HHS Public Access

Author manuscript

Nat Genet. Author manuscript; available in PMC 2014 May 01.

Published in final edited form as:

Nat Genet. 2013 November ; 45(11): 1345–1352. doi:10.1038/ng.2795.

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 ($P<5\times10^{-8}$ 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 worldwide[1]. 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 epidemiology[4], especially given the correlations among triglycerides, LDL-C, and HDL-C[3].

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

†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 CAD[9] and have cast doubt on whether HDL-C directly influences risk for CAD[10-15].

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-C[16-18], 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 $P<5\times10^{-8}$ for triglycerides, LDL-C, or HDL-C in a meta-analysis involving 188,578 genotyped individuals (see companion manuscript[20]). For each SNP, we obtained effect estimates for triglycerides ($\beta_{TRIGLYCERIDES}$), LDL-C ($\beta_{LDL\text{-}C}$), and HDL-C ($\beta_{HDL\text{-}C}$) (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 $\beta_{LDL\text{-}C}$ and $\beta_{TRIGLYCERIDES}$ 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 $\beta_{TRIGLYCERIDES}$) but minimal effect on LDL-C (small $\beta_{LDL\text{-}C}$). 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 ($P<5\times10^{-8}$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 ($\beta_{TRIGLYCERIDES}$=−0.078, P=2×10^{-124}) and lower LDL-C ($\beta_{LDL\text{-}C}$=−0.055, P=4×10^{-51}) and showed the expected association with lower CAD risk (β_{CAD}=−0.056, P=6×10^{-5}).

Next, we identified SNPs that had strong association with both triglycerides and LDL-C (P<5×10^{-8} for each) but had opposite directions for $\beta_{TRIGLYCERIDES}$ and $\beta_{LDL\text{-}C}$ (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 ($\beta_{TRIGLYCERIDES}$=−0.021, P=1×10^{-8}) and higher LDL-C ($\beta_{LDL\text{-}C}$=0.030, P=7×10^{-14}) but had no discernible effect on CAD risk (β_{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 $\beta_{TRIGLYCERIDES}$ (>0.01 or <−0.01) but small $\beta_{LDL\text{-}C}$ (between −0.01 and 0.01)]. In regression analysis, we confirmed that $\beta_{LDL\text{-}C}$ 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 $\beta_{TRIGLYCERIDES}$ and β_{CAD} (P=3×10^{-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 ($\beta_{TRIGLYCERIDES}$, $\beta_{LDL\text{-}C}$, and $\beta_{HDL\text{-}C}$) 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 $\beta_{LDL\text{-}C}$ and $\beta_{HDL\text{-}C}$ in our regression model (Supplementary Figure 1). We then tested the association of $\beta_{TRIGLYCERIDES}$ 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, $\beta_{LDL\text{-}C}$ was strongly associated with β_{CAD}, after adjusting for either $\beta_{TRIGLYCERIDES}$ individually, $\beta_{HDL\text{-}C}$ individually, or both $\beta_{TRIGLYCERIDES}$ and $\beta_{HDL\text{-}C}$ (all P < 1×10^{-18}, Table 3). The pattern for $\beta_{HDL\text{-}C}$ was different. Across the 185 SNPs, $\beta_{HDL\text{-}C}$ was associated with β_{CAD}, after adjusting for $\beta_{LDL\text{-}C}$ (P=0.005); however, this association was greatly attenuated after adjusting for $\beta_{TRIGLYCERIDES}$ individually (P=0.057) and rendered non-significant after accounting for both $\beta_{TRIGLYCERIDES}$ and $\beta_{LDL\text{-}C}$ (P=0.35, Table 3).

The results for triglycerides were similar to those observed for LDL-C. Across the 185 SNPs, $\beta_{TRIGLYCERIDES}$ was strongly associated with β_{CAD}, after adjusting for both $\beta_{LDL\text{-}C}$ and $\beta_{HDL\text{-}C}$ (P =1×10^{-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 $\beta_{TRIGLYCERIDES}$, $\beta_{LDL\text{-}C}$ and $\beta_{HDL\text{-}C}$ considered jointly (Supplementary Table 5). Results were similar with $\beta_{TRIGLYCERIDES}$ and

$\beta_{LDL\text{-}C}$ showing association with β_{CAD} ($P=2\times10^{-10}$ and $P=1\times10^{-22}$, respectively) but $\beta_{HDL\text{-}C}$ 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* gene[22], a common SNP upstream of the *TRIB1* gene[23], and a nonsense polymorphism at the *APOC3* gene[24] all predominantly associate with plasma triglycerides and each SNP has been convincingly related to clinical CAD[11,25] or subclinical atherosclerosis[24].

