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# Rare *SCARB1* mutations associate with high-density lipoprotein cholesterol but not with coronary artery disease

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**Aims** Scavenger receptor Class B Type 1 (SR-BI) is a major receptor for high-density lipoprotein (HDL) that promotes hepatic uptake of cholesterol from HDL. A rare mutation p.P376L, in the gene encoding SR-BI, *SCARB1*, was recently reported to associate with elevated HDL cholesterol (HDL-C) and increased risk of coronary artery disease (CAD), suggesting that increased HDL-C caused by SR-BI impairment might be an independent marker of cardiovascular risk. We tested the hypothesis that alleles in or close to *SCARB1* that associate with elevated levels of HDL-C also associate with increased risk of CAD in the relatively homogeneous population of Iceland.

**Methods and results** Using a large resource of whole-genome sequenced Icelanders, we identified thirteen *SCARB1* coding mutations that we examined for association with HDL-C ($n = 136\,672$). Three rare *SCARB1* mutations, encoding p.G319V, p.V111M, and p.V32M (combined allelic frequency = 0.2%) associate with elevated levels of HDL-C (p.G319V: $\beta = 11.1$ mg/dL, $P = 8.0 \times 10^{-7}$; p.V111M: $\beta = 8.3$ mg/dL, $P = 1.1 \times 10^{-6}$; p.V32M: $\beta = 10.2$ mg/dL, $P = 8.1 \times 10^{-4}$). These mutations do not associate with CAD (36 886 cases/306 268 controls) (odds ratio = 0.90, 95% confidence interval 0.67–1.22, $P = 0.49$), despite effects on HDL-C comparable to that reported for p.P376L, both in terms of direction and magnitude. Furthermore, HDL-C raising alleles of three common *SCARB1* non-coding variants, including one previously unreported (rs61941676-C: $\beta = 1.25$ mg/dL, $P = 1.7 \times 10^{-18}$), and of one low frequency coding variant (p.V135I) that independently associate with higher HDL-C, do not confer increased risk of CAD.

**Conclusion** Elevated HDL-C due to genetically compromised SR-BI function is not a marker of CAD risk.

**Keywords** SR-BI • HDL cholesterol • Mutation • Coronary artery disease

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## Translational perspective

The current study shows that decreased function of Scavenger receptor Class B Type 1 (SR-BI), resulting in reduced hepatic reverse cholesterol transport and increased high-density lipoprotein cholesterol levels, does not translate into increased coronary artery disease risk. Thus, increasing hepatic reverse cholesterol transport through pharmacological activation of SR-B1 is not likely to improve outcome. However, the study provides evidence that modulating other functions of SR-BI might do so. The results highlight the complexities of potential therapeutic development with SR-BI modulating agents.

# Introduction

Despite marked improvements in treatment and prevention, cardiovascular diseases remain the most common cause of death in Iceland like in other European countries.[1] Epidemiological studies consistently show an inverse relationship between levels of high-density lipoprotein cholesterol (HDL-C) and the risk of coronary artery disease (CAD).[2] This relationship has been explained by a potential antiatherogenic properties of HDL, including its role in reverse cholesterol transport,[3] in which cholesterol from peripheral tissues is returned to the liver for excretion in bile. However, neither Mendelian randomization studies[4–6] nor interventional studies[7–9] support the notion that HDL-C directly protects against CAD. This implies that HDL-C is not antiatherogenic itself, but rather a marker of other antiatherogenic factors. Accordingly, the most recent European Society of Cardiology and European Atherosclerosis Society Guidelines for the management of dyslipidaemias[10] do not recommend HDL-C as a target for treatment.

A recent study reported that a rare missense mutation p.P376L in *SCARB1* encoding the scavenger receptor Class B Type I (SR-BI), associates with impaired function of the encoded protein and elevated HDL-C levels.[11] The mutation was also found to associate with CAD in a meta-analysis of 16 studies with an odds ratio (OR) of 1.79 and $P = 0.018$. The investigators concluded that reduced hepatic SR-BI function in humans causes impaired reverse cholesterol transport, leading to increased risk of CAD.[11] This would suggest that high HDL-C might in some cases be an independent marker of increased risk of cardiovascular disease.[12] However, given the extremely low and variable carrier rate of the mutation between study groups (overall 86 carriers in 137 995 or 1 in 1600 individuals), the possibility has been raised,[13] that the p.P376L variant may be an indirect marker for a substratum of the population.

Scavenger receptor Class B Type 1, an integral membrane protein expressed most abundantly in the liver and endocrine organs that make steroids, is a receptor for HDL. Mouse studies have demonstrated that SR-BI plays a key role in reverse cholesterol transport, promoting the hepatic selective uptake of cholesterol from HDL[14] and facilitating the secretion of cholesterol into bile.[15] In SR-BI deficient mice biliary cholesterol is decreased, but HDL-C levels in blood are elevated,[16,17] and there is acceleration of atherosclerosis.[18,19] Hepatic overexpression of SR-BI in mice has the opposite effect; enhanced hepatocellular cholesterol uptake and increased cholesterol secretion to bile,[15,16,20] lower levels of circulating HDL-C,[15] and attenuated atherosclerosis.[21,22] Scavenger receptor Class B Type 1 up-regulation in mouse models is also associated with biliary cholesterol hypersecretion and increased gallstone formation.[23]

The effects of SR-BI mutations on HDL-C levels in humans have been clearly demonstrated.[11,24,25] Three rare missense mutations in *SCARB1*,[24,25] other than the mutation encoding p.P376L, were reported to have HDL-C increasing effects comparable to that of p.P376L (8.4–18.9 mg/dL). In addition, genome wide association studies (GWAS) have found two common non-coding variants within the *SCARB1* locus that associate with HDL-C levels,[6,26] both with small effects relative to those of the rare coding ones. Neither the rare variants (encoding p.297S, p.S112F, and p.T175A),[24,25] nor the common HDL-C associating variants[6] have been reported to associate with CAD, although, we note that the sample sizes in the studies describing the rare mutations may have been too small to detect such an association.

In view of the contradictory results of previous studies, assessing the effects of rare *SCARB1* variants on the risk of CAD, a further inquiry is called for. Herein, we use the relatively homogeneous population of Iceland to test the hypothesis that alleles in or close to *SCARB1* that associate with elevated levels of HDL-C also associate with increased risk of CAD. Further, we examine whether *SCARB1* variants that associate with HDL-C in humans alter the susceptibility to gallstone formation,[27] as suggested by mouse models.[15,23]

# Methods

The study was approved by The National Bioethics Committee in Iceland (Approval no. 07–085, with amendments) and the Data Protection Authority of Iceland (Approval no.2007060474ThS/—, with amendments). All participating subjects donating samples signed informed consents. Personal identities of the phenotypes and biological samples were encrypted by a third party system provided by the Icelandic Data Protection Authority.

