F.F.; (FBPP) A.C., G.B.E.; (FENLAND) T.P., C.Pomilla; (FENLAND GWAS) J.H.Z., J.Luan; (FIN-D2D 2007) A.U.J.; (FINCAVAS) L.Lyytikäinen; (Framingham) L.A.C., G.M.P.; (FRISCI and NSPHS) Å.J.; (FUSION stage 2) T.M.T.; (GenomEUTwin-FINRISK) J.Kettunen; (GenomEUTwin-FINTWIN) K.Heikkilä; (GenomEUTwin-GENMETS) I.S.; (GenomEUTwin-SWETWIN) P.K.M.; (GenomEUTwin-UK-TWINS) M.Mangino; (GLACIER) D.Shungin; (GLACIER) P.W.F.; (Go-DARTS) C.N.P., L.A.D.; (GxE/Spanish Town) C.D.P.; (HUNT) A.U.J.; (IMPROVE) R.J.S.; (InCHIANTI) T.T.; (KORAF3)

M.Müller-Nurasyid; (KORAF4) A.Petersen; (LifeLines) I.M.N.; (LOLIPOP) W.Z.; (LURIC) M.E.K.; (MDC) B.F.V.; (MDC) P.F., R.D.; (METSIM) A.U.J.; (MRC/UVRI GPC GWAS) R.N.N.; (MRC National Survey of Health & Development) A.W., J.Luan; (NFBC1986) M.Kaakinen, I.S., S.K.S.; (NSPHS and FRISCII) Å.J.; (PARC) X.L.; (PIVUS) C.Song, E.I.; (PROMIS) J.D., D.F.F., K.Stirrup; (Rotterdam Study) A.I.; (SardiNIA) C.Sidore, J.L.Bragg-Gresham, S.Sanna; (SCARFSHEEP) R.J.S.; (SEYCHELLES) G.B.E., M.Bochud; (SUVIMAX) T.J.; (Swedish Twin Reg.) C.Song, E.I.; (TAICHI) D.Absher, T.L.A., H.Chang, M.G., C.A.H., T.Q., L.L.W; (THISEAS) S.Kanoni; (Tromsø) A.U.J.; (TWINGENE) A.G., E.I.; (ULSAM) C.Song, E.I., S.G.; (WGHS) D.I.C.; (Whitehall II) S.Shah

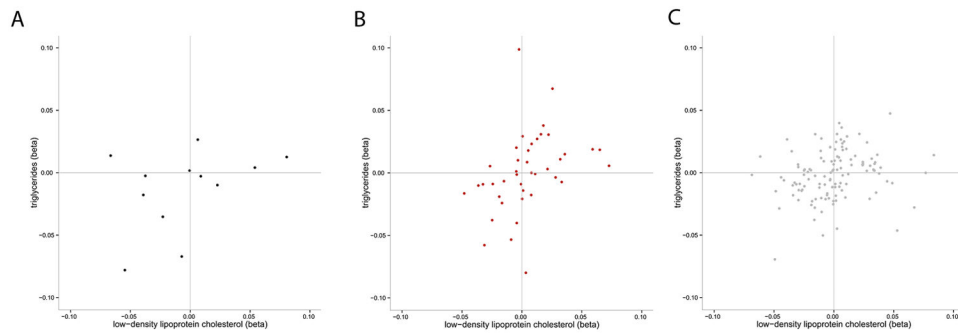


Figure 1. Effect of a single nucleotide polymorphism on triglycerides, low-density lipoprotein cholesterol, and risk for coronary artery disease

Black dots represent SNPs with CAD $P < 0.001$; B. Red dots represent SNPs with $0.01 < \text{CAD } P < 0.001$; C. Grey dots represent CAD $P > 0.10$). Loci strongly associated with CAD tend to have consistent directions for both triglycerides and LDL-C (bottom left and top right quadrants). In contrast to the grey points, the black and red points are concentrated in the bottom left and top right quadrants. Betas are in standard deviation units. SNPs with $-0.10 < \beta_{\text{LDL-C}} < 0.10$ and $-0.10 < \beta_{\text{TRIGLYCERIDES}} < 0.10$ are shown.

SNPs with consistent direction of genetic effects on LDL-C and triglycerides and their subsequent relationship to risk for CAD.