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 CAD[27].

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 CAD[2]? 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-C[26]. 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 diabetes[28]. 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 oils[29] or with fibrates[30-32] 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 ($\beta_{TRIGLYCERIDES,}$ $\beta_{LDL\text{-}C}$ and $\beta_{HDL\text{-}C}$) 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 study[21]. 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 $P<5\times10^{-8}$. 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 ancestryfrom northern and western Europe (CEU) samples from the 1000 Genomes project[33], 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 ($\beta_{TRIGLYCERIDES}$), LDL-C ($\beta_{LDL\text{-}C}$), HDL-C ($\beta_{HDL\text{-}C}$) 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 $\beta_{TRIGLYCERIDES,}$ $\beta_{LDL\text{-}C}$ and/or $\beta_{HDL\text{-}C}$. We then performed linear regression analysis in a second model on the effect size of the primary lipid trait ($\beta_{TRIGLYCERIDES,}$ $\beta_{LDL\text{-}C}$ or $\beta_{HDL\text{-}C}$) 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 $\beta_{TRIGLYCERIDES}$ and $\beta_{HDL\text{-}C}$ in our regression model. In a second regression model, we then performed association of residual β_{CAD} with $\beta_{LDL\text{-}C.}$ All possible combinations of linear regression analysis was performed between $\beta_{TRIGLYCERIDES}$, $\beta_{LDL\text{-}C}$ or $\beta_{HDL\text{-}C}$ 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 $\beta_{TRIGLYCERIDES}$, $\beta_{LDL\text{-}C}$ and $\beta_{HDL\text{-}C}$ jointly considered (Supplementary Table 5). We also performed several sensitivity analyses to test for the effect of using different thresholds on $\beta_{TRIGLYCERIDES}$ and $\beta_{LDL\text{-}C}$ 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 statistic[34] (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

Refer to Web version on PubMed Central for supplementary material.

Authors

Ron Do[1,2,3,4], Cristen J. Willer[5,6,7,8], Ellen M. Schmidt[6], Sebanti Sengupta[8], Chi Gao[1,2,4], Gina M. Peloso[2,4,9], Stefan Gustafsson[10,11], Stavroula Kanoni[12], Andrea Ganna[10,11,13], Jin Chen[8], Martin L. Buchkovich[14], Samia Mora[15,16], Jacques S. Beckmann[17,18], Jennifer L. Bragg-Gresham[8], Hsing-Yi Chang[19], Ayşe Demirkan[20], Heleen M. Den Hertog[21], Louise A. Donnelly[22], Georg B. Ehret[23,24], Tõnu Esko[4,25,26], Mary F. Feitosa[27], Teresa Ferreira[28], Krista Fischer[25], Pierre Fontanillas[4], Ross M. Fraser[29], Daniel F. Freitag[30], Deepti Gurdasani[12,30], Kauko Heikkilä[31], Elina Hyppönen[32], Aaron Isaacs[20,33], Anne U. Jackson[8], Åsa Johansson[34,35], Toby Johnson[36,37], Marika Kaakinen[38,39], Johannes Kettunen[40,41], Marcus E. Kleber[42,43], Xiaohui Li[44], Jian'an Luan[45], Leo-Pekka Lyytikäinen[46,47],