Enrolment of participants, the phenotypic definitions for CAD, information on lipid measurements, genotyping, imputation methods, and association analysis have previously been described in detail[5,28–31] (see also Supplementary material online, *Note*). Briefly, lipid measurements were obtained from three of the largest clinical laboratories in Iceland. We used HDL-C measurements from 136 672 Icelanders, 93 169 were chip-typed and directly imputed, and 43 503 were first and second degree relatives of chip-typed individuals and had their genotypes inferred based on genealogy. Coronary artery disease cases ($n = 36\,886$ of which 17 591 were chip-typed) were identified based on International Classification of Diseases-9 and 10 discharge codes from Landspitali—The National University Hospital of Iceland, and from death registries. The controls ($n = 306\,268$ of which 121 163 were chip-typed) included population controls from the Icelandic genealogical database and individuals recruited through different genetic studies at deCODE genetics. Description of genetic risk scores is provided in Supplementary material online, *Note*.

# Results and discussion

Using our population-based resource of 8453 whole-genome sequenced Icelanders, we identified thirteen *SCARB1* coding variants

**Table 1 Association of *SCARB1* locus variants with high-density lipoprotein cholesterol and the corresponding effect on coronary artery disease**

| Comment on variant | Variant type | rs-name | A1/A2 | EA freq. (%) | HDL-C ($n$ = 136 672) | | | CAD ($n$ = 36 886/306 268) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | *P*-value | β (mg/dL) | SE | *P*-value | OR | 95% CI |
| Rare coding | Missense (p.319V) | rs150728540 | A/C | 0.056 | $8.0 \times 10^{-7}$ | 11.119 | 2.253 | 0.365 | 0.788 | 0.47–1.32 |
| Rare coding | Missense (p.V111M) | rs5890 | T/C | 0.111 | $1.1 \times 10^{-6}$ | 8.254 | 1.691 | 0.775 | 1.063 | 0.70–1.62 |
| Rare coding | Missense (p.V32M) | rs771247110 | T/C | 0.026 | $8.1 \times 10^{-4}$ | 10.198 | 3.046 | 0.377 | 0.703 | 0.32–1.54 |
| Low frequency coding | Missense (p.V135I) | rs5891 | T/C | 1.226 | $6.4 \times 10^{-6}$ | 2.063 | 0.457 | 0.584 | 1.031 | 0.92–1.15 |
| Common novel | Intronic | rs61941676 | A/C | 84.8 | $1.7 \times 10^{-18}$ | 1.245 | 0.140 | $1.2 \times 10^{-3}$ | 0.945 | 0.92–0.98 |
| Common GWAS | Downstream | rs838876 | A/G | 34.1 | $2.4 \times 10^{-17}$ | 0.921 | 0.107 | 0.083 | 0.977 | 0.95–1.00 |
| Common GWAS | Intronic | rs838909 | G/A | 53.9 | $1.9 \times 10^{-17}$ | 0.870 | 0.102 | 0.788 | 1.003 | 0.98–1.02 |

The combined allele frequency for p.G319V, p.V111M, and p.V32M is ~0.2% (~0.4% carrier frequency). This corresponds to 147 carriers (of any of the three rare HDL-C raising mutations) among the 36 886 CAD cases and 1225 carriers among the 306 268 controls. Effects, β in mg/dL and OR, are given for the A1, except for rs61941676 and rs838909 the effects are given for the A2. Variant type, with coding changes in protein sequence NP_001076428.1 given in bracket.
A1, minor allele; A2, major allele; CAD, coronary artery disease; CI, confidence interval; EA freq., effect allelic frequency; GWAS, signal previously reported in genome wide association study; HDL-C, high-density lipoprotein cholesterol; OR, odds ratio; SE, standard error.

and one splice region variant (Supplementary material online, *Table S1*) that we imputed into chip-genotyped Icelanders and their close relatives[28–31] and tested for association with HDL-C ($n$ = 136 672). Three very rare *SCARB1* missense variants that never occur together on the same chromosome, p.G319V, p.V111M, and p.V32M (allelic frequency 0.056%, 0.111%, and 0.026%, respectively) associate with elevated levels of HDL-C (p.G319V: β = 11.1 mg/dL, $P = 8.0 \times 10^{-7}$; p.V111M: β = 8.3 mg/dL, $P = 1.1 \times 10^{-6}$; p.V32M: β = 10.2 mg/dL, $P = 8.1 \times 10^{-4}$) (*Table 1*). The associations of these variants with HDL-C have not been reported before. Overall, one in 250 Icelanders carries one of these three variants and none of them associates with other lipid fractions (Supplementary material online, *Table S3*). Although the missense variants p.P376L, p.P297S, p.S112F, and p.T175A previously reported to associate with increased HDL-C[11,24,25] (reported effects: 8.4–18.9 mg/dL) were not observed in Iceland, the three rare missense variants identified have effects in the same direction and of comparable magnitude (8–11 mg/dL) as the published ones. Similar to all previously described HDL-C increasing variants in *SCARB1*,[11,24,25] the variants encoding p.G319V and p.V111M occur in the large extracellular loop of the SR-BI protein, within highly conserved regions and are predicted to be damaging (Supplementary material online, *Table S1*). The missense variant p.V32M is predicted to be benign, and is in a region less conserved between species (Supplementary material online, *Table S1*). In addition to the rare variants, we observed one low frequency missense variant p.V135I (frequency 1.23%) that associates with increased HDL-C, albeit with considerably less effect (β = 2.1 mg/dL, $P = 6.4 \times 10^{-6}$) than the rare ones (*Table 1*). Two of the rare coding sequence variants (p.G319V and p.V111M) are reported in the Genome Aggregation Database (gnomAD at http://gnomad.broadinstitute.org, assessed March 2018)[32] in European populations, but at much lower frequencies than in Iceland.

We tested the missense variants encoding p.G319V, p.V111M, p.V32M, and p.V135I for association with CAD among 36 886 cases and 306 268 controls (*Table 1*). None of the variants associates with CAD risk ($P > 0.05$). To increase power to detect association we aggregated the three rare large impact variants p.G319V, p.V111M, and p.V32M (combined allelic frequency = 0.2%) and tested for association with increased risk of CAD. This aggregate test gives an $OR_{CAD} = 0.90$, 95% confidence interval (CI) 0.67–1.22; $P = 0.49$ (Supplementary material online, *Table S2*).

