JAMA | Original Investigation

Association of Genetic Variants Related to Combined Exposure to Lower Low-Density Lipoproteins and Lower Systolic Blood Pressure With Lifetime Risk of Cardiovascular Disease

Brian A. Ference, MD, MPhil, MSc; Deepak L. Bhatt, MD, MPH; Alberico L. Catapano, PhD; Chris J. Packard, DSc; Ian Graham, MD; Stephen Kaptoge, PhD; Thatcher B. Ference; Qi Guo, PhD; Ulrich Laufs, MD, PhD; Christian T. Ruff, MD, MPH; Arjen Cupido; G. Kees Hovingh, MD, PhD; John Danesh, DPhil; Michael V. Holmes, MBBS, PhD; George Davey Smith, MD, DSc; Kausik K. Ray, MD, MPhil; Stephen J. Nicholls, MBBS, PhD; Marc S. Sabatine, MD, MPH

IMPORTANCE The relationship between exposure to lower low-density lipoprotein cholesterol (LDL-C) and lower systolic blood pressure (SBP) with the risk of cardiovascular disease has not been reliably quantified.

OBJECTIVE To assess the association of lifetime exposure to the combination of both lower LDL-C and lower SBP with the lifetime risk of cardiovascular disease.

DESIGN, SETTING, AND PARTICIPANTS Among 438 952 participants enrolled in the UK Biobank between 2006 and 2010 and followed up through 2018, genetic LDL-C and SBP scores were used as instruments to divide participants into groups with lifetime exposure to lower LDL-C, lower SBP, or both. Differences in plasma LDL-C, SBP, and cardiovascular event rates between the groups were compared to estimate associations with lifetime risk of cardiovascular disease.

EXPOSURES Differences in plasma LDL-C and SBP compared with participants with both genetic scores below the median. Genetic risk scores higher than the median were associated with lower LDL-C and lower SBP.

MAIN OUTCOMES AND MEASURES Odds ratio (OR) for major coronary events, defined as coronary death, nonfatal myocardial infarction, or coronary revascularization.

RESULTS The mean age of the 438 952 participants was 65.2 years (range, 40.4-80.0 years), 54.1% were women, and 24 980 experienced a first major coronary event. Compared with the reference group, participants with LDL-C genetic scores higher than the median had 14.7-mg/dL lower LDL-C levels and an OR of 0.73 for major coronary events (95% CI, 0.70-0.75; $P < .001$). Participants with SBP genetic scores higher than the median had 2.9-mm Hg lower SBP and an OR of 0.82 for major coronary events (95% CI, 0.79-0.85, $P < .001$). Participants in the group with both genetic scores higher than the median had 13.9-mg/dL lower LDL-C, 3.1-mm Hg lower SBP, and an OR of 0.61 for major coronary events (95% CI, 0.59-0.64; $P < .001$). In a 4 × 4 factorial analysis, exposure to increasing genetic risk scores and lower LDL-C levels and SBP was associated with dose-dependent lower risks of major coronary events. In a meta-regression analysis, combined exposure to 38.67-mg/dL lower LDL-C and 10-mm Hg lower SBP was associated with an OR of 0.22 for major coronary events (95% CI, 0.17-0.26; $P < .001$), and 0.32 for cardiovascular death (95% CI, 0.25-0.40; $P < .001$).

CONCLUSIONS AND RELEVANCE Lifelong genetic exposure to lower levels of low-density lipoprotein cholesterol and lower systolic blood pressure was associated with lower cardiovascular risk. However, these findings cannot be assumed to represent the magnitude of benefit achievable from treatment of these risk factors.

JAMA. doi:10.1001/jama.2019.14120
Published online September 2, 2019.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Brian A. Ference, MD, MPhil, MSc, Centre for Naturally Randomized Trials, University of Cambridge, Two Worts' Causeway, Cambridge CB1 8RN, United Kingdom (baf29@medschl.cam.ac.uk).

Numerous randomized trials have demonstrated that treatment for up to 5 years with therapies that reduce low-density lipoprotein cholesterol (LDL-C) and systolic blood pressure (SBP) reduce the risk of cardiovascular events.[1-3] In addition, mendelian randomization studies suggest that the benefit of exposure to lower LDL-C levels and lower SBP may accumulate over time.[4-8] Because the biological effects of LDL-C and SBP may be cumulative, long-term exposure to the combination of both could potentially substantially reduce the lifetime risk of cardiovascular disease.[9-11] However, the association of combined lifetime exposure to both lower LDL-C and lower SBP with the risk of cardiovascular disease has not been reliably quantified.

Ideally, this question would be addressed by conducting a randomized trial to minimize the effect of confounding that can occur in observational studies. However, a randomized trial evaluating the association between maintaining prolonged exposure to both lower LDL-C levels and lower SBP with the risk of cardiovascular disease would take several decades to complete, and therefore is unlikely to ever be conducted. In an attempt to fill this evidence gap, this study used genetic variants associated with lower LDL-C levels and SBP as instruments of randomization to divide participants into groups with lifelong exposure to lower LDL-C levels, lower SBP, or both; and then compared the differences in plasma LDL-C, SBP, and cardiovascular event rates in each group to estimate the association of combined lifetime exposure with the lifetime risk of cardiovascular disease in a manner analogous to a long-term randomized clinical trial. The primary objective of this study was to assess and quantify the association of prolonged exposure to the combination of both lower LDL-C and lower SBP with the lifetime risk of cardiovascular disease.

Key Points

Question What is the association between genetic variants related to lower low-density lipoprotein cholesterol (LDL-C) levels and lower systolic blood pressure (SBP) with lifetime risk of cardiovascular disease?

Findings In mendelian randomization analyses involving 438 952 participants, genetic variants related to lower LDL-C and lower SBP were significantly associated with independent, additive, and dose-dependent lower risk of cardiovascular disease. For example, participants with genetic variants associated with both 14-mg/dL lower LDL-C and 3-mm Hg lower SBP had an odds ratio of 0.61 for major coronary events (coronary death, myocardial infarction, or coronary revascularization).

Meaning Lifelong genetic exposure to lower levels of low-density lipoprotein cholesterol and lower systolic blood pressure was associated with lower cardiovascular risk.

Methods

Study Population

The study included individual-level data from participants enrolled in the UK Biobank study recruited between 2006 and 2010 from 22 assessment centers across the United Kingdom who self-identified as being of white ancestry.[12] Participants who had missing values for either cardiovascular outcomes; 1 or more of the variants included in the LDL-C or SBP genetic scores; 1 or more of the first 5 principal components of ancestry; or both plasma LDL-C and SBP were excluded from the analysis. The KING [Kinship-based Inference for Genome-wide association studies] toolset was used to identify up to third-degree relatedness based on kinship coefficients of more than 0.044.[13] The UK Biobank has ethical approval from the Northwest Multi-Center Research Ethics Committee, and all participants provided written informed consent.

Instruments of Randomization

To construct the genetic LDL-C score, a total of 100 exome variants were identified that have been previously shown to be associated with LDL-C at the genome-wide level of significance and were in low-linkage disequilibrium with each other (r^2<0.1).[14] The exposure allele for each variant was defined as the allele associated with lower LDL-C. A weighted genetic LDL-C score was then calculated for each participant by summing the number of LDL-C–lowering alleles that persons inherited at each variant included in the score weighted by the association of each variant with LDL-C measured in milligrams per deciliter conditional on the association of all other variants included in the score as measured among participants in the UK Biobank without cardiovascular disease (eTable 1 in the Supplement).

Similarly, to construct the genetic SBP score, a total of 61 exome variants were identified that were previously shown to be associated with SBP at the genome-wide level of significance and that were in low-linkage disequilibrium with each other (r^2<0.1).[15,16] The exposure allele for each variant was defined as the allele associated with lower SBP. A weighted genetic SBP score was then calculated for each participant by summing the number of SBP-lowering alleles that persons inherited at each variant included in the score weighted by the association of each variant with SBP measured in millimeters of mercury (mm Hg) conditional on the association of all other variants included in the score as measured among UK Biobank participants without cardiovascular disease (eTable 2 in the Supplement).