Patrik K.E. Magnusson[13], Massimo Mangino[48], Evelin Mihailov[25,26], May E. Montasser[49], Martina Müller-Nurasyid[50,51,52], Ilja M. Nolte[53], Jeffrey R. O'Connell[49], Cameron D. Palmer[4,54,55], Markus Perola[25,40,41], Ann-Kristin Petersen[50], Serena Sanna[56], Richa Saxena[2], Susan K. Service[57], Sonia Shah[58], 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 Tanaka[65], Tanya M. Teslovich[8], Gudmar Thorleifsson[66], Evita G. Van den Herik[21], Benjamin F. Voight[67,68], Kelly A. Volcik[69], Lindsay L. Waite[70], Andrew Wong[71], Ying Wu[14], Weihua Zhang[72,73], Devin Absher[70], Gershim Asiki[74], Inês Barroso[12,75], Latonya F. Been[76], Jennifer L. Bolton[29], Lori L Bonnycastle[77], Paolo Brambilla[78], Mary S. Burnett[79], Giancarlo Cesana[80], Maria Dimitriou[81], Alex S.F. Doney[22], Angela Döring[82,83], Paul Elliott[39,72,84], Stephen E. Epstein[79], Gudmundur Ingi Eyjolfsson[85], Bruna Gigante[86], Mark O. Goodarzi[87], Harald Grallert[88], Martha L. Gravito[76], Christopher J. Groves[89], Göran Hallmans[90], Anna-Liisa Hartikainen[91], Caroline Hayward[92], Dena Hernandez[93], Andrew A. Hicks[94], Hilma Holm[66], Yi-Jen Hung[95], Thomas Illig[88,96], Michelle R. Jones[87], Pontiano Kaleebu[74], John J.P. Kastelein[97], Kay-Tee Khaw[98], Eric Kim[44], Norman Klopp[88,96], Pirjo Komulainen[99], Meena Kumari[58], Claudia Langenberg[45], Terho Lehtimäki[46,47], Shih-Yi Lin[100], Jaana Lindström[101], Ruth J.F. Loos[45,102,103,104], François Mach[23], Wendy L McArdle[105], Christa Meisinger[82], Braxton D. Mitchell[49], Gabrielle Müller[106], Ramaiah Nagaraja[107], Narisu Narisu[77], Tuomo V.M. Nieminen[108,109,110], Rebecca N. Nsubuga[74], Isleifur Olafsson[111], 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 Rudan[29], Aimo Ruokonen[121], Nilesh Samani[122,123], Hubert Scharnagl[124], Janet Seeley[74,125], Kaisa Silander[40,41], Alena Stančáková[126], Kathleen Stirrups[12], Amy J. Swift[77], Laurence Tiret[127], 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. Wild[29], Gonneke Willemsen[131], Tom Wilsgaard[132], James F. Wilson[29], Elizabeth H. Young[12,30], Jing Hua Zhao[45], Linda S. Adair[133], Dominique Arveiler[134], Themistocles L. Assimes[135], Stefania Bandinelli[136], Franklyn Bennett[137], Murielle Bochud[138], Bernhard O. Boehm[139,140], Dorret I. Boomsma[131], Ingrid B. Borecki[27], Stefan R. Bornstein[141], Pascal Bovet[138,142], Michel Burnier[143], Harry Campbell[29], Aravinda Chakravarti[24], John C. Chambers[72,73,144], Yii-Der Ida Chen[145,146], Francis S. Collins[77], Richard S. Cooper[147], John Danesh[30], George Dedoussis[81], Ulf de Faire[86], Alan B. Feranil[148], Jean Ferrières[149], Luigi Ferrucci[65], Nelson B. Freimer[57,150], Christian Gieger[50], Leif C. Groop[151,152], Vilmundur Gudnason[153], Ulf Gyllensten[34], Anders Hamsten[63,64,154], Tamara B. Harris[155], Aroon Hingorani[58], Joel N. Hirschhorn[4,54,55], Albert Hofman[118,120], G. Kees Hovingh[97], Chao Agnes Hsiung[156], Steve E. Humphries[157], Steven C. Hunt[158], Kristian Hveem[159], Carlos Iribarren[160], Marjo-Riitta Järvelin[38,39,72,84,115,161], Antti Jula[162], Mika Kähönen[163], Jaakko Kaprio[31,40,164], Antero Kesäniemi[165], Mika Kivimaki[58], Jaspal S. Kooner[73,144,166], Peter J. Koudstaal[21], Ronald M. Krauss[167], Diana Kuh[71], Johanna Kuusisto[168], Kirsten O. Kyvik[169,170], Markku Laakso[168], Timo A. Lakka[99,171], Lars Lind[172], Cecilia M. Lindgren[28], Nicholas G. Martin[173], Winfried März[43,124,174], Mark