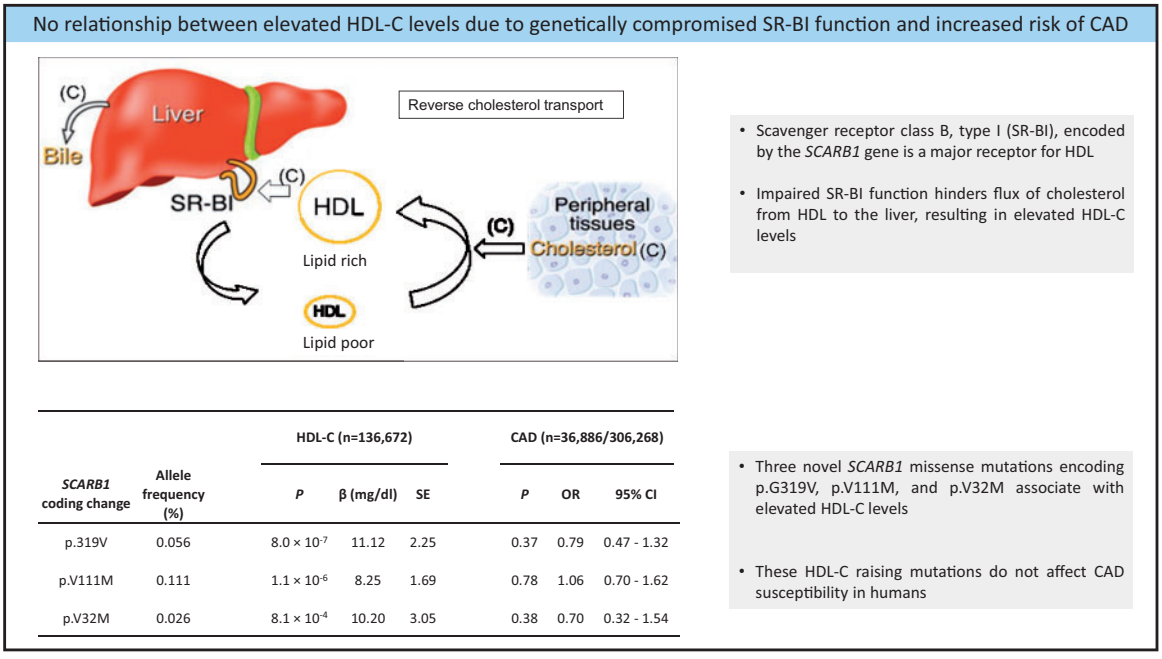
We further tested three common non-coding variants that independently associate with HDL-C, for association with CAD in Iceland and in the publicly available CARDIOGRAM/C4D 1000G data (*Table 2*). Of these common HDL-C associating variants one is novel (rs61941676) and two represent previously reported[6] GWAS signals (rs838876 and rs838909) (Supplementary material online, *Note* and *Table S3*). In the combined results from the Icelandic and CARDIOGRAM/C4D datasets, two of the three common variants show weak evidence for association with CAD (rs61941676-C: OR = 0.97, 95% CI 0.95–1.00; $P = 0.03$ and rs838876-A: OR = 0.98, 95% CI 0.96–0.99; $P = 0.0026$) (*Table 2*), with the HDL-C increasing allele trending towards reduced risk of CAD.

In light of the seemingly discrepant effects of rare *SCARB1* variants on the risk of CAD, it could be argued that the three Icelandic rare variants that associate with raised HDL-C could do so without inhibiting the hepatocellular trafficking of cholesterol to bile; thus explaining the lack of association with CAD. In this scenario, enhancement of cholesteryl ester transfer protein (CETP)-mediated exchange of cholesteryl esters from HDL to apoB containing lipoproteins, would counteract the genetically compromized SR-BI, resulting in minimal or no net effect on the hepatic cholesterol removal in carriers of the Icelandic variants. These effects would contrast the hindered hepatic cholesterol uptake observed in the SR-BI deficient mice (mice do not express CETP) and in hepatocytes derived from human induced pluripotent stem cells, carrying the p.P376L mutation.[11] To test the impact of the Icelandic *SCARB1* mutations, and other HDL-C associating variants at the locus, on transhepatic cholesterol flux, we used gallstone risk as a proxy. It has been shown that gallstone formation largely results from cholesterol hypersecretion to bile,[23,27,33] and in mice, overexpression of SR-BI associates with biliary cholesterol hypersecretion and increased gallstone formation. The effects of the *SCARB1* variants on gallstone risk was assessed in 8281 cases and 377 474 controls. Three of the seven HDL-C

**Table 2 Meta-analyses of the association of *SCARB1* locus variants with coronary artery disease in Iceland and CARDIOGRAM/C4D**

| | CAD variant *rs11057837 [T]* EA freq. = 9.5% | | HDL-C variant *rs61941676 [C]* EA freq. = 84.8% | | HDL-C variant *rs838876 [A]* EA freq. = 34.4% | | HDL-C variant *rs838909 [A]* EA freq. = 53.9% | |
|---|---|---|---|---|---|---|---|---|
| | *P*-value | OR (95% CI) | *P*-value | OR (95% CI) | *P*-value | OR (95% CI) | *P*-value | OR (95% CI) |
| CAD (Iceland) | $1.2 \times 10^{-6}$ | 1.108 (1.06–1.15) | 0.0012 | 0.945 (0.92–0.98) | 0.137 | 0.981 (0.96–1.01) | 0.788 | 1.003 (0.98–1.02) |
| CAD (CARDIOGRAM/C4D) | $9.5 \times 10^{-4}$ | 1.058 (1.02–1.09) | 0.894 | 0.998 (0.97–1.03) | $7.8 \times 10^{-3}$ | 0.973 (0.95–0.99) | 0.177 | 0.987 (0.97–1.01) |
| Combined | $1.9 \times 10^{-8}$ | 1.08 (1.05–1.11) | 0.03 | 0.97 (0.95–1.00) | $2.6 \times 10^{-3}$ | 0.98 (0.96–0.99) | 0.40 | 0.99 (0.98–1.01) |

The reported[34] CAD variant rs11057830 ($R^2$ = 0.71 with rs11057837) associates with CAD with OR = 1.085, $P = 1.6 \times 10^{-5}$ in Iceland. Effects are calculated based on the EA given in [ ]. Results from the Icelandic and CARDIOGRAM/C4D case-control groups were combined using inverse variance weighted fixed effect model.
CAD, coronary artery disease; CI, confidence interval; EA freq., effect allele frequency; EA, effect allele; HDL-C, high-density lipoprotein cholesterol; OR, odds ratio.




| | | HDL-C (n=136,672) | | | CAD (n=36,886/306,268) | | |
|---|---|---|---|---|---|---|---|
| *SCARB1* coding change | Allele frequency (%) | *P* | β (mg/dl) | SE | *P* | OR | 95% CI |
| p.319V | 0.056 | $8.0 \times 10^{-7}$ | 11.12 | 2.25 | 0.37 | 0.79 | 0.47 - 1.32 |
| p.V111M | 0.111 | $1.1 \times 10^{-6}$ | 8.25 | 1.69 | 0.78 | 1.06 | 0.70 - 1.62 |
| p.V32M | 0.026 | $8.1 \times 10^{-4}$ | 10.20 | 3.05 | 0.38 | 0.70 | 0.32 - 1.54 |

**Take home figure** Schematic showing the role of SR-BI in reverse cholesterol transport; promoting hepatic uptake of cholesterol from HDL and cholesterol secretion to bile. Rare missense mutations that compromise this SR-BI function do not affect the risk of coronary artery disease.

variants showed nominally significant association with gallstones (Supplementary material online, *Table S3*). A genetic risk score for HDL-C, constructed on the basis of seven *SCARB1* HDL-C associating variants, associates with gallstones. For each standard deviation (SD), increase in HDL-C due to the genetic risk score, the risk of gallstones decreases by 61% (OR = 0.39, 95% CI 0.24–0.63; $P = 1.0 \times 10^{-4}$) (Supplementary material online, *Table S2*). This finding supports the conclusion that *SCARB1* variants associating with increased HDL-C in humans impair cholesterol excretion through bile, thus playing a role in the late stages of reverse cholesterol transport, as described in the mouse and for other *SCARB1* mutations.[11,24] However, in concordance with the results for individual variants, the *SCARB1* HDL-C genetic risk score does not associate with CAD risk (for one SD of genetically elevated HDL-C: OR = 0.84, 95% CI 0.58–1.22; $P = 0.36$, Supplementary material online, *Table S2*) further tilting the scale against the hypothesis that hindered flux of HDL-C to the liver due to SR-BI impairment increases CAD susceptibility in humans.