For sensitivity analyses, unweighted genetic scores and genetic scores weighted by the association of each variant with LDL-C and SBP reported in the exome consortia were also calculated for each participant.

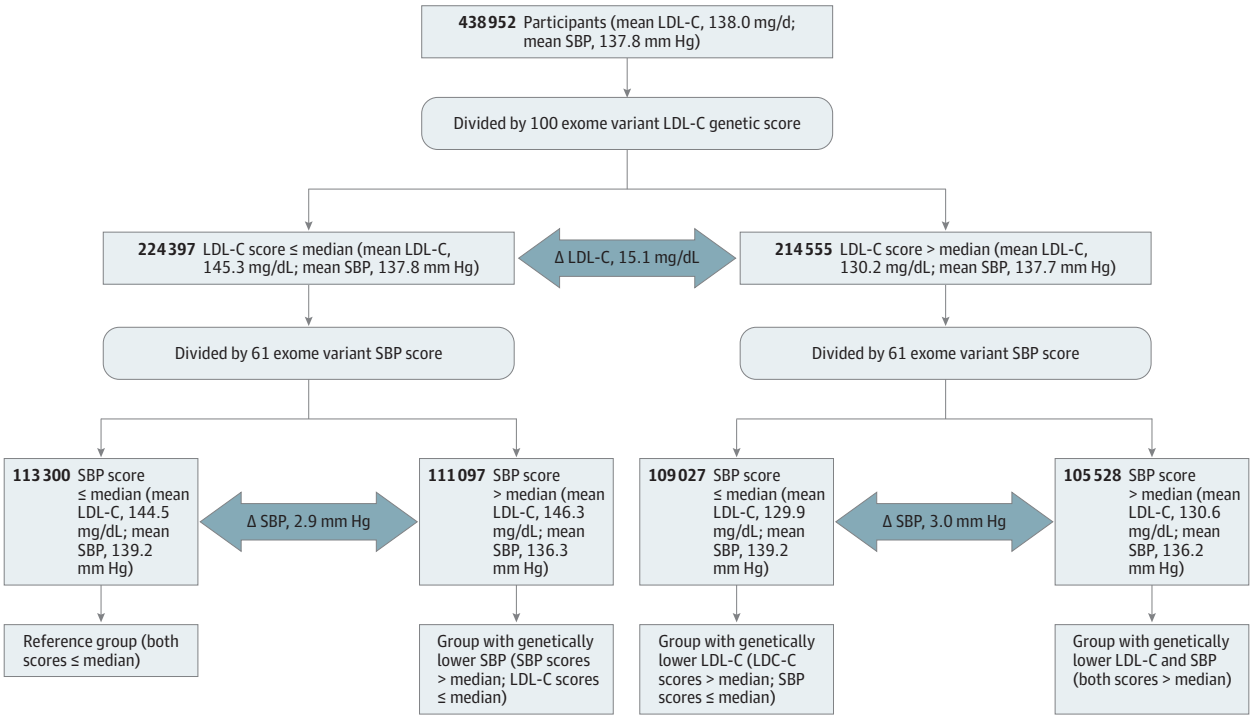
Study Outcomes

The primary outcome was major coronary events defined as a composite of coronary death, nonfatal myocardial infarction, or coronary revascularization. The key secondary outcome was major cardiovascular events (MCVEs) defined as the occurrence of a major coronary event or ischemic stroke (eTable 3 in the Supplement).

Study Design

To conduct the 2 × 2 factorial analysis, each genetic score was first dichotomized as higher than or lower than the median value for that score. Because the LDL-C– or SBP-lowering allele at each variant included in either score is inherited approximately randomly at the time of conception[17,18] and because each variant is inherited independently from all other variants included in either score by virtue of being in low-linkage disequilibrium with all

Figure 1. Organization of Study Participants by Genetic Score and Clinical Variables



Participants were first divided into 2 groups based on whether their low-density lipoprotein cholesterol (LDL-C) genetic score was equal to or lower than or was higher than the median. Participants in each of these 2 groups were then divided into 2 more groups based on whether their systolic blood pressure (SBP) genetic score was equal to or lower than or was higher than the median. This process produced 4 groups: a reference group, a group with lower SBP, a group with lower LDL-C, and a group with both lower LDL-C and lower SBP. To convert LDL-cholesterol from mg/dL to mmol/L, multiply by 0.0259.

other variants, the number of LDL-C lowering alleles and SBP lowering alleles, respectively, that each person inherits in either score should also be random. These genetic scores were used as instruments of randomization to divide participants into 4 groups.[19-21] First, participants were divided into 2 groups based on whether their genetic LDL-C score was equal to or lower than, or higher than the median value. Next, participants in either of these 2 groups were then divided into 2 more groups based on whether their genetic SBP score was equal to or lower than or was higher than the median value. This process divided all participants into 1 of 4 groups: the reference group, a group with LDL-C genetic scores higher than the median (resulting in lower LDL-C), a group with SBP genetic scores higher than the median (resulting in lower SBP), and a group with both LDL-C and SBP genetic scores higher than the median (resulting in both lower LDL-C and lower SBP) as shown in **Figure 1**. The success of the randomization scheme was assessed by comparing baseline characteristics among participants in each group. To assess dose-response, participants were divided into 4 groups based on the quartile values of their LDL-C and SBP scores, respectively, and a 4 × 4 factorial analysis was conducted.

Statistical Analysis

The genetic scores were used only as instruments of randomization without further assumptions. The mean differences in LDL-C, SBP, and cardiovascular event rates between each group being compared was directly measured to estimate the separate and combined associations of exposure to lower LDL-C, lower SBP, or both with the risk of cardiovascular events. The differences in LDL-C and SBP between groups was calculated as the difference in the crude means in each group, and by using linear regression adjusted for age, sex, body mass index, current smoking status, and the first 5 principal components of ancestry. The differences in the risk of cardiovascular events was measured by comparing the number of events in each group, and by using logistic regression using the same adjustments as performed in the linear regression analyses. A *z* test was used to assess for interactions between pairs of subgroups, and Cochran *Q* test was used when comparing more than 2 subgroups.

Incident and prevalent cases of disease were combined to maximize power, under the implicit assumption that all events occur incident to a genetic exposure. Because the date of occurrence for prevalent events was not known, a sensitivity analyses using generalized linear models was performed to calculate relative risks using log-binomial regression and a log link function. The relative risk estimates were then compared to the estimates of association derived from the logistic regression analyses to assess the quantitative change of combining incident and prevalent outcomes in the primary analysis.

To estimate the association of combined exposure to both 38.67 mg/dL or 1 mmol/L (to convert mg/dL to mmol/L, multiply by 0.0259) lower LDL-C and 10 mm Hg lower SBP on the

Table. Baseline Characteristics of Participants in a Study of Exposure to Lower LDL-C and Lower SBP and Cardiovascular Disease

