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10.1001/jama.2019.14120

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

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**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.

Published online September 2, 2019.

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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.\(^1\,^2\) In addition, mendelian randomization studies suggest that the benefit of exposure to lower LDL-C levels and lower SBP may accumulate over time.\(^4\,^5\) 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.\(^9\,^10\) 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.

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 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 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
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 low-density lipoprotein cholesterol (LDL-C) genetic score was equal to or lower than, or was higher than the median. Next, participants in either 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.

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 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
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 (CARDIoGRAM plus C4D) meta-analysis of genome-wide association studies. 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.
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 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

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

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

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

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.)

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

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.
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 LDL-C genetic score (P for heterogeneity = .81) (Figure 2A).

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 0.82 (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).

Table 3. Associations for the Observed Difference in LDL-C and SBP vs Reference Group

<table>
<thead>
<tr>
<th>LDL-C Score, mg/dL</th>
<th>Difference in LDL-C Score, mg/dL</th>
<th>Difference in SBP, mm Hg</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower LDL-C and lower SBP</td>
<td>0.51 (0.46-0.57)</td>
<td>0.22 (0.21-0.24)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Lower LDL-C</td>
<td>0.43 (0.40-0.46)</td>
<td>0.22 (0.21-0.24)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Lower SBP</td>
<td>0.82 (0.80-0.85)</td>
<td>0.22 (0.21-0.24)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>1.00 (0.99-1.00)</td>
<td>1.00 (0.99-1.00)</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Associations for the Scaled Difference in LDL-C and SBP vs Reference Group

<table>
<thead>
<tr>
<th>LDL-C Score, mg/dL</th>
<th>Difference in LDL-C Score, mg/dL</th>
<th>Difference in SBP, mm Hg</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower LDL-C and lower SBP</td>
<td>0.51 (0.46-0.57)</td>
<td>0.22 (0.21-0.24)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Lower LDL-C</td>
<td>0.43 (0.40-0.46)</td>
<td>0.22 (0.21-0.24)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Lower SBP</td>
<td>0.82 (0.80-0.85)</td>
<td>0.22 (0.21-0.24)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>1.00 (0.99-1.00)</td>
<td>1.00 (0.99-1.00)</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

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, 10-mm Hg lower SBP, or both vs the reference group.

To convert mg/dL to mmol/L, multiply by 0.0259.
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 log-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; \( P < .001 \)).

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).
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...
cardiovascular disease was less than additive. Specific-25,27 ally, 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 logarithmically 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.

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.
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

Lifetime 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

Research Original Investigation

Lifetime Exposure to Lower LDL-C and Lower Systolic Blood Pressure and Cardiovascular Disease

E10 JAMA Published online September 2, 2019

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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, dailCOR, Silence Therapeutics, Integral Therapeutics, CIVI Pharma, Krika Pharmaceuticals, Mylan, American College of Cardiology, European Atherosclerosis Society, and European Society of Cardiology, and grants from Afinimmune. Dr Bhatt reported receiving grants from Amarin, AstraZeneca, Bristol-Myers Squibb, Elsai, Ethicon, Medtronic, Sanofi-Aventis, The Medicines Company, Roche, Forest Laboratories and AstraZeneca, Ischemix, Pfizer, Phaselisio, Abbott, Regeneron, Idorsia, Synaptic, Amgen, Lilly, Chiesi, Ironwood, and Abbott; other support from FlowCo, PLx Pharma, Taienda, 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 Bain Institute for Clinical Research), TobeSoft, Boehinger Ingelheim, Bayer, Cleveland Clinic, Mount Sinai School of Medicine, MedNetelligence/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 Agena; 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 Anthera 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, Arazel, 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, Dojima, 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, and Novartis and personal fees from AbbVie, Boehinger Ingelheim, Cerenis, Cipla, Dr Reddy’s Laboratories, Novartis, Kowa, Esperion, The Medicines Company, Novo Nordisk, AstraZeneca, Daiichi Sankyo, Bayer, Algorhythm, Alcoxa, Zueling 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.
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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, Daichi-Sankyo, Daicor, Dynamin, 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, Arakel, 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.

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