Although we have demonstrated that *SCARB1* variants leading to decreased flux of HDL-C to the liver do not increase CAD risk (*Take home figure*), other SR-BI functions may still do so. In the Icelandic data a common *SCARB1* intronic variant rs11057837-T (allele frequency = 9.5%) associates with CAD (OR = 1.11, $P = 1.2 \times 10^{-6}$) (*Table 2*), but not with HDL-C or gallstones after adjusting for HDL-C variants in the region (Supplementary material online, *Table S3* and *Note*). Rs11057837-T also associates with CAD in the public 1000G data from CARDIOGRAM/C4D[34] (OR = 1.08 and $P = 1.9 \times 10^{-8}$ for Iceland and CARDIOGRAM/C4D combined) (*Table 2*). The

rs11057837 correlates ($R^2 = 0.7$) with other intronic variants (rs11057841, rs11057830, and rs10846744) that have previously been found to associate with Lp-PLA2 activity and mass,[35] vitamin E levels,[36] subclinical atherosclerosis,[37] and with CAD.[34,35] The association of correlated variants with vitamin E levels support the notion that rs11057837 mediates its effect through *SCARB1*, rather than other genes in the region, since *in vitro* studies have demonstrated the influence of SR-BI on tissue antioxidant uptake (vitamin E and carotenoids).[38,39] These effects, or other functions that have been linked to SR-BI, such as the effect on endothelial cell nitric oxide metabolism,[40] bacterial or viral recognition and degradation,[41–43] or induction of apoptosis,[44] are mechanisms that could explain the association of rs11057837 with CAD. Further, effects on other genes in the region cannot be ruled out.

To summarize, the HDL-C increasing effects (8–11 mg/dL) of the three rare *SCARB1* missense variants described in our study, encoding p.G319V, p.V111M, and p.V32M, are comparable to the HDL-C increasing effects (8–19 mg/dL) of the previously reported variants (encoding p.P376L, p.P297S, p.S112F, and p.T175A),[11,24,25] compatible with similar impact on SR-BI function. The variants do not associate with risk of CAD, and our estimate of the CAD effect, conferred by carrying one copy of any of the three rare HDL-C raising mutations ($OR_{CAD}$ = 0.90, 95% CI 0.67–1.22), is significantly different from the OR of 1.79 reported for p.P376L.[11] Importantly the 95% CI indicates that OR above 1.22 is unlikely. Assuming a true association between the HDL-C raising variants and increased risk of CAD, we have 90% power to detect variant association with OR = 1.29 at *P*-value <0.05. It is conceivable that the mutation encoding p.P376L has CAD susceptibility effects that are not shared by other HDL-C raising variants. However, given that it is relatively specific to Ashkenazi Jews (carried by about 1 in 20 Ashkenazi Jews vs. about 1 in 10 000 Europeans that are not Ashkenazi Jews)[45,46] it is more likely that differences in population substructure between cases and controls is the main explanation of the reported association of p. P376L with CAD. Specifically, this striking difference in carrier frequency, together with a relatively small imbalance in the number of Ashkenazi Jews between CAD cases and controls, could introduce a false association of similar degree as the one reported.[11]

In conclusion, our results do not support a relationship between elevated HDL-C levels due to genetically compromised SR-BI function and increased risk of CAD. These findings are in keeping with recent genetic and interventional studies[4–9] failing to show causal relationship between HDL-C levels and atherosclerosis and support current dyslipidaemia guidelines.

# Supplementary material

Supplementary material is available at *European Heart Journal* online.