Baseline Characteristics	Group, Mean (SD)			
	Reference (Both Genetic Scores ≤ Median)	Genetically Lower SBP (SBP Genetic Score > Median; LDL-C Genetic Score ≤ Median)	Genetically Lower LDL-C (LDL-C Genetic Score > Median; SBP Genetic Score ≤ Median)	Both Genetically Lower SBP and Lower LDL-C (Both Genetic Scores > Median)
No. of participants	113 300	111 097	109 027	105 528
Age, y	65.2 (8.0)	65.2 (8.0)	65.3 (8.0)	65.3 (8.0)
Sex, No. (%)				
Women	61 295 (54.1)	60 437 (54.4)	59 202 (54.3)	57 091 (54.1)
Men	52 005 (45.9)	50 660 (45.6)	49 825 (45.7)	48 437 (45.9)
Height, cm	168.6 (9.2)	168.6 (9.2)	168.7 (9.3)	168.8 (9.3)
Weight, kg	77.9 (15.8)	78.1 (15.9)	78.3 (15.9)	78.5 (16.0)
BMI	27.3 (4.7)	27.4 (4.7)	27.4 (4.8)	27.5 (4.8)
Hip, cm	103.2 (9.1)	103.4 (9.1)	103.4 (9.2)	103.6 (9.3)
Waist, cm	90.0 (13.4)	90.2 (13.5)	90.3 (13.5)	90.5 (13.5)
Waist-to-hip ratio	0.87 (0.1)	0.87 (0.1)	0.87 (0.1)	0.87 (0.1)
Smoker, No. (%)				
Current	8044 (7.1)	7888 (7.1)	8068 (7.4)	7492 (7.1)
Former	27 192 (24.0)	26 885 (24.2)	26 385 (24.2)	25 432 (24.1)
Ever	35 236 (31.1)	34 773 (31.3)	34 453 (31.7)	32 925 (31.2)
Creatinine, mg/dL	71.9 (17.8)	72.0 (18.8)	72.5 (17.4)	72.6 (17.6)
Cystatin-C, mg/L	0.91 (0.2)	0.91 (0.2)	0.91 (0.2)	0.91 (0.2)
Lipids, mg/dL				
LDL-C	144.5 (34.4)	146.3 (34.5)	129.9 (30.9)	130.6 (30.8)
Apo B	108.9 (23.9)	110.1 (24.0)	96.8 (21.9)	97.3 (21.9)
Total cholesterol	228.3 (45.5)	230.5 (45.5)	211.5 (41.0)	212.4 (40.9)
HDL-C	55.8 (14.6)	55.8 (14.5)	56.6 (15.1)	56.6 (15.0)
Triglycerides, median (IQR)	157.2 (94.6-193.0)	158.8 (95.2-195.3)	151.8 (91.2-186.3)	152.7 (91.5-188.0)
Non-HDL-C	172.5 (42.4)	174.7 (42.6)	154.9 (38.6)	155.8 (38.6)
Blood pressure, mm Hg				
Systolic	139.2 (18.7)	136.3 (18.4)	139.2 (18.7)	136.2 (18.4)
Diastolic	82.6 (10.1)	81.2 (10.0)	82.8 (10.2)	81.4 (10.1)
Current treatment, No. (%)				
Current lipid-lowering therapy	24 532 (21.7)	21 921 (19.7)	15 796 (14.5)	13 799 (13.1)
Current BP-lowering therapy	27 006 (23.8)	19 949 (18.0)	25 289 (23.2)	18 294 (17.3)
Both current lipid- and BP-lowering therapy	15 950 (14.1)	12 296 (11.1)	11 304 (10.4)	8711 (8.3)

Abbreviation: apo B, apolipoprotein B; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

SI conversion factors: To convert cholesterol from mg/dL to mmol/L, multiply by 0.0259; creatinine from mg/dL to μmol/L, multiply by 88.4; triglycerides from mg/dL to mmol/L, multiply by 0.0113.

risk of cardiovascular events, a meta-regression analysis was performed by regressing the association with major coronary events for each of the 15 groups in the 4 × 4 factorial analysis by the differences in LDL-C and SBP for each group compared with the reference group (defined as the group with the lowest quartile value for both the LDL-C and SBP scores).

In a test of external replication, genetic LDL-C and SBP scores were calculated using summary data from 184 305 participants enrolled in the Coronary Artery Disease Genome-Wide Replication and Meta-analysis (CARDIOGRAM) plus the Coronary Artery Disease (C4D) genetics consortium (CARDIoGRAMplusC4D) meta-analysis of genome-wide association studies.[22] The association between a 38.67-mg/dL lower LDL-C and a 10-mm Hg lower SBP was estimated by regressing the log odds for coronary heart disease for each variant measured in the CARDIOGRAMplusC4D study by the conditional association of that variant with both LDL-C and SBP among participants in the UK Biobank in a 2-sample multivariable mendelian randomization regression analysis forced to pass through the origin. Pleiotropy was assessed using the MR Egger method.[23]

All analyses were performed using Stata (version 16; StataCorp), or R (version 3.2.2; R Project for Statistical Computing). A 2-tailed *P* value less than .05 was considered statistically significant. Because no adjustment was made for multiple testing, findings from secondary and sensitivity analyses should be interpreted as exploratory.

Additional information is provided in the Supplement.

Results

Participant Characteristics

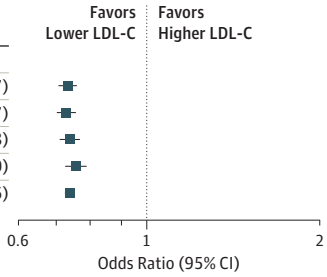
A total of 459 322 participants self-identified as being of white ancestry. Of these, a total of 20 370 participants (4.4%) had missing data for either cardiovascular outcomes, 1 or more of the variants included in the LDL-C or SBP genetic scores, 1 or more of the first 5 principal components of ancestry, or both plasma LDL-C and SBP; and were therefore excluded from the analysis. Among the 438 952 remaining participants included in this study, the mean age was 65.2 years (range, 40.4-80.0 years), 54.1% were

Figure 2. Assessment of Independent Associations of Lower LDL-C and Lower SBP With the Risk of Major Coronary Events

A Association of exposure to lower LDL-C with risk of major coronary events stratified by quartiles of SBP score

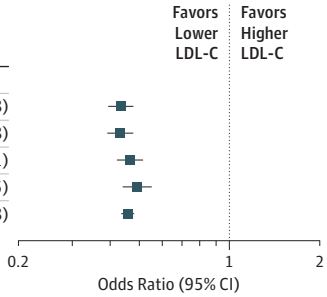
Associations for the observed difference in LDL-C

	No. of Participants	Difference in LDL-C Score, mg/dL	Odds Ratio (95% CI)	P Value
By quartiles of SBP score				
1	111 951	-14.7	0.73 (0.69-0.77)	<.001
2	110 376	-14.7	0.73 (0.69-0.77)	<.001
3	109 196	-15.5	0.74 (0.70-0.78)	<.001
4	107 429	-15.7	0.75 (0.71-0.80)	<.001
Overall	438 952	-15.1	0.74 (0.72-0.76)	<.001



Associations scaled for a 38.67 mg/dL difference in LDL-C

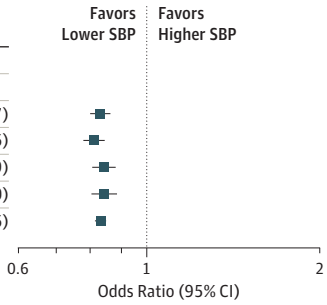
	No. of Participants	Difference in LDL-C Score, mg/dL	Odds Ratio (95% CI)	P Value
By quartiles of SBP score				
1	111 951	-38.67	0.43 (0.39-0.48)	<.001
2	110 376	-38.67	0.43 (0.39-0.48)	<.001
3	109 196	-38.67	0.47 (0.42-0.51)	<.001
4	107 429	-38.67	0.49 (0.44-0.55)	<.001
Overall	438 952	-38.67	0.46 (0.43-0.48)	<.001



B Association of exposure to lower SBP with risk of major coronary events stratified by quartiles of LDL-C score

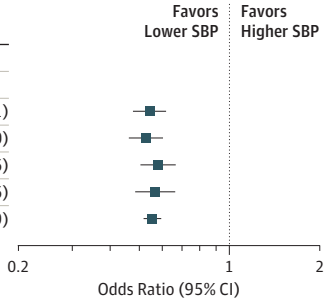
Associations for the observed difference in SBP

	No. of Participants	Difference in SBP, mm Hg	Odds Ratio (95% CI)	P Value
By quartiles of SBP score				
LDL-C score quartile				
1	113 257	-2.8	0.83 (0.79-0.87)	<.001
2	111 140	-3	0.81 (0.77-0.86)	<.001
3	108 799	-3	0.84 (0.80-0.89)	<.001
4	105 756	-2.8	0.85 (0.80-0.90)	<.001
Overall	438 952	-2.9	0.83 (0.81-0.86)	<.001



Associations scaled for a 10-mm Hg difference in SBP

	No. of Participants	Difference in SBP, mm Hg	Odds Ratio (95% CI)	P Value
By quartiles of SBP score				
LDL-C score quartile				
1	113 257	-10	0.54 (0.48-0.61)	<.001
2	111 140	-10	0.53 (0.46-0.60)	<.001
3	108 799	-10	0.58 (0.50-0.66)	<.001
4	105 756	-10	0.57 (0.48-0.66)	<.001
Overall	438 952	-10	0.55 (0.52-0.59)	<.001



A, The top part of the panel presents the observed differences in low-density lipoprotein cholesterol (LDL-C) level and odds ratio for major coronary events for participants with LDL-C genetic scores higher than the median compared with participants with LDL-C scores equal to or lower than the median, both overall and stratified by quartiles of the systolic blood pressure (SBP) genetic score. The bottom part of panel A presents the same comparisons scaled for a 38.67 mg/dL difference in LDL-C. (To convert mg/dL to mmol/L, multiply by 0.0259.)