I. McCarthy[28,89], Colin A. McKenzie[175], Pierre Meneton[176], Andres Metspalu[25,26], Leena Moilanen[177], Andrew D. Morris[22], Patricia B. Munroe[36,37], Inger Njølstad[132], Nancy L. Pedersen[13], Chris Power[32], Peter P. Pramstaller[94,178,179], Jackie F. Price[29], Bruce M. Psaty[180,181], Thomas Quertermous[135], Rainer Rauramaa[99,182], Danish Saleheen[30,183,184], Veikko Salomaa[185], Dharambir K. Sanghera[76], Jouko Saramies[186], Peter E.H. Schwarz[141,187], Wayne H-H Sheu[188], Alan R. Shuldiner[49,189], Agneta Siegbahn[10,35,172], Tim D. Spector[48], Kari Stefansson[66,190], David P. Strachan[191], Bamidele O. Tayo[147], Elena Tremoli[192], Jaakko Tuomilehto[101,193,194,195], Matti Uusitupa[196,197], Cornelia M. van Duijn[20,33], Peter Vollenweider[198], Lars Wallentin[35,172], Nicholas J. Wareham[45], John B. Whitfield[173], Bruce H.R. Wolffenbuttel[129,199], David Altshuler[2,3,4], Jose M. Ordovas[200,201,202], Eric Boerwinkle[69], Colin N.A. Palmer[22], Unnur Thorsteinsdottir[66,190], Daniel I. Chasman[15,16], Jerome I. Rotter[44], Paul W. Franks[59,61,203], Samuli Ripatti[12,40,41], L. Adrienne Cupples[9,204], Manjinder S. Sandhu[12,30], Stephen S. Rich[205], Michael Boehnke[8], Panos Deloukas[12], Karen L. Mohlke[14], Erik Ingelsson[10,11,28], Goncalo R. Abecasis[8], Mark J. Daly[2,4,206,*,†], Benjamin M. Neale[2,4,206,*,†], and Sekar Kathiresan[1,2,3,4,*,†]

Affiliations

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

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

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

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

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

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

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

Acknowledgments

We thank the Global Lipids Genetics Consortium for early access to the association results of the Metabochip study. S.Kathiresan is supported by a Research Scholar award from the Massachusetts General Hospital (MGH), the Howard Goodman Fellowship from MGH, the Donovan Family Foundation, R01HL107816, and a grant from Fondation Leducq. R.D. is supported by a Banting Fellowship from the Canadian Institutes of Health Research. G.P. is supported by Award Number T32HL007208 from the National Heart, Lung, and Blood Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, And Blood Institute or the National Institutes of Health.

References

1. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet. 1997; 349:1436–42. [PubMed: 9164317]
2. Di Angelantonio E, et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA. 2009; 302:1993–2000. [PubMed: 19903920]
3. Sarwar N, et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. Circulation. 2007; 115:450–8. [PubMed: 17190864]
4. Sheehan NA, Didelez V, Burton PR, Tobin MD. Mendelian randomisation and causal inference in observational epidemiology. PLoS Med. 2008; 5:e177. [PubMed: 18752343]
5. Davey Smith G, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? Int J Epidemiol. 2003; 32:1–22. [PubMed: 12689998]
6. Ebrahim S, Davey Smith G. Mendelian randomization: can genetic epidemiology help redress the failures of observational epidemiology? Hum Genet. 2008; 123:15–33. [PubMed: 18038153]