Table 1

Locus	rs ID	AI	LDL-C		TRIGLYCERIDES		CAD	
			β_{LDL-C}	P	$\beta_{TRIGLYCERIDES}$	P	β_{CAD}	P
<i>ANGPTL3</i>	rs4587594	A	-0.049	3×10^{-37}	-0.069	3×10^{-87}	0.017	0.26
<i>APOB</i>	rs1367117	A	0.12	2×10^{-196}	0.025	3×10^{-12}	0.035	0.02
<i>GCKR</i>	rs3817588	T	0.026	3×10^{-8}	0.067	7×10^{-58}	0.034	0.08
<i>TIMD4</i>	rs6882076	T	-0.046	5×10^{-33}	-0.029	1×10^{-16}	-0.021	0.15
<i>HLA-B</i>	rs2247056	T	-0.025	6×10^{-9}	-0.038	2×10^{-22}	-0.030	0.06
<i>TRIB1</i>	rs2980885	A	-0.031	4×10^{-12}	-0.058	5×10^{-45}	-0.041	0.02
<i>TRIB1</i>	rs2954022	A	-0.055	4×10^{-51}	-0.078	2×10^{-124}	-0.056	6×10^{-5}
<i>ABCA1</i>	rs1883025	T	-0.030	1×10^{-11}	-0.022	3×10^{-8}	-0.014	0.41
<i>APOA1</i>	rs10790162	A	0.076	3×10^{-26}	0.23	1×10^{-276}	0.13	2×10^{-6}
<i>CETP</i>	rs9989419	A	0.028	8×10^{-13}	0.024	3×10^{-12}	0.010	0.61
<i>CILP2</i>	rs10401969	T	0.12	2×10^{-60}	0.12	3×10^{-76}	0.11	2×10^{-4}

Shown are SNPs that have strong association with both LDL-C and triglycerides ($P < 5 \times 10^{-8}$ for each), have consistent direction of effect size for LDL-C and triglycerides, and have a ratio of magnitude of effect size of LDL-C to triglycerides within a factor of 5. Five loci confer risk for CAD ($P < 0.05$) and ten of the eleven loci show consistent direction of effect size for both lipid traits with the effect size of CAD.

AI: All beta estimates were calculated with respect to this allele.

SNPs with opposite direction of genetic effects on LDL-C and triglycerides and their subsequent relationship to risk for CAD.

Table 2

Locus	rs ID	A1	LDL-C		TRIGLYCERIDES		CAD	
			$\beta_{\text{LDL-C}}$	<i>P</i>	$\beta_{\text{TRIGLYCERIDES}}$	<i>P</i>	β_{CAD}	<i>P</i>
<i>MIR148A</i>	rs4722551	T	-0.039	7×10^{-16}	0.027	2×10^{-9}	-0.033	0.23
<i>GPAM</i>	rs2255141	A	0.030	7×10^{-14}	-0.021	1×10^{-8}	-0.0076	0.63
<i>FADS1-2-3</i>	rs1535	A	0.053	3×10^{-43}	-0.046	1×10^{-40}	0.0019	0.90
<i>APOE</i>	rs7254892	A	-0.49	8×10^{-365}	0.12	4×10^{-31}	-0.14	0.09

Shown are SNPs that have strong association with both LDL-C and triglycerides ($P < 5 \times 10^{-8}$ for each), but have opposite direction of effect size for LDL-C and triglycerides, and have a ratio of magnitude of effect size of LDL-C to triglycerides within a factor of 5. Four SNPs displayed this pattern and none showed significant association with CAD (all $P > 0.05$).

A1: All beta estimates were calculated with respect to this allele.

Table 3

Association of the strength of a SNP's effect on plasma lipids with its strength of effect on CAD risk.

Outcome	Predictor	Covariate	Beta	SE	P
β_{CAD}	β_{LDL-C}	-	0.41	0.039	4×10^{-20}
β_{CAD}	β_{LDL-C}	β_{HDL-C}	0.38	0.039	9×10^{-19}
β_{CAD}	β_{LDL-C}	$\beta_{TRIGLYCERIDES}$	0.40	0.034	1×10^{-23}
β_{CAD}	β_{LDL-C}	$\beta_{HDL-C}, \beta_{TRIGLYCERIDES}$	0.38	0.034	2×10^{-22}
β_{CAD}	β_{HDL-C}	-	-0.18	0.052	0.0006
β_{CAD}	β_{HDL-C}	β_{LDL-C}	-0.12	0.041	0.005
β_{CAD}	β_{HDL-C}	$\beta_{TRIGLYCERIDES}$	-0.09	0.048	0.057
β_{CAD}	β_{HDL-C}	$\beta_{LDL-C}, \beta_{TRIGLYCERIDES}$	-0.04	0.037	0.35
β_{CAD}	$\beta_{TRIGLYCERIDES}$	-	0.44	0.074	2×10^{-8}
β_{CAD}	$\beta_{TRIGLYCERIDES}$	β_{LDL-C}	0.42	0.057	5×10^{-12}
β_{CAD}	$\beta_{TRIGLYCERIDES}$	β_{HDL-C}	0.36	0.074	3×10^{-6}
β_{CAD}	$\beta_{TRIGLYCERIDES}$	$\beta_{LDL-C}, \beta_{HDL-C}$	0.36	0.057	1×10^{-9}

Residuals for β_{CAD} were calculated after adjustment of a SNP's effect on the denoted lipid trait. A total of 185 SNPs identified from GWAS for LDL-C, HDL-C and triglycerides were included in regression analysis. β_{LDL-C} , β_{HDL-C} , and $\beta_{TRIGLYCERIDES}$ represent the effect sizes for a SNP on LDL-C, HDL-C and triglycerides in the GWAS meta-analysis for lipids. Regression was performed with the predictor variable of the effect size on lipid traits (β from predictor column) and the outcome variable of residual CAD effect size after adjusting for covariates. SE: standard error.