B, The top part of the panel presents the observed differences in SBP and odds ratio for major coronary events for participants with SBP genetic scores higher than the median compared with participants with SBP scores equal to or lower than the median, both overall and stratified by quartiles of the LDL-C genetic score. The bottom part of panel B presents the same comparisons scaled for a 10-mm Hg difference in SBP.

women, and 24 980 experienced a first major coronary event. There were no significant differences in any nonlipid- or non-blood pressure–related baseline characteristics between the groups, which is consistent with random partitioning of participants into each group by the LDL-C and SBP genetic scores (**Table**).

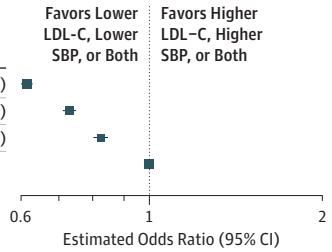
Independent Associations of LDL-C and SBP

In the entire study sample, participants with LDL-C genetic scores higher than the median had 15.1-mg/dL lower LDL-C and an OR for major coronary events of 0.74 (95% CI, 0.72-0.76; $P < .001$) compared with participants with LDL-C scores equal

Figure 3. Associations of Exposure to Lower LDL-C, Lower SBP, or Both With Risk of Major Coronary Events

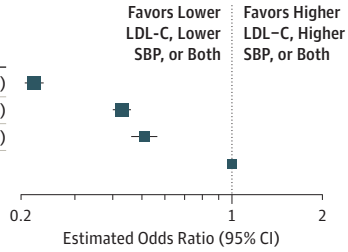
A Associations for the observed difference in LDL-C and SBP vs reference group

	No. of Participants	No. of Events	Difference in LDL-C Score, mg/dL	Difference in SBP, mm Hg	Odds Ratio (95% CI)	P Value
Lower LDL-C and lower SBP	105 528	4832	-13.9	-3.1	0.61 (0.59-0.64)	<.001
Lower LDL-C	109 027	5784	-14.7	-0.1	0.73 (0.70-0.75)	<.001
Lower SBP	111 097	6515	1.6	-2.9	0.82 (0.80-0.85)	<.001
Reference	113 300	7849				



B Associations scaled for a 38.67-mg/dL lower LDL-C, 10-mm Hg lower SBP, or both vs the reference group

	No. of Participants	No. of Events	Difference in LDL-C Score, mg/dL	Difference in SBP, mm Hg	Odds Ratio (95% CI)	P Value
Lower LDL-C and lower SBP	105 528	4832	-38.67	-10.0	0.22 (0.21-0.24)	<.001
Lower LDL-C	109 027	5784	-38.67	0	0.43 (0.40-0.46)	<.001
Lower SBP	111 097	6515	0	-10.0	0.51 (0.46-0.57)	<.001
Reference	113 300	7849				



The differences in low-density lipoprotein cholesterol (LDL-C) and systolic blood pressure (SBP) in each group are relative to the reference group.

A, Presents the observed odds ratios for major coronary events compared with the reference group.

B, Presents the odds ratios scaled for a difference of 38.67-mg/dL lower LDL-C (for the group allocated to lower LDL-C), 10-mm Hg lower SBP (for the group allocated to lower SBP), and the combined difference of both 38.67-mg/dL lower LDL-C and 10-mm Hg lower SBP (for the group allocated to both lower LDL-C and lower SBP).

To convert mg/dL to mmol/L, multiply by 0.0259.

to or lower than the median. This scaled to an OR of 0.46 (95% CI, 0.43-0.48) per 38.67-mg/dL lower LDL-C values. The magnitude of this association was very similar among participants divided into increasing quartiles of the SBP genetic score (*P* for heterogeneity = .81) (**Figure 2**A).

Similarly, in the entire study sample, participants with SBP genetic scores higher than the median had 2.9-mm Hg lower SBP and an OR of 0.83 for major coronary events (95% CI, 0.81-0.86; *P* < .001) compared with participants with SBP scores equal to or lower than the median. This scaled to an OR of 0.55 (95% CI, 0.52-0.59) per 10-mm Hg lower SBP. The magnitude of this association was quantitatively similar among participants divided into increasing quartiles of the LDL-C genetic score (*P* for heterogeneity = 0.89) (Figure 2B).

In analyses that included the LDL-C and SBP genetic scores as continuous variables, there was no evidence for interaction between the associations of lower LDL-C and lower SBP with the risk of major coronary events (OR for interaction, 1.00; 95% CI, 0.9996-1.0012; *P* = .92). Together, these analyses demonstrate that the associations of LDL-C and SBP with the risk of major coronary events appeared to be independent.

Associations of Combined Exposure to Lower LDL-C and SBP

In the 2 × 2 factorial analysis participants in the group with LDL-C scores higher than the median compared with the reference group had 14.7-mg/dL lower LDL-C and an OR of 0.73 (95% CI, 0.70-0.75, *P* < .001) for major coronary events. Participants with SBP scores higher than the median had 2.9-mm Hg lower SBP and an OR of 0.82 (95% CI, 0.79-0.85, *P* < .001) for major coronary events. Participants in the group with both LDL-C and SBP scores higher than the median had both 13.9-mg/dL lower LDL-C and 3.1-mm Hg lower SBP and an OR of 0.61 (95% CI, 0.59-0.64; *P* < .001) for major coronary events. The magnitude of the association in the combined exposure group was approximately equivalent to the log-additive associations with the risk of major coronary events in the groups with lower LDL-C and lower SBP, respectively (0.73 × 0.82 = 0.60). When scaled, combined exposure to 38.67-mg/dL lower LDL-C and 10-mm Hg lower SBP was associated with an OR of 0.22 (95% CI, 0.21-0.24) for major coronary events (**Figure 3**).

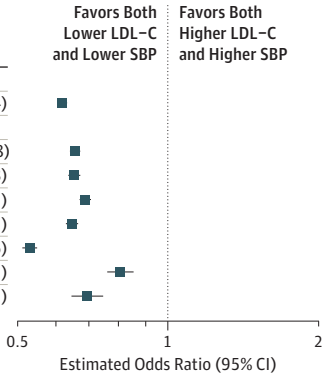
The association between combined exposure to both lower LDL-C and lower SBP was quantitatively similar for multiple different composite cardiovascular outcomes, and for the individual components of the composite outcomes including cardiovascular death (**Figure 4**). Combined exposure to 38.67-mg/dL lower LDL-C and 10-mm Hg lower SBP was associated with an OR of 0.32 (95% CI, 0.25-0.40; *P* < .001) for lifetime risk of cardiovascular death.

The association between combined exposure to both lower LDL-C and lower SBP on the lifetime risk of major coronary events was quantitatively similar among men and women, and among participants with and without diabetes (all *P* values for interaction >.05) (**Figure 5**). However, this association appeared to be attenuated among current smokers (*P* for interaction <.001).