7. Smith GD, et al. Clustered environments and randomized genes: a fundamental distinction between conventional and genetic epidemiology. PLoS Med. 2007; 4:e352. [PubMed: 18076282]
8. Smith GD, Ebrahim S. Mendelian randomization: prospects, potentials, and limitations. Int J Epidemiol. 2004; 33:30–42. [PubMed: 15075143]
9. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med. 2006; 354:1264–72. [PubMed: 16554528]
10. Willer CJ, et al. Newly identified loci that influence lipid concentrations and risk of coronary artery disease. Nat Genet. 2008; 40:161–9. [PubMed: 18193043]
11. Voight BF, et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. Lancet. 2012
12. Haase CL, et al. LCAT, HDL cholesterol and ischemic cardiovascular disease: a Mendelian randomization study of HDL cholesterol in 54,500 individuals. J Clin Endocrinol Metab. 2012; 97:E248–56. [PubMed: 22090275]
13. Haase CL, Tybjaerg-Hansen A, Grande P, Frikke-Schmidt R. Genetically elevated apolipoprotein A-I, high-density lipoprotein cholesterol levels, and risk of ischemic heart disease. J Clin Endocrinol Metab. 2010; 95:E500–10. [PubMed: 20826588]
14. Frikke-Schmidt R, et al. Association of loss-of-function mutations in the ABCA1 gene with high-density lipoprotein cholesterol levels and risk of ischemic heart disease. JAMA. 2008; 299:2524–32. [PubMed: 18523221]
15. Johannsen TH, et al. Hepatic lipase, genetically elevated high-density lipoprotein, and risk of ischemic cardiovascular disease. J Clin Endocrinol Metab. 2009; 94:1264–73. [PubMed: 19088157]
16. Kathiresan S, et al. Common variants at 30 loci contribute to polygenic dyslipidemia. Nat Genet. 2009; 41:56–65. [PubMed: 19060906]
17. Teslovich TM, et al. Biological, clinical and population relevance of 95 loci for blood lipids. Nature. 2010; 466:707–13. [PubMed: 20686565]
18. Sarwar N, et al. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. Lancet. 2010; 375:1634–9. [PubMed: 20452521]
19. Lewis SJ. Mendelian randomization as applied to coronary heart disease, including recent advances incorporating new technology. Circ Cardiovasc Genet. 2010; 3:109–17. [PubMed: 20160203]
20. The Global Lipids Genetics Consortium. Discovery and Refinement of Loci Associated with Lipid Levels. Nature Genetics. In press.
21. Schunkert H, et al. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. Nat Genet. 2011; 43:333–8. [PubMed: 21378990]
22. Pennacchio LA, et al. An apolipoprotein influencing triglycerides in humans and mice revealed by comparative sequencing. Science. 2001; 294:169–73. [PubMed: 11588264]
23. Kathiresan S, et al. Six new loci associated with blood low-density lipoprotein cholesterol, high-density lipoprotein cholesterol or triglycerides in humans. Nat Genet. 2008; 40:189–97. [PubMed: 18193044]
24. Pollin TI, et al. A null mutation in human APOC3 confers a favorable plasma lipid profile and apparent cardioprotection. Science. 2008; 322:1702–5. [PubMed: 19074352]
25. Deloukas P, et al. Large-scale association analysis identifies new risk loci for coronary artery disease. Nat Genet. 2013; 45:25–33. [PubMed: 23202125]
26. Miller M, et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2011; 123:2292–333. [PubMed: 21502576]
27. Varbo A, et al. Remnant cholesterol as a causal risk factor for ischemic heart disease. J Am Coll Cardiol. 2013; 61:427–36. [PubMed: 23265341]
28. Wilson PW, et al. Prediction of coronary heart disease using risk factor categories. Circulation. 1998; 97:1837–47. [PubMed: 9603539]
29. Bosch J, et al. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. N Engl J Med. 2012; 367:309–18. [PubMed: 22686415]
30. Rubins HB, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein

Cholesterol Intervention Trial Study Group. N Engl J Med. 1999; 341:410–8. [PubMed: 10438259]

31. Keech A, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005; 366:1849–61. [PubMed: 16310551]
32. Ginsberg HN, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010; 362:1563–74. [PubMed: 20228404]
33. 1000 Genomes Project Consortium. A map of human genome variation from population-scale sequencing. Nature. 2010; 467:1061–73. [PubMed: 20981092]
34. Cook RD. Detection of Influential Observations in Linear Regression. Technometrics. 1977; 19:15–18.

Sequence accession numbers

ANGPTL3 (NM_014495), *APOB* (NM_000384), *GCKR* (NM_001486), *TIMD4* (NM_138379), *HLA-B* (NM_005514), *TRIB1* (NM_025195), *ABCA1* (NM_005502), *APOA1* (NM_000039), *CETP* (NM_000078), *CILP2* (NM_153221), *MIR148A* (NR_029597), *GPAM* (NM_020918), *FADS1-2-3* (NM_013402-NM_004265-NM_021727), *APOE* (NM_000041), *APOA5* (NM_052968), *APOC3* (NM_000040)

Disclosures

CHS

Bruce Psaty serves on the DSBM of a clinical trial funded by the manufacturer (Zoll), and he serves on the Steering Committee of the Yale Open-Data Project funded by the Medtronic.