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## References

1. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. *Eur Heart J* 2016;**37**:3232–3245.
2. Emerging Risk Factors Collaboration, Angelantonio ED, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, Wood AM, Lewington S, Sattar N, Packard CJ, Collins R, Thompson SG, Danesh J. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009;**302**:1993–2000.
3. Brunham LR, Hayden MR. Human genetics of HDL: insight into particle metabolism and function. *Prog Lipid Res* 2015;**58**:14–25.
4. Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, Hindy G, Hólm H, Ding EL, Johnson T, Schunkert H, Samani NJ, Clarke R, Hopewell JC, Thompson JF, Li M, Thorleifsson G, Newton-Cheh C, Musunuru K, Pirruccello JP, Saleheen D, Chen L, Stewart AFR, Schillert A, Thorsteinsdottir U, Thorgeirsson G, Anand S, Engert JC, Morgan T, Spertus J, Stoll M, Berger K, Martinelli N, Girelli D, McKeown PP, Patterson CC, Epstein SE, Devaney J, Burnett M-S, Mooser V, Ripatti S, Surakka I, Nieminen MS, Sinisalo J, Lokki M-L, Perola M, Havulinna A, de Faire U, Gigante B, Ingelsson E, Zeller T, Wild P, de Bakker PIW, Klungel OH, Maitland-van der Zee A-H, Peters BJM, de Boer A, Grobbee DE, Kamphuisen PW, Deneer VHM, Elbers CC, Onland-Moret NC, Hofker MH, Wijmenga C, Verschuren WMM, Boer JMA, van der Schouw YT, Rasheed A, Frossard P, Demissie S, Willer C, Do R, Ordovas JM, Abecasis GR, Boehnke M, Mohlke KL, Daly MJ, Guiducci C, Burtt NP, Surti A, Gonzalez E, Purcell S, Gabriel S, Marrugat J, Peden J, Erdmann J, Diemert P, Willenborg C, König IR, Fischer M, Hengstenberg C, Ziegler A, Buysschaert I, Lambrechts D, Van de Werf F, Fox KA, El Mokhtari NE, Rubin D, Schrezenmeir J, Schreiber S, Schäfer A, Danesh J, Blankenberg S, Roberts R, McPherson R, Watkins H, Hall AS, Overvad K, Rimm E, Boerwinkle E, Tybjaerg-Hansen A, Cupples LA, Reilly MP, Melander O, Mannucci PM, Ardissino D, Siscovick D, Elosua R, Stefansson K, O'Donnell CJ, Salomaa V, Rader DJ, Peltonen L, Schwartz SM, Altshuler D, Kathiresan S. Plasma HDL cholesterol and risk of myocardial infarction: a Mendelian randomisation study. *Lancet* 2012;**380**:572–580.
5. Helgadottir A, Gretarsdottir S, Thorleifsson G, Hjartarson E, Sigurdsson A, Magnusdottir A, Jonasdottir A, Kristjansson H, Sulem P, Oddsson A, Sveinbjornsson G, Steinthorsdottir V, Rafnar T, Masson G, Jonsdottir I, Olafsson I, Eyjolfsson GI, Sigurdardottir O, Daneshpour MS, Khalili D, Azizi F, Swinkels DW, Kiemeney L, Quyyumi AA, Levey AI, Patel RS, Hayek SS, Gudmundsdottir IJ, Thorgeirsson G, Thorsteinsdottir U, Gudbjartsson DF, Holm H, Stefansson K. Variants with large effects on blood lipids and the role of cholesterol and triglycerides in coronary disease. *Nat Genet* 2016;**48**:634–639.
6. Do R, Willer CJ, Schmidt EM, Sengupta S, Gao C, Peloso GM, Gustafsson S, Kanoni S, Ganna A, Chen J, Buchkovich ML, Mora S, Beckmann JS, Bragg-Gresham JL, Chang H-Y, Demirkan A, Den Hertog HM, Donnelly LA, Ehret GB, Esko T, Feitosa MF, Ferreira T, Fischer K, Fontanillas P, Fraser RM, Freitag DF, Gurdasani D, Heikkilä K, Hyppönen E, Isaacs A, Jackson AU, Johansson Å, Johnson T, Kaakinen M, Kettunen J, Kleber ME, Li X, Luan J, Lyytikäinen L-P, Magnusson PKE, Mangino M, Mihailov E, Montasser ME, Müller-Nurasyid M, Nolte IM, O'Connell JR, Palmer CD, Perola M, Petersen A-K, Sanna S, Saxena R, Service SK, Shah S, Shungin D, Sidore C, Song C, Strawbridge RJ, Surakka I, Tanaka T, Teslovich TM, Thorleifsson G, Van den Herik EG, Voight BF, Volcik KA, Waite LL, Wong A, Wu Y, Zhang W, Absher D, Asiki G, Barroso I, Been LF, Bolton JL, Bonnycastle LL, Brambilla P, Burnett MS, Cesana G, Dimitriou M, Doney ASF, Döring A, Elliott P, Epstein SE, Eyjolfsson GI, Gigante B, Goodarzi MO, Grallert H, Gravito ML, Groves CJ, Hallmans G, Hartikainen A-L, Hayward C, Hernandez D, Hicks AA, Holm H, Hung Y-J, Illig T, Jones MR, Kaleebu P, Kastelein JJP, Khaw K-T, Kim E, Klopp N, Komulainen P, Kumari M, Langenberg C, Lehtimäki T, Lin S-Y, Lindström J, Loos RJF, Mach F, McArdle WL, Meisinger C, Mitchell BD, Müller G, Nagaraja R, Narisu N, Nieminen TVM, Nsubuga RN, Olafsson I, Ong KK, Palotie A, Papamarkou T, Pomilla C, Pouta A, Rader DJ, Reilly MP, Ridker PM, Rivadeneira F, Rudan I, Ruokonen A, Samani N, Scharnagl H, Seeley J, Silander K, Stančáková A, Stirrups K, Swift AJ, Tiret L, Uitterlinden AG, van Pelt LJ, Vedantam S, Wainwright N, Wijmenga C, Wild SH, Willemsen G, Wilsgaard T, Wilson JF, Young EH, Zhao JH, Adair LS, Arveiler D, Assimes TL, Bandinelli S, Bennett F, Bochud M, Boehm BO, Boomsma DI, Borecki IB, Bornstein SR, Bovet P, Burnier M, Campbell H, Chakravarti A, Chambers JC, Chen Y-DI, Collins FS, Cooper RS, Danesh J, Dedoussis G, de Faire U, Feranil AB, Ferrières J, Ferrucci L, Freimer NB, Gieger C, Groop LC, Gudnason V,

Gyllensten U, Hamsten A, Harris TB, Hingorani A, Hirschhorn JN, Hofman A, Hovingh GK, Hsiung CA, Humphries SE, Hunt SC, Hveem K, Iribarren C, Järvelin M-R, Jula A, Kähönen M, Kaprio J, Kesäniemi A, Kivimaki M, Kooner JS, Koudstaal PJ, Krauss RM, Kuh D, Kuusisto J, Kyvik KO, Laakso M, Lakka TA, Lind L, Lindgren CM, Martin NG, März W, McCarthy MI, McKenzie CA, Meneton P, Metspalu A, Moilanen L, Morris AD, Munroe PB, Njølstad I, Pedersen NL, Power C, Pramstaller PP, Price JF, Psaty BM, Quertermous T, Rauramaa R, Saleheen D, Salomaa V, Sanghera DK, Saramies J, Schwarz PEH, Sheu WH-H, Shuldiner AR, Siegbahn A, Spector TD, Stefansson K, Strachan DP, Tayo BO, Tremoli E, Tuomilehto J, Uusitupa M, van Duijn CM, Vollenweider P, Wallentin L, Wareham NJ, Whitfield JB, Wolffenbuttel BHR, Altshuler D, Ordovas JM, Boerwinkle E, Palmer CNA, Thorsteinsdottir U, Chasman DI, Rotter JI, Franks PW, Ripatti S, Cupples LA, Sandhu MS, Rich SS, Boehnke M, Deloukas P, Mohlke KL, Ingelsson E, Abecasis GR, Daly MJ, Neale BM, Kathiresan S. Common variants associated with plasma triglycerides and risk for coronary artery disease. *Nat Genet* 2013; **45**:1345–1352.

7. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJP, Komajda M, Lopez-Sendon J, Mosca L, Tardif J-C, Waters DD, Shear CL, Revkin JH, Buhr KA, Fisher MR, Tall AR, Brewer B. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 2007;**357**:2109–2122.
8. Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, Chaitman BR, Holme IM, Kallend D, Leiter LA, Leitersdorf E, McMurray JJV, Mundl H, Nicholls SJ, Shah PK, Tardif J-C, Wright RS. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;**367**:2089–2099.
9. Landray MJ, Haynes R, Hopewell JC, Parish S, Aung T, Tomson J, Wallendszus K, Craig M, Jiang L, Collins R, Armitage J. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med* 2014;**371**:203–212.
10. Catapano AL, Graham I, Backer G, De Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Ž, Riccardi G, Taskinen M-R, Tokgozoglu L, Verschuren WMM, Vlachopoulos C, Wood DA, Zamorano JL; ESC Scientific Document Group. 2016 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J* 2016;**37**:2999–3058.
11. Zanoni P, Khetarpal SA, Larach DB, Hancock-Cerutti WF, Millar JS, Cuchel M, DerOhannessian S, Kontush A, Surendran P, Saleheen D, Trompet S, Jukema JW, De Craen A, Deloukas P, Sattar N, Ford I, Packard C, Majumder A. A S, Alam DS, Di Angelantonio E, Abecasis G, Chowdhury R, Erdmann J, Nordestgaard BG, Nielsen SF, Tybjærg-Hansen A, Schmidt RF, Kuulasmaa K, Liu DJ, Perola M, Blankenberg S, Salomaa V, Männistö S, Amouyel P, Arveiler D, Ferrieres J, Müller-Nurasyid M, Ferrario M, Kee F, Willer CJ, Samani N, Schunkert H, Butterworth AS, Howson JMM, Peloso GM, Stitziel NO, Danesh J, Kathiresan S, Rader DJ. Rare variant in scavenger receptor BI raises HDL cholesterol and increases risk of coronary heart disease. *Science* 2016;**351**:1166–1171.
12. Couzin-Frankel J. LIPID BIOLOGY. Why high "good cholesterol" can be bad news. *Science* 2016;**351**:1126.
13. Trigatti BL, Hegele RA. Rare genetic variants and high-density lipoprotein: marching to a different drum. *Arterioscler Thromb Vasc Biol* 2016;**36**:e53–e55.
14. Acton S, Rigotti A, Landschulz KT, Xu S, Hobbs HH, Krieger M. Identification of scavenger receptor SR-BI as a high density lipoprotein receptor. *Science* 1996; **271**:518–520.
15. Kozarsky KF, Donahee MH, Rigotti A, Iqbal SN, Edelman ER, Krieger M. Overexpression of the HDL receptor SR-BI alters plasma HDL and bile cholesterol levels. *Nature* 1997;**387**:414–417.
16. Brundert M, Ewert A, Heeren J, Behrendt B, Ramakrishnan R, Greten H, Merkel M, Rinninger F. Scavenger receptor class B type I mediates the selective uptake of high-density lipoprotein-associated cholesteryl ester by the liver in mice. *Arterioscler Thromb Vasc Biol* 2005;**25**:143–148.
17. Ji Y, Wang N, Ramakrishnan R, Sehayek E, Huszar D, Breslow JL, Tall AR. Hepatic scavenger receptor BI promotes rapid clearance of high density lipoprotein free cholesterol and its transport into bile. *J Biol Chem* 1999;**274**: 33398–33402.
18. Trigatti B, Rayburn H, Viñals M, Braun A, Miettinen H, Penman M, Hertz M, Schrenzel M, Amigo L, Rigotti A, Krieger M. Influence of the high density lipoprotein receptor SR-BI on reproductive and cardiovascular pathophysiology. *Proc Natl Acad Sci USA* 1999;**96**:9322–9327.
19. Braun A, Trigatti BL, Post MJ, Sato K, Simons M, Edelberg JM, Rosenberg RD, Schrenzel M, Krieger M. Loss of SR-BI expression leads to the early onset of occlusive atherosclerotic coronary artery disease, spontaneous myocardial infarctions, severe cardiac dysfunction, and premature death in apolipoprotein E-deficient mice. *Circ Res* 2002;**90**:270–276.
20. Ueda Y, Royer L, Gong E, Zhang J, Cooper PN, Francone O, Rubin EM. Lower plasma levels and accelerated clearance of high density lipoprotein (HDL) and non-HDL cholesterol in scavenger receptor class B type I transgenic mice. *J Biol Chem* 1999;**274**:7165–7171.
21. Arai T, Wang N, Bezouevski M, Welch C, Tall AR. Decreased atherosclerosis in heterozygous low density lipoprotein receptor-deficient mice expressing the scavenger receptor BI transgene. *J Biol Chem* 1999;**274**:2366–2371.
22. Kozarsky KF, Donahee MH, Glick JM, Krieger M, Rader DJ. Gene transfer and hepatic overexpression of the HDL receptor SR-BI reduces atherosclerosis in the cholesterol-fed LDL receptor-deficient mouse. *Arterioscler Thromb Vasc Biol* 2000;**20**:721–727.
23. Fuchs M, Ivandic B, Müller O, Schalla C, Scheibner J, Bartsch P, Stange EF. Biliary cholesterol hypersecretion in gallstone-susceptible mice is associated with hepatic up-regulation of the high-density lipoprotein receptor SRBI. *Hepatology* 2001; **33**:1451–1459.
24. Vergeer M, Korporaal SJA, Franssen R, Meurs I, Out R, Hovingh GK, Hoekstra M, Sierts JA, Dallinga-Thie GM, Motazacker MM, Holleboom AG, Berkel TJCV, Kastelein JJP, Eck MV, Kuivenhoven JA. Genetic variant of the scavenger receptor BI in humans. *N Engl J Med* 2011;**364**:136–145.