Figure 4. Association of Combined Exposure to Both Lower LDL-C and Lower SBP With Various Cardiovascular Outcomes

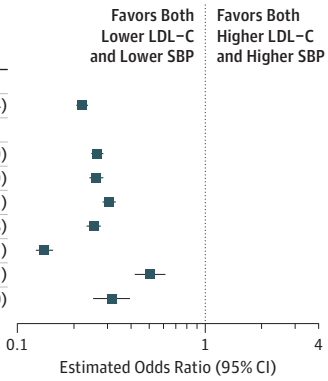
A Association for the observed differences in LDL-C and SBP vs the reference group

	No. of Events	Difference in LDL-C Score, mg/dL	Difference in SBP, mm Hg	Odds Ratio (95% CI)	P Value
Primary outcome					
Major coronary events	24980	-13.9	-3.1	0.61 (0.59-0.64)	<.001
Secondary outcomes					
Major cardiovascular events	26799	-13.9	-3.1	0.65 (0.63−0.68)	<.001
Coronary death or nonfatal MI	19243	-13.9	-3.1	0.65 (0.62-0.68)	<.001
Coronary death, nonfatal MI, or ischemic stroke	23796	-13.9	-3.1	0.68 (0.66-0.71)	<.001
Nonfatal MI	18093	-13.9	-3.1	0.64 (0.61-0.67)	<.001
Coronary revascularization	8388	-13.9	-3.1	0.53 (0.50-0.56)	<.001
Ischemic stroke	5565	-13.9	-3.1	0.80 (0.74-0.87)	<.001
Coronary death	2907	-13.9	-3.1	0.69 (0.62-0.77)	<.001



B Associations scaled for 38.67-mg/dL lower LDL-C and 10-mm Hg lower SBP vs the reference group

	No. of Events	Difference in LDL-C Score, mg/dL	Difference in SBP, mm Hg	Odds Ratio (95% CI)	P Value
Primary outcome					
Major coronary events	24980	-38.67	-10	0.22 (0.21-0.24)	<.001
Secondary outcomes					
Major cardiovascular events	26799	-38.67	-10	0.27 (0.25-0.29)	<.001
Coronary death or nonfatal MI	19243	-38.67	-10	0.26 (0.24-0.29)	<.001
Coronary death, nonfatal MI, or ischemic stroke	23796	-38.67	-10	0.31 (0.28-0.33)	<.001
Nonfatal MI	18093	-38.67	-10	0.25 (0.23-0.28)	<.001
Coronary revascularization	8388	-38.67	-10	0.14 (0.13-0.15)	<.001
Ischemic stroke	5565	-38.67	-10	0.51 (0.42-0.61)	<.001
Coronary death	2907	-38.67	-10	0.32 (0.25-0.40)	<.001



A, Presents differences in low-density lipoprotein cholesterol (LDL-C) levels and systolic blood pressure (SBP), and the odds ratio for various cardiovascular events for the group with both LDL-C and SBP genetic scores higher than the median compared with the reference group.

B, Presents the same associations scaled for the combined exposure to 38.67-mg/dL lower LDL-C and 10-mm Hg lower SBP.

To convert mg/dL to mmol/L, multiply by 0.0259.

Assessment of Dose-Response

In a 4 × 4 factorial analysis, exposure to any increasingly greater combination of lower LDL-C and lower SBP was associated with a correspondingly lower risk of major coronary events (**Figure 6**). In a meta-regression analysis of the associations between differences in LDL-C and SBP and the risk of a major coronary event in each of these 16 groups, combined exposure to 38.67-mg/dL lower and 10-mm Hg lower SBP was associated with an OR of 0.22 for major coronary events (95% CI, 0.17-0.26; $P < .001$), which is very similar to the scaled ORs presented above (eTable 4 in the Supplement).

Sensitivity Analyses

The results of all analyses remained essentially unchanged when repeated using unweighted LDL-C and SBP genetic scores and when using genetic scores weighted by external exome consortia associations with LDL-C and SBP, respectively (eTable 5 in the Supplement). Furthermore, in analyses using generalized linear models to estimate relative risks (RRs) using log-binomial regression and a log link function, the RR associated with lifetime exposure to 38.67-mg/dL lower LDL-C and 10-mm Hg lower SBP was very similar to the OR estimated using both logistic regression or a logit-binomial regression (RR, 0.24; 95% CI, 0.19-0.29; $P < .001$). Because the associations of LDL-C with cardiovascular disease may be mediated by changes in the concentration of circulating LDL particles as measured by apolipoprotein B (apo B), rather than by the concentration of cholesterol carried by those particles as measured by plasma LDL-C, all analyses were repeated using directly measured changes in apo B rather than changes in LDL-C.[24] In these analyses, combined exposure to 30-mg/dL lower apo B and 10-mm Hg lower SBP was associated with an OR of 0.20 for major coronary events (95% CI, 0.18-0.21; $P < .001$) (eTable 6 in the Supplement).

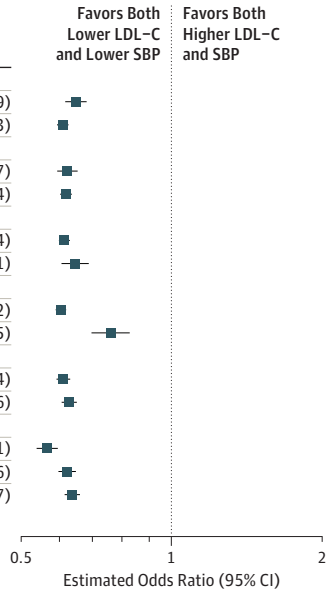
External Replication

Among 60 801 coronary artery disease cases and 123 504 controls in the CARDIoGRAMplusC4D consortium studies, a 38.67-mg/dL lower LDL-C was associated with an OR of 0.48 (95%CI, 0.43-0.54; $P < .001$) for coronary artery disease and a 10-mm Hg lower SBP was associated with an OR of 0.57 (95% CI, 0.50-0.65, $P < .001$). These associations were quantitatively similar to the associations measured using individual participant data in the UK Biobank. There was no evidence of any pleiotropic effects ($P = .52$) (eTable 7 in the Supplement).

Figure 5. Association of Combined Exposure to Both Lower LDL-C and Lower SBP With Major Coronary Events Within Subgroups

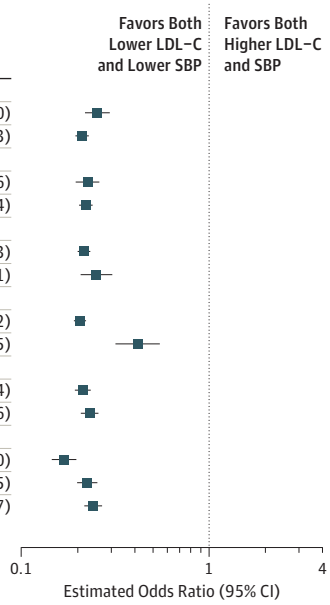
A Associations for the observed difference in LDL-C and SBP vs the reference group

	No. of Participants	Difference in LDL-C Score, mg/dL	Difference in SBP, mm Hg	Odds Ratio (95% CI)	P Value	P for Interaction
Sex						
Women	238 004	-15.7	-3.6	0.64 (0.60-0.69)	<.001	>.05
Men	200 948	-11.8	-2.6	0.60 (0.58-0.63)	<.001	
Age, y						
≤65	214 350	-16.9	-3.3	0.62 (0.57-0.67)	<.001	>.05
>65	224 602	-10.9	-2.9	0.61 (0.59-0.64)	<.001	
Diabetes						
No	368 728	-13.9	-3.2	0.61 (0.58-0.64)	<.001	>.05
Yes	70 224	-13.9	-2.8	0.64 (0.58-0.71)	<.001	
Current smoker						
No	407 380	-13.9	-3.1	0.60 (0.58-0.62)	<.001	<.001
Yes	31 572	-14.9	-3.0	0.75 (0.67-0.85)	<.001	
Ever smoker						
No	301 463	-14.4	-3.3	0.61 (0.58-0.64)	<.001	>.05
Yes	137 489	-12.8	-2.8	0.62 (0.59-0.66)	<.001	
BMI, tertile						
1	147 346	-15.7	-3.6	0.56 (0.52-0.61)	<.001	
2	146 467	-13.7	-3.2	0.62 (0.58-0.66)	<.001	.05
3	145 139	-12.3	-2.6	0.63 (0.60-0.67)	<.001	



B Associations scaled for 38.67-mg/dL lower LDL-C and 10-mm Hg lower SBP vs the reference group