CoLaus

Peter Vollenweider received an unrestricted grant from GSK to build the CoLaus study

deCODE

Authors affiliated with deCODE Genetics/Amgen, a biotechnology company, are employees of deCODE Genetics/Amgen

GLACIER

Inês Barroso and spouse own stock in GlaxoSmithKline and Incyte Ltd.

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.Stirrups; (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.Stančáková; (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 FRISCII) 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.Stirrups, 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.; (FRISCII 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.Stirrups; (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

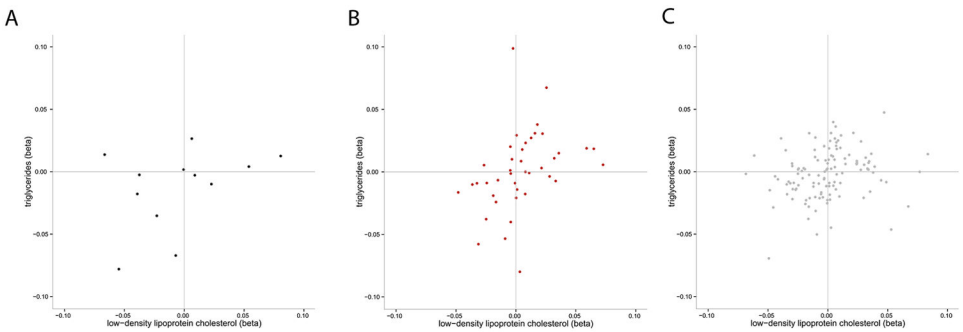

Figure 1. Effect of a single nucleotide polymorphism on triglycerides, low-density lipoprotein cholesterol, and risk for coronary artery disease

Black dots represent SNPs with CAD $P<0.001$; B. Red dots represent SNPs with $0.01 <$ 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.

Table 1

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

			LDL-C		TRIGLYCERIDES		CAD	
Locus	**rs ID**	**A1**	$\beta_{LDL\text{-}C}$	***P***	$\beta_{TRIGLYCERIDES}$	***P***	β_{CAD}	***P***
ANGPTL3	rs4587594	A	−0.049	3×10^{-37}	−0.069	3×10^{-87}	0.017	0.26
APOB	rs1367117	A	0.12	2×10^{-196}	0.025	3×10^{-12}	0.035	0.02
GCKR	rs3817588	T	0.026	3×10^{-8}	0.067	7×10^{-58}	0.034	0.08
TIMD4	rs6882076	T	−0.046	5×10^{-33}	−0.029	1×10^{-16}	−0.021	0.15
HLA-B	rs2247056	T	−0.025	6×10^{-9}	−0.038	2×10^{-22}	−0.030	0.06
TRIB1	rs2980885	A	−0.031	4×10^{-12}	−0.058	5×10^{-45}	−0.041	0.02
TRIB1	rs2954022	A	−0.055	4×10^{-51}	−0.078	2×10^{-124}	−0.056	6×10^{-5}
ABCA1	rs1883025	T	−0.030	1×10^{-11}	−0.022	3×10^{-8}	−0.014	0.41
APOA1	rs10790162	A	0.076	3×10^{-26}	0.23	1×10^{-276}	0.13	2×10^{-6}
CETP	rs9989419	A	0.028	8×10^{-13}	0.024	3×10^{-12}	0.010	0.61
CILP2	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 ($P<5\times10^{-8}$ 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.

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

Table 2

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

			LDL-C		TRIGLYCERIDES		CAD	
Locus	**rs ID**	**A1**	$\beta_{LDL\text{-}C}$	***P***	$\beta_{TRIGLYCERIDES}$	***P***	β_{CAD}	***P***
MIR148A	rs4722551	T	−0.039	7×10^{-16}	0.027	2×10^{-9}	−0.033	0.23
GPAM	rs2255141	A	0.030	7×10^{-14}	−0.021	1×10^{-8}	−0.0076	0.63
FADS1-2-3	rs1535	A	0.053	3×10^{-43}	−0.046	1×10^{-40}	0.0019	0.90
APOE	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 ($P<5\times10^{-8}$ 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.

Nat Genet. Author manuscript; available in PMC 2014 May 01.

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