25. Brunham LR, Tietjen I, Bochem AE, Singaraja RR, Franchini PL, Radomski C, Mattice M, Legendre A, Hovingh GK, Kastelein JJP, Hayden MR. Novel mutations in scavenger receptor BI associated with high HDL cholesterol in humans. *Clin Genet* 2011;**79**:575–581.
26. Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, Pirruccello JP, Ripatti S, Chasman DI, Willer CJ, Johansen CT, Fouchier SW, Isaacs A, Peloso GM, Barbalic M, Ricketts SL, Bis JC, Aulchenko YS, Thorleifsson G, Feitosa MF, Chambers J, Orho-Melander M, Melander O, Johnson T, Li X, Guo X, Li M, Shin Cho Y, Jin Go M, Jin Kim Y, Lee J-Y, Park T, Kim K, Sim X, Twee-Hee Ong R, Croteau-Chonka DC, Lange LA, Smith JD, Song K, Hua Zhao J, Yuan X, Luan J, Lamina C, Ziegler A, Zhang W, Zee RYL, Wright AF, Witteman JCM, Wilson JF, Willemsen G, Wichmann H-E, Whitfield JB, Waterworth DM, Wareham NJ, Waeber G, Vollenweider P, Voight BF, Vitart V, Uitterlinden AG, Uda M, Tuomilehto J, Thompson JR, Tanaka T, Surakka I, Stringham HM, Spector TD, Soranzo N, Smit JH, Sinisalo J, Silander K, Sijbrands EJG, Scuteri A, Scott J, Schlessinger D, Sanna S, Salomaa V, Saharinen J, Sabatti C, Ruokonen A, Rudan I, Rose LM, Roberts R, Rieder M, Psaty BM, Pramstaller PP, Pichler I, Perola M, Penninx BWJH, Pedersen NL, Pattaro C, Parker AN, Pare G, Oostra BA, O'Donnell CJ, Nieminen MS, Nickerson DA, Montgomery GW, Meitinger T, McPherson R, McCarthy MI, McArdle W, Masson D, Martin NG, Marroni F, Mangino M, Magnusson PKE, Lucas G, Luben R, Loos RJF, Lokki M-L, Lettre G, Langenberg C, Launer LJ, Lakatta EG, Laaksonen R, Kyvik KO, Kronenberg F, König IR, Khaw K-T, Kaprio J, Kaplan LM, Johansson Å, Jarvelin M-R, Janssens AC, Ingelsson E, Igl W, Kees Hovingh G, Hottenga J-J, Hofman A, Hicks AA, Hengstenberg C, Heid IM, Hayward C, Havulinna AS, Hastie ND, Harris TB, Haritunians T, Hall AS, Gyllensten U, Guiducci C, Groop LC, Gonzalez E, Gieger C, Freimer NB, Ferrucci L, Erdmann J, Elliott P, Ejebe KG, Döring A, Dominiczak AF, Demissie S, Deloukas P, de Geus EJC, de Faire U, Crawford G, Collins FS, Chen Y-D. I, Caulfield MJ, Campbell H, Burtt NP, Bonnycastle LL, Boomsma DI, Boekholdt SM, Bergman RN, Barroso I, Bandinelli S, Ballantyne CM, Assimes TL, Quertermous T, Altshuler D, Seielstad M, Wong TY, Tai E-S, Feranil AB, Kuzawa CW, Adair LS, Taylor HA Jr, Borecki IB, Gabriel SB, Wilson JG, Holm H, Thorsteinsdottir U, Gudnason V, Krauss RM, Mohlke KL, Ordovas JM, Munroe PB, Kooner JS, Tall AR, Hegele RA, Kastelein JJP, Schadt EE, Rotter JI, Boerwinkle E, Strachan DP, Mooser V, Stefansson K, Reilly MP, Samani NJ, Schunkert H, Cupples LA, Sandhu MS, Ridker PM, Rader DJ, van Duijn CM, Peltonen L, Abecasis GR, Boehnke M, Kathiresan S. Biological, clinical and population relevance of 95 loci for blood lipids. *Nature* 2010;**466**:707–713.
27. Marschall H-U, Einarsson C. Gallstone disease. *J Intern Med* 2007;**261**:529–542.
28. Styrkarsdottir U, Thorleifsson G, Sulem P, Gudbjartsson DF, Sigurdsson A, Jonasdottir A, Jonasdottir A, Oddsson A, Helgason A, Magnusson OT, Walters GB, Frigge ML, Helgadottir HT, Johannsdottir H, Bergsteinsdottir K, Ogmundsdottir MH, Center JR, Nguyen TV, Eisman JA, Christiansen C, Steingrimsson E, Jonasson JG, Tryggvadottir L, Eyjolfsson GI, Theodors A, Jonsson T, Ingvarsson T, Olafsson I, Rafnar T, Kong A, Sigurdsson G, Masson G, Thorsteinsdottir U, Stefansson K. Nonsense mutation in the LGR4 gene is associated with several human diseases and other traits. *Nature* 2013;**497**:517–520.
29. Kong A, Masson G, Frigge ML, Gylfason A, Zusmanovich P, Thorleifsson G, Olason PI, Ingason A, Steinberg S, Rafnar T, Sulem P, Mouy M, Jonsson F, Thorsteinsdottir U, Gudbjartsson DF, Stefansson H, Stefansson K. Detection of sharing by descent, long-range phasing and haplotype imputation. *Nat Genet* 2008;**40**:1068–1075.
30. Kong A, Steinthorsdottir V, Masson G, Thorleifsson G, Sulem P, Besenbacher S, Jonasdottir A, Sigurdsson A, Kristinsson KT, Jonasdottir A, Frigge ML, Gylfason A, Olason PI, Gudjonsson SA, Sverrisson S, Stacey SN, Sigurgeirsson B, Benediktsdottir KR, Sigurdsson H, Jonsson T, Benediktsson R, Olafsson JH, Johannsson OT, Hreidarsson AB, Sigurdsson G, Ferguson-Smith AC, Gudbjartsson DF, Thorsteinsdottir U, Stefansson K. Parental origin of sequence variants associated with complex diseases. *Nature* 2009;**462**:868–874.
31. Gudbjartsson DF, Helgason H, Gudjonsson SA, Zink F, Oddson A, Gylfason A, Besenbacher S, Magnusson G, Halldorsson BV, Hjartarson E, Sigurdsson GT, Stacey SN, Frigge ML, Holm H, Saemundsdottir J, Helgadottir HT, Johannsdottir H, Sigfusson G, Thorgeirsson G, Sverrisson JT, Gretarsdottir S, Walters GB, Rafnar T, Thjodleifsson B, Bjornsson ES, Olafsson S, Thorarinsdottir H,