	No. of Participants	Difference in LDL-C Score, mg/dL	Difference in SBP, mm Hg	Odds Ratio (95% CI)	P Value	P for Interaction
Sex						
Women	238 004	-38.67	-10	0.25 (0.22-0.30)	<.001	>.05
Men	200 948	-38.67	-10	0.21 (0.19-0.23)	<.001	
Age, y						
≤65	214 350	-38.67	-10	0.23 (0.20-0.26)	<.001	>.05
>65	224 602	-38.67	-10	0.22 (0.20-0.24)	<.001	
Diabetes						
No	368 728	-38.67	-10	0.22 (0.20-0.23)	<.001	>.05
Yes	70 224	-38.67	-10	0.25 (0.21-0.31)	<.001	
Current smoker						
No	407 380	-38.67	-10	0.21 (0.19-0.22)	<.001	<.001
Yes	31 572	-38.67	-10	0.42 (0.32-0.55)	<.001	
Ever smoker						
No	301 463	-38.67	-10	0.21 (0.19-0.24)	<.001	>.05
Yes	137 489	-38.67	-10	0.23 (0.21-0.26)	<.001	
BMI, tertile						
1	147 346	-38.67	-10	0.17 (0.15-0.20)	<.001	
2	146 467	-38.67	-10	0.23 (0.20-0.25)	<.001	.05
3	145 139	-38.67	-10	0.24 (0.22-0.27)	<.001	



A, Presents differences in low-density lipoprotein cholesterol (LDL-C) levels and SBP, and the odds ratio for major coronary events for the group with both LDL-C and SBP genetic scores higher than the median compared with the reference group for subgroups of participants.

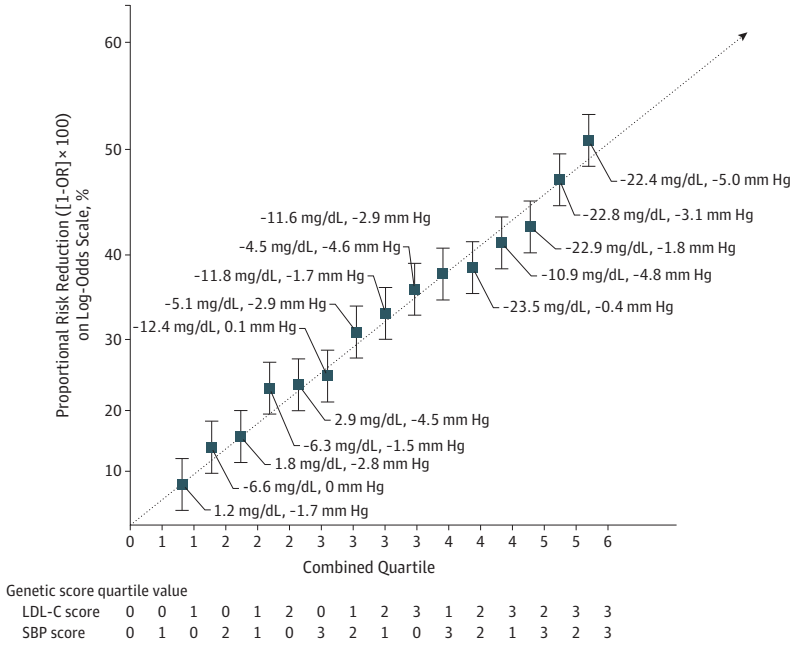
B, Presents the same associations scaled for the combined exposure to 38.67-mg/dL lower LDL-C and 10-mm Hg lower SBP.

Discussion

In this study, long-term exposure to the combination of both lower LDL-C and lower SBP was associated with independent, additive, and dose-dependent lower risks of cardiovascular events. Exposure to any combination of lower LDL-C and lower SBP was associated with a corresponding log-linear, dose-dependent lower risk of cardiovascular events. The results of this study have several potential implications.

First, this study helps to support the independent associations of LDL-C and SBP with the risk of cardiovascular disease. Three separate large-scale meta-analyses of prospective cohort studies including almost 2 million participants in total have previously reported that the association of combined exposure to plasma cholesterol and SBP with the risk of

Figure 6. Dose-Dependent Associations and Meta-Regression Analysis for Combinations of Increasingly Lower LDL-C and Lower SBP on the Risk of Major Coronary Events



For this analysis, participants were first divided into 4 groups based on quartile value of their low-density lipoprotein cholesterol (LDL-C) genetic score; and then each group was divided into another 4 groups based on the quartile value of their systolic blood pressure (SBP) genetic score. This process produced 16 groups with exposure to increasingly greater genetic risk scores and correspondingly lower LDL-C and lower SBP compared with the reference group (defined as the group with the lowest quartile of both the LDL-C and SBP genetic scores). The risk of major coronary events for each group relative to the reference group is plotted and expressed as a proportional risk reduction (calculated as [1 −odds ratio] × 100). The dashed line is the multivariable meta-regression line. The tabular data for these analyses are presented in the Supplement.

cardiovascular disease was less than additive.[25-27] Specifically, each of these meta-analyses reported that the association between LDL-C (or equivalently non-HDL-C) and the risk of cardiovascular disease became progressively attenuated among participants with higher baseline SBP levels. Unlike the studies included in those meta-analyses, this mendelian randomization study used genetic variants as instruments for lower LDL-C and SBP. Because genetic variants are randomly allocated at birth, this study design should be less susceptible to confounding and reverse causation compared with prospective cohort studies. Therefore, the independent and additive associations of LDL-C and SBP with the risk of cardiovascular events observed in this mendelian randomization study suggest that the less-than-additive associations observed in the prospective cohort studies may have been due to residual confounding.

Second, the log-linear, dose-dependent associations observed in this study help to clarify the shape of the association of combined exposure to lower LDL-C and SBP with the risk of cardiovascular disease. Prior meta-analyses of observational epidemiological studies, mendelian randomization studies, and randomized clinical trials have all consistently reported a dose-dependent, log-linear association between LDL-C and the risk of cardiovascular disease; and a similar dose-dependent, log-linear association with SBP.[1-8,25-27] This study extends the results of those previous studies by demonstrating that the association between combined exposure to both lower LDL-C and lower SBP is also dose-dependent and log-linearly proportional to the combined absolute differences in LDL-C and SBP.

Third, the results of this study suggest that the magnitude of the association between combined exposure to LDL-C and SBP with lifetime risk of cardiovascular disease may depend on both the magnitude and duration of exposure to LDL-C and SBP. This conclusion is based on the observation that in this study relatively small absolute differences in combined exposure to lower LDL-C and SBP were associated with corresponding relatively large differences in risk. This finding is consistent with previous mendelian randomization studies, which have reported much larger associations with cardiovascular disease per unit change in LDL-C or SBP, respectively, compared with those reported in epidemiological studies and randomized trials.[5,8-10] This study extends those findings to combined exposure to both LDL-C and SBP and suggests that the cumulative exposure to LDL-C and SBP (defined as an integration of the magnitude and duration of exposure) may be an important risk factor for lifetime risk of cardiovascular disease. Because trajectories of LDL-C and particularly SBP can vary between individuals, further research is needed to quantify more precisely the cumulative lifetime exposure to LDL-C and SBP that incorporates differing individual trajectories over the life course.[28,29]

Fourth, by quantifying the magnitude and clarifying the shape of the association between long-term exposure to the combination of both lower LDL and lower SBP with the risk of cardiovascular events, the results of this study can be used to inform the design of new algorithms that estimate the lifetime risk of cardiovascular disease based on a person's cumulative exposure to LDL-C and SBP. These new lifetime risk-estimating algorithms can in turn be used to inform the next iteration of cardiovascular medicine prevention guidelines by providing a quantitatively rigorous method to estimate and compare the potential differences in cardiovascular risk that might be achieved with various public health strategies.

Limitations

This study has several limitations. First, this study used genetic variants associated with lower LDL-C and lower SBP, respectively, as instruments of randomization to compare the association between lifetime exposure to lower LDL-C and SBP with the lifetime risk of cardiovascular disease. It did not evaluate medications that lower LDL-C or SBP. As a result, this study does not estimate the benefits and risks associated with the long-term use of medications to maintain lower LDL-C and SBP. Second, this study does not provide evidence that outcomes associated with intrinsic physiological findings, such as naturally occurring lower levels of LDL-C or SBP, are the same as outcomes that would be associated with extrinsic drug treatment or other interventions to achieve similar plasma LDL-C or SBP levels. Therefore, the findings in this study cannot be assumed to represent the magnitude of benefit achievable from various treatments to lower LDL-C, SBP, or both.

Conclusions

Lifelong genetic exposure to lower levels of low-density lipoprotein cholesterol and lower systolic blood pressure was associated with lower cardiovascular risk. However, these findings cannot be assumed to represent the magnitude of benefit achievable from treatment of these risk factors.

ARTICLE INFORMATION

Accepted for Publication: August 16, 2019.

Published Online: September 2, 2019. doi:10.1001/jama.2019.14120

Author Affiliations: Centre for Naturally Randomized Trials, University of Cambridge, Cambridge, United Kingdom (B. A. Ference, T. B. Ference, Guo, Cupido); MRC/BHF Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom (B. A. Ference, Kaptoge, Guo, Danesh); Brigham and Women's Hospital Heart and Vascular Center, Harvard Medical School, Boston, Massachusetts (Bhatt); Department of Pharmacological and Biomolecular Sciences, University of Milan, Multimedica IRCCS, Milano, Italy (Catapano); Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom (Packard); School of Medicine, Trinity College, Dublin, Ireland (Graham); Department of Cardiology, University of Leipzig, Leipzig, Germany (Laufs); Thrombolysis in Myocardial Infarction (TIMI) Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Ruff, Sabatine); Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands (Cupido, Hovingh); MRC Population Health Research Unit, Clinical Trial Service Unit, and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom (Holmes); MRC Integrative Epidemiology Unit, University of Bristol, Bristol, United Kingdom (Smith); School of Public Health, Imperial Centre for Cardiovascular Disease Prevention, Department of Primary Care and Public Health, Imperial College London, London, United Kingdom (Ray); Monash University, Melbourne, Australia (Nicholls).

Author Contributions: Dr Ference had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: B. Ference, Catapano, Packard, Graham, T. Ference, Hovingh, Davey-Smith.
Acquisition, analysis, or interpretation of data: B. Ference, Bhatt, Catapano, Packard, Graham, Kaptoge, T. Ference, Guo, Laufs, Ruff, Cupido, Danesh, Holmes, Ray, Nicholls, Sabatine.
Drafting of the manuscript: B. Ference, Packard, Laufs.
Critical revision of the manuscript for important intellectual content: B. Ference, Bhatt, Catapano, Graham, Kaptoge, T. Ference, Guo, Laufs, Ruff, Cupido, Hovingh, Danesh, Holmes, Davey-Smith, Ray, Nicholls, Sabatine.
Statistical analysis: B. Ference, Kaptoge, T. Ference, Guo, Ruff.
Obtained funding: Danesh.
Administrative, technical, or material support: B. Ference, Guo, Ray, Nicholls.
Supervision: B. Ference, Packard, Holmes, Davey-Smith, Ray.

Conflict of Interest Disclosures: Dr B. Ference reported receiving grants and personal fees from Amgen, Merck & Co, and Regeneron; grants from Novartis and Esperion Therapeutics; and personal fees from Ionis Pharmaceuticals, Medicines Co, Novo Nordisk, Sanofi, Pfizer, Eli Lilly, dalCOR, Silence Therapeutics, Integral Therapeutics, CiVi Pharma, KrKa Pharmaceuticals, Mylan, American College of Cardiology, European Atherosclerosis Society, and European Society of Cardiology, and grants from Afimmune. Dr Bhatt reported receiving grants from Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Sanofi-Aventis, The Medicines Company, Roche, Forest Laboratories and AstraZeneca, Ischemix, Pfizer, PhaseBio, Abbott, Regeneron, Idorsia, Synaptic, Amgen, Lilly, Chiesi, Ironwood, and Abbott; other support from FlowCo, PLx Pharma, Takeda, St Jude Medical (now Abbott), American College of Cardiology, Duke Clinical Research Institute, Medscape Cardiology, Regado Biosciences, Boston VA Research Institute, Clinical Cardiology, Veterans Affairs, Biotronik, Cardax, Boston Scientific, Merck, Svelte, PhaseBio, Merck, Novo Nordisk, Fractyl, and Cereno Scientific; personal fees from Belvoir Publications, Slack Publications, WebMD, Elsevier, Mayo Clinic, Population Health Research Institute, *Journal of the American College of Cardiology*, Harvard Clinical Research Institute (now Baim Institute for Clinical Research), TobeSoft, Boehringer Ingelheim, Bayer, Cleveland Clinic, Mount Sinai School of Medicine, Medtelligence/ReachMD, CSL Behring, HMP Global, and Ferring Pharmaceuticals; personal fees and nonfinancial support from Society of Cardiovascular Patient Care; and nonfinancial support from the American Heart Association. Dr Catapano reported receiving grants from Pfizer, Merck, Sanofi, Regeneron, Mediolanum, and Amgen; nonfinancial support from SigmaTau, Menarini, Kowa, Recordati, and Eli Lilly; and personal fees from Merck, Sanofi, Regeneron, Pfizer, AstraZeneca, Amgen, Sigma Tau, Recordati, Aegerion, Kowa, Menarini, Eli Lilly, Amaryt, Medco, and Genzyme. Dr Packard reported receiving grants and personal fees from Merck Sharp & Dohme and personal fees from Sanofi, Regeneron, Amgen, Daiichi-Sankyo, and Dalcor. Dr Kaptoge reported receiving grants from the UK Medical Research Council, the British Heart Foundation, and the UK National Institute of Health Research. Dr Laufs reported receiving personal fees from Merck & Co, Amgen, Pfizer, and Sanofi. Dr Ruff reported receiving grants and personal fees from Boehringer Ingelheim, Daiichi Sankyo, MedImmune, and the National Institutes of Health; personal fees from Bayer, Bristol-Myers Squibb, Janssen, Pfizer, Portola, and Anthos and serving as a member of the TIMI Study Group, which has received institutional research grant support through Brigham and Women's Hospital, Abbott, Amgen, Aralez, AstraZeneca, Bayer Healthcare Pharmaceuticals Inc, BRAHMS, GlaxoSmithKline, Intarcia, Novartis Pfizer, Poxel, Quark Pharmaceuticals, Roche, Takeda, The Medicines Company, and Zora Biosciences. Dr Cupido reported receiving grants from Amgen. Dr Hovingh reported receiving grants from ZonMW, national science institute, and VIDI; serving as consultant and speaker for biotech and pharmaceutical companies that develop molecules that influence lipoprotein metabolism, including Regeneron, Pfizer, Merck Sharp & Dohme, Sanofi, and Amgen; having served until April 2019 as principal investigator for clinical trials funded by Amgen, Sanofi, Eli Lilly, Novartis, Kowa, Genzyme, Cerenis, Pfizer, Dezima, AstraZeneca; and being partly employed by Novo Nordisk. Dr Danesh reported receiving grants, personal fees, and nonfinancial support from Merck Sharp & Dohme and Novartis and grants from the British Heart Foundation, the European Research Council, the National Institute for Health Research, National Health Service Blood and Transplant, Pfizer, UK Medical Research Council, Wellcome Trust, and AstraZeneca. Dr Ray reported receiving grants and personal fees from Amgen, Merck Sharp & Dohme, Regeneron, Sanofi, and Pfizer and personal fees from AbbVie, Boehringer Ingelheim, Cerenis, Cipla, Dr Reddy's Laboratories, Novartis, Kowa, Esperion, The Medicines Company, Novo Nordisk, AstraZeneca, Daiichi Sankyo, Bayer, Algorhythm, Akcea, Zuelliing Pharma, and Takeda. Dr Nicholls reported receiving grants from AstraZeneca, Amgen, Anthera, Eli Lilly, Esperion, Novartis, Cerenis, The Medicines Company, Resverlogix, InfraReDx, Roche, Sanofi-Regeneron, and LipoScience; in addition, Dr Nicholls is a named inventor on a patent focused on PCSK9 inhibitors issued, he receives no funds in respect to this.