Steingrimsdottir T, Gudmundsdottir TS, Theodors A, Jonasson JG, Sigurdsson A, Bjornsdottir G, Jonsson JJ, Thorarensen O, Ludvigsson P, Gudbjartsson H, Eyjolfsson GI, Sigurdardottir O, Olafsson I, Arnar DO, Magnusson OT, Kong A, Masson G, Thorsteinsdottir U, Helgason A, Sulem P, Stefansson K. Large-scale whole-genome sequencing of the Icelandic population. *Nat Genet* 2015;**47**: 435–444.

32. Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks E, Fennell T, O'Donnell-Luria AH, Ware JS, Hill AJ, Cummings BB, Tukiainen T, Birnbaum DP, Kosmicki JA, Duncan LE, Estrada K, Zhao F, Zou J, Pierce-Hoffman E, Berghout J, Cooper DN, Deflaux N, DePristo M, Do R, Flannick J, Fromer M, Gauthier L, Goldstein J, Gupta N, Howrigan D, Kiezun A, Kurki MI, Moonshine AL, Natarajan P, Orozco L, Peloso GM, Poplin R, Rivas MA, Ruano-Rubio V, Rose SA, Ruderfer DM, Shakir K, Stenson PD, Stevens C, Thomas BP, Tiao G, Tusie-Luna MT, Weisburd B, Won H-H, Yu D, Altshuler DM, Ardissino D, Boehnke M, Danesh J, Donnelly S, Elosua R, Florez JC, Gabriel SB, Getz G, Glatt SJ, Hultman CM, Kathiresan S, Laakso M, McCarroll S, McCarthy MI, McGovern D, McPherson R, Neale BM, Palotie A, Purcell SM, Saleheen D, Scharf JM, Sklar P, Sullivan PF, Tuomilehto J, Tsuang MT, Watkins HC, Wilson JG, Daly MJ, MacArthur DG; Exome Aggregation Consortium. Analysis of protein-coding genetic variation in 60,706 humans. *Nature* 2016;**536**:285–291.
33. von Kampen O, Buch S, Nothnagel M, Azocar L, Molina H, Brosch M, Erhart W, von Schönfels W, Egberts J, Seeger M, Arlt A, Balschun T, Franke A, Lerch MM, Mayerle J, Kratzer W, Boehm BO, Huse K, Schniewind B, Tiemann K, Jiang Z-Y, Han T-Q, Mittal B, Srivastava A, Fenger M, Jørgensen T, Schirin-Sokhan R, Tönjes A, Wittenburg H, Stumvoll M, Kalthoff H, Lammert F, Tepel J, Puschel K, Becker T, Schreiber S, Platzer M, Völzke H, Krawczak M, Miquel JF, Schafmayer C, Hampe J. Genetic and functional identification of the likely causative variant for cholesterol gallstone disease at the ABCG5/8 lithogenic locus. *Hepatology* 2013; **57**:2407–2417.
34. Webb TR, Erdmann J, Stirrups KE, Stitziel NO, Masca NGD, Jansen H, Kanoni S, Nelson CP, Ferrario PG, König IR, Eicher JD, Johnson AD, Hamby SE, Betsholtz C, Ruusalepp A, Franzén O, Schadt EE, Björkegren JLM, Weeke PE, Auer PL, Schick UM, Lu Y, Zhang H, Dube M-P, Goel A, Farrall M, Peloso GM, Won H-H, Do R, van Iperen E, Kruppa J, Mahajan A, Scott RA, Willenborg C, Braund PS, van Capelleveen JC, Doney ASF, Donnelly LA, Asselta R, Merlini PA, Duga S, Marziliano N, Denny JC, Shaffer C, El-Mokhtari NE, Franke A, Heilmann S, Hengstenberg C, Hoffmann P, Holmen OL, Hveem K, Jansson J-H, Jöckel K-H, Kessler T, Kriebel J, Laugwitz KL, Marouli E, Martinelli N, McCarthy MI, Van Zuydam NR, Meisinger C, Esko T, Mihailov E, Escher SA, Alver M, Moebus S, Morris AD, Virtamo J, Nikpay M, Olivieri O, Provost S, AlQarawi A, Robertson NR, Akinsansya KO, Reilly DF, Vogt TF, Yin W, Asselbergs FW, Kooperberg C, Jackson RD, Stahl E, Müller-Nurasyid M, Strauch K, Varga TV, Waldenberger M, Zeng L, Chowdhury R, Salomaa V, Ford I, Jukema JW, Amouyel P, Kontto J, Nordestgaard BG, Ferrières J, Saleheen D, Sattar N, Surendran P, Wagner A, Young R, Howson JMM, Butterworth AS, Danesh J, Ardissino D, Bottinger EP, Erbel R, Franks PW, Girelli D, Hall AS, Hovingh GK, Kastrati A, Lieb W, Meitinger T, Kraus WE, Shah SH, McPherson R, Orho-Melander M, Melander O, Metspalu A, Palmer CNA, Peters A, Rader DJ, Reilly MP, Loos RJF, Reiner AP, Roden DM, Tardif J-C, Thompson JR, Wareham NJ, Watkins H, Willer CJ, Samani NJ, Schunkert H, Deloukas P, Kathiresan S; Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia Investigators. Systematic evaluation of pleiotropy identifies 6 further loci associated with coronary artery disease. *J Am Coll Cardiol* 2017;**69**:823–836.
35. Grallert H, Dupuis J, Bis JC, Dehghan A, Barbalic M, Baumert J, Lu C, Smith NL, Uitterlinden AG, Roberts R, Khuseyinova N, Schnabel RB, Rice KM, Rivadeneira F, Hoogeveen RC, Fontes JD, Meisinger C, Keaney JF, Lemaitre R, Aulchenko YS, Vasan RS, Ellis S, Hazen SL, van Duijn CM, Nelson JJ, Marz W, Schunkert H, McPherson RM, Stirnadel-Farrant HA, Psaty BM, Gieger C, Siscovick D, Hofman A, Illig T, Cushman M, Yamamoto JF, Rotter JI, Larson MG, Stewart AFR, Boerwinkle E, Witteman JCM, Tracy RP, Koenig W, Benjamin EJ, Ballantyne CM. Eight genetic loci associated with variation in lipoprotein-associated phospholipase A2 mass and activity and coronary heart disease: meta-analysis of genome-wide association studies from five community-based studies. *Eur Heart J* 2012;**33**: 238–251.
36. Major JM, Yu K, Wheeler W, Zhang H, Cornelis MC, Wright ME, Yeager M, Snyder K, Weinstein SJ, Mondul A, Eliassen H, Purdue M, Hazra A, McCarty CA, Hendrickson S, Virtamo J, Hunter D, Chanock S, Kraft P, Albanes D. Genome-wide association study identifies common variants associated with circulating vitamin E levels. *Hum Mol Genet* 2011;**20**:3876–3883.
37. Manichaikul A, Naj AC, Herrington D, Post W, Rich SS, Rodriguez A. Association of SCARB1 variants with subclinical atherosclerosis and incident cardiovascular disease: the multi-ethnic study of atherosclerosis. *Arterioscler Thromb Vasc Biol* 2012;**32**:1991–1999.
38. Reboul E, Klein A, Bietrix F, Gleize B, Malezet-Desmoulins C, Schneider M, Margotat A, Lagrost L, Collet X, Borel P. Scavenger receptor class B type I (SR-BI) is involved in vitamin E transport across the enterocyte. *J Biol Chem* 2006; **281**:4739–4745.
39. Goti D, Reicher H, Malle E, Kostner GM, Panzenboeck U, Sattler W. High-density lipoprotein (HDL3)-associated alpha-tocopherol is taken up by HepG2 cells via the selective uptake pathway and resecreted with endogenously synthesized apo-lipoprotein B-rich lipoprotein particles. *Biochem J* 1998;**332**:57–65.
40. Yuhanna IS, Zhu Y, Cox BE, Hahner LD, Osborne-Lawrence S, Lu P, Marcel YL, Anderson RG, Mendelsohn ME, Hobbs HH, Shaul PW. High-density lipoprotein binding to scavenger receptor-BI activates endothelial nitric oxide synthase. *Nat Med* 2001;**7**:853–857.
41. Yesilaltay A, Kocher O, Pal R, Leiva A, Quiñones V, Rigotti A, Krieger M. PDZK1 is required for maintaining hepatic scavenger receptor, class B, type I (SR-BI) steady state levels but not its surface localization or function. *J Biol Chem* 2006; **281**:28975–28980.
42. Schäfer G, Guler R, Murray G, Brombacher F, Brown GD. The role of scavenger receptor B1 in infection with mycobacterium tuberculosis in a murine model. *PLoS One* 2009;**4**:e8448.
43. Vishnyakova TG, Kurlander R, Bocharov AV, Baranova IN, Chen Z, Abu-Asab MS, Tsokos M, Malide D, Basso F, Remaley A, Csako G, Eggerman TL, Patterson AP. CLA-1 and its splicing variant CLA-2 mediate bacterial adhesion and cytosolic bacterial invasion in mammalian cells. *Proc Natl Acad Sci USA* 2006;**103**: 16888–16893.
44. Li X-A, Guo L, Dressman JL, Asmis R, Smart EJ. A novel ligand-independent apoptotic pathway induced by scavenger receptor class B, type I and suppressed by endothelial nitric-oxide synthase and high density lipoprotein. *J Biol Chem* 2005;**280**:19087–19096.
45. Stevens C, Avila BE, Neale BM, Kurki M, Ganna A, Graham D, Glaser B, Karczewski KJ, Minikel EV. Insights into the genetic epidemiology of Crohn's and rare diseases in the Ashkenazi Jewish population. *BioRxiv Prepr Serv Biol* 2016;**9**: 1–37.
46. IBD Exomes Portal, Cambridge, MA (http://ibd.broadinstitute.org, accessed March 2018).