Dr Sabatine reported receiving grants and personal fees from Amgen, AstraZeneca, Intarcia, Janssen Research and Development, The Medicines Company, MedImmune, Merck, and Novartis; grants from Bayer, Eisai, Esperion, GlaxoSmithKline, IFM Therapeutics, Pfizer, Poxel, Quark Pharmaceuticals, and Takeda; personal fees from Anthos Therapeutics, Bristol-Myers Squibb, CVS Caremark, Daiichi-Sankyo, DalCor, Dyrnamix, and Ionis; serving as a member of the TIMI Study Group, which has also received institutional research grant support through Brigham and Women's Hospital from: Abbott, Aralez, Roche, and Zora Biosciences.

Funding/Support: Dr Ference is supported by the National Institute for Health Research Cambridge Biomedical Research Centre at the Cambridge University Hospitals NHS Foundation Trust. Dr Danesh is supported by the Medical Research Council, British Heart Foundation, and the National Institute for Health Research. Dr Holmes is supported by the Medical Research Council and the British Heart Foundation. Dr Davey Smith is supported by the Medical Research Council and the British Heart Foundation. Dr Ray is supported by the Imperial NIHR Biomedical Research Centre.

Role of the Funder/Sponsor: The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Meeting Presentation: This paper was presented at the meeting of the European Society of Cardiology Congress, September 2, 2019, Paris, France.

REFERENCES

1. Baigent C, Blackwell L, Emberson J, et al; Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376(9753):1670-1681. doi:10.1016/S0140-6736(10)61350-5

2. Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA*. 2016;316(12):1289-1297. doi:10.1001/jama.2016.13985

3. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387(10022):957-967. doi:10.1016/S0140-6736(15)01225-8

4. 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(12):1264-1272. doi:10.1056/NEJMoa054013

5. Ference BA, Yoo W, Alesh I, et al. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. *J Am Coll Cardiol*. 2012;60(25):2631-2639. doi:10.1016/j.jacc.2012.09.017

6. Holmes MV, Asselbergs FW, Palmer TM, et al; UCLEB consortium. Mendelian randomization of blood lipids for coronary heart disease. *Eur Heart J*. 2015;36(9):539-550. doi:10.1093/eurheartj/eht571

7. Ehret GB, Munroe PB, Rice KM, et al; International Consortium for Blood Pressure Genome-Wide Association Studies; CARDIoGRAM consortium; CKDGen Consortium; KidneyGen Consortium; EchoGen consortium; CHARGE-HF consortium. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature*. 2011;478(7367):103-109. doi:10.1038/nature10405

8. Ference BA, Julius S, Mahajan N, Levy PD, Williams KA Sr, Flack JM. Clinical effect of naturally random allocation to lower systolic blood pressure beginning before the development of hypertension. *Hypertension*. 2014;63(6):1182-1188. doi:10.1161/HYPERTENSIONAHA.113.02734

9. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease, I; evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2017;38(32):2459-2472. doi:10.1093/eurheartj/ehx144

10. Packard CJ, Weintraub WS, Laufs U. New metrics needed to visualize the long-term impact of early LDL-C lowering on the cardiovascular disease trajectory. *Vascul Pharmacol*. 2015;71:37-39. doi:10.1016/j.vph.2015.03.008

11. Robinson JG, Williams KJ, Gidding S, et al. Eradicating the burden of atherosclerotic cardiovascular disease by lowering apolipoprotein B lipoproteins earlier in life. *J Am Heart Assoc*. 2018;7(20):e009778. doi:10.1161/JAHA.118.009778

12. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12(3):e1001779. doi:10.1371/journal.pmed.1001779

13. Manichaikul A, Mychaleckyj JC, Rich SS, Daly K, Sale M, Chen W-M. Robust relationship inference in genome-wide association studies. *Bioinformatics*. 2010;26(22):2867-2873. doi:10.1093/bioinformatics/btq559

14. Liu DJ, Peloso GM, Yu H, et al; Charge Diabetes Working Group; EPIC-InterAct Consortium; EPIC-CVD Consortium; GOLD Consortium; VA Million Veteran Program. Exome-wide association study of plasma lipids in >300,000 individuals. *Nat Genet*. 2017;49(12):1758-1766. doi:10.1038/ng.3977

15. Kraja AT, Cook JP, Warren HR, et al; Understanding Society Scientific Group; CHARGE EXOME BP, CHD Exome+, Exome BP, GoT2D:T2DGenes Consortia, The UK Biobank Cardio-Metabolic Traits Consortium Blood Pressure Working Group†. New blood pressure-associated loci identified in meta-analyses of 475 000 individuals. *Circ Cardiovasc Genet*. 2017;10(5):e001778. doi:10.1161/CIRCGENETICS.117.001778

16. Liu C, Kraja AT, Smith JA, et al; CHD Exome+ Consortium; ExomeBP Consortium; GoT2DGenes Consortium; T2D-GENES Consortium; Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia; CKDGen Consortium. Meta-analysis identifies common and rare variants influencing blood pressure and overlapping with metabolic trait loci. *Nat Genet*. 2016;48(10):1162-1170. doi:10.1038/ng.3660

17. Palmer TM, Lawlor DA, Harbord RM, et al. Using multiple genetic variants as instrumental variables for modifiable risk factors. *Stat Methods Med Res*. 2012;21(3):223-242. doi:10.1177/0962280210394459

18. Lawlor DA, Harbord RM, Sterne JA, Timpson N, Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med*. 2008;27(8):1133-1163. doi:10.1002/sim.3034

19. Ference BA, Majeed F, Penumetcha R, Flack JM, Brook RD. Effect of naturally random allocation to lower low-density lipoprotein cholesterol on the risk of coronary heart disease mediated by polymorphisms in NPC1L1, HMGCR, or both: a 2 × 2 factorial Mendelian randomization study. *J Am Coll Cardiol*. 2015;65(15):1552-1561. doi:10.1016/j.jacc.2015.02.020

20. Ference BA, Robinson JG, Brook RD, et al. Variation in PCSK9 and HMGCR and risk of cardiovascular disease and diabetes. *N Engl J Med*. 2016;375(22):2144-2153. doi:10.1056/NEJMoa1604304

21. Ference BA, Kastelein JJP, Ginsberg HN, et al. Association of genetic variants related to CETP inhibitors and statins with lipoprotein levels and cardiovascular risk. *JAMA*. 2017;318(10):947-956. doi:10.1001/jama.2017.11467

22. Nikpay M, Goel A, Won HH, et al. A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. *Nat Genet*. 2015;47(10):1121-1130. doi:10.1038/ng.3396

23. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol*. 2015;44(2):512-525. doi:10.1093/ije/dyv080

24. Ference BA, Kastelein JJP, Ray KK, et al. Association of triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants with risk of coronary heart disease. *JAMA*. 2019;321(4):364-373. doi:10.1001/jama.2018.20045

25. Lewington S, Whitlock G, Clarke R, et al; Prospective Studies Collaboration. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet*. 2007;370(9602):1829-1839. doi:10.1016/S0140-6736(07)61778-4

26. Asia Pacific Cohort Studies Collaboration. Joint effects of systolic blood pressure and serum cholesterol on cardiovascular disease in the Asia Pacific region. *Circulation*. 2005;112(22):3384-3390. doi:10.1161/CIRCULATIONAHA.105.537472

27. Di Angelantonio E, Sarwar N, Perry P, et al; Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA*. 2009;302(18):1993-2000. doi:10.1001/jama.2009.1619

28. Allen NB, Siddique J, Wilkins JT, et al. Blood pressure trajectories in early adulthood and subclinical atherosclerosis in middle age. *JAMA*. 2014;311(5):490-497. doi:10.1001/jama.2013.285122

29. Duncan MS, Vasan RS, Xanthakis V. Trajectories of blood lipid concentrations over the adult life course and risk of cardiovascular disease and all-cause mortality: observations from the Framingham Study over 35 years. *J Am Heart Assoc*. 2019;8(11):e011433. doi:10.1161/JAHA.118.011433