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

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Key Points

Question
What is the association between genetic variants related to lower low-density lipoproteins and lower systolic blood pressure with lifetime risk of cardiovascular disease?

Findings
In Mendelian randomization analyses involving 438,952 participants, genetic variants related to LDL-C and SBP were significantly associated with independent, additive, and dose-dependent lower risk of cardiovascular disease. For example, participants with genetic scores above the median for both variables compared with those below the median for both variables an odds ratio of 0.61 for major coronary events (coronary death, myocardial infarction, or coronary revascularization).

Meaning
Lifelong genetic exposure to lower SBP and lower levels of LDL-C was associated with lower cardiovascular risk.

ALTERNATIVE suggestion for “FINDINGS”

FINDINGS:
In Mendelian randomization analyses involving 438,952 participants, genetically determined exposure to the combination of both lower LDL-C and lower SBP was 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 mmHg lower SBP had an odds ratio of 0.61 for major coronary events (coronary death, myocardial infarction, or coronary revascularization).
ABSTRACT

IMPORTANCE: The association of combined exposure to both 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 to 2010 and followed through 2018, genetic LDL-C and SBP scores were used as instruments to randomly 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 as compared to participants with both genetic scores below the median.

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

RESULTS: The mean age of participants was 65.2 years [range:40.4-80.0] and 54.1% were females. Compared to the reference group, participants with LDL-C genetic scores above the median had 14.7 mg/dL lower LDL-C and an OR of 0.73 for MCE (95%CI:0.70-0.75,p<0.001); participants with SBP genetic scores above the median had 2.9 mmHg lower SBP and an OR of 0.82 for MCE (95%CI:0.79-0.85,p<0.001); and participants in the group with both genetic scores above the median had 13.9 mg/dL lower LDL-C, 3.1 mmHg lower SBP and an OR of 0.61 for MCE (95%CI:0.59-0.64,p<0.001). In a 4x4 factorial analysis, exposure to increasing combinations of lower LDL-C and SBP was associated with dose-dependent lower risks of MCE. In a meta-regression analysis, combined exposure to 38.67 mg/dl (1 mmol/L) lower LDL-C and 10 mmHg lower SBP was associated with an OR of 0.22 for MCE (95%CI:0.17-0.26,p<0.001), and 0.32 for cardiovascular death (95%CI:0.25-0.40,p<0.001).
CONCLUSIONS AND RELEVANCE: Lifelong genetic exposure to lower SBP and lower levels of LDL-C 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.
INTRODUCTION

Numerous randomized trials have demonstrated that treatment for up to five years with therapies that reduce low-density lipoprotein cholesterol (LDL-C) and systolic blood pressure (SBP) reduce the risk of cardiovascular events.\textsuperscript{1,2,3} In addition, Mendelian randomization studies suggest that the benefit of exposure to lower LDL-C and lower SBP may accumulate over time.\textsuperscript{4,5,6,7,8} Because the biological effects of LDL-C and SBP may be cumulative, long-term exposure to the combination of both lower LDL-C and lower SBP could potentially substantially reduce the lifetime risk of cardiovascular disease.\textsuperscript{9,10,11} 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. Unfortunately, a randomized trial evaluating the association between maintaining prolonged exposure to both lower LDL-C and SBP 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 and SBP as instruments of randomization to divide participants into groups with lifelong exposure to lower LDL-C, 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 to both lower LDL-C and lower SBP with the lifetime risk of cardiovascular disease in a manner analogous to a long-term randomized 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. Participants who had missing values for either cardiovascular outcomes; one or more of the variants included in the LDL-C or SBP genetic scores; one or more of the first 5 principal components of ancestry; or both plasma LDL-C and SBP were excluded from the analysis. The KING toolset was used to identify up to third-degree relatedness based on kinship coefficients > 0.044. 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 genome-wide level of significance and were in low linkage disequilibrium with each other ($r^2<0.1$). 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 person inherited at each variant included in the score weighted by the association of each variant with LDL-C measured in mg/dL 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).

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 genome-wide level of significance and that were in low linkage disequilibrium with each other ($r^2<0.1$). 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 person inherited at each
variant included in the score weighted by the association of each variant with SBP measured in mmHg conditional on the association of all other variants included in the score as measured among UK Biobank participants without cardiovascular disease (eTable 2).

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 (MCE) defined as a composite of non-fatal myocardial infarction (MI), coronary revascularization or coronary death. The key secondary outcome was major cardiovascular events (MCVE) defined as the occurrence of a major coronary event or ischemic stroke (eTable 3).

STUDY DESIGN

To conduct the 2x2 factorial analysis, each genetic score was first dichotomized as above or below 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, 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 four groups. First, participants were divided into two groups based on whether their genetic LDL-C score was equal to or below, or above the median value. Next, participants in either of these two groups were then divided into two further groups based on whether their genetic SBP score was equal to or below, or above the median value. This process randomly divided all participants into
one of 4 groups: the reference group, a group with LDL-C genetic scores above the median (resulting in lower LDL-C), a group with SBP genetic scores above the median (resulting in lower SBP), and a group with both LDL-C and SBP genetic scores above 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 randomly divided into four groups based on the quartile values of their LDL-C and SBP scores, respectively, and a 4x4 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 effects of exposure to lower LDL-C, lower SBP, or both on 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's Q test was used when comparing more than two 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 impact of combining incident and prevalent outcomes in the primary analysis.

To estimate the association of combined exposure to both 38.67 mg/dl (1 mmol/L) lower LDL-C and 10 mmHg 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 4x4 factorial analysis by the differences in LDL-C and SBP for each group as compared to 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 enrolled in the CARDIoGRAMplusC4D 1000 Genomes-based meta-analysis of genome-wide association studies. The association between a 38.67 mg/dl (1 mmol/L) lower LDL-C and a 10 mmHg lower SBP was estimated by regressing the log-odds for coronary heart disease for each variant measured in CARDIoGRAMplusC4D 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 MR Egger analysis.

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. 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, one or more of the variants included in the LDL-C or SBP genetic scores, one 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], 54.1% were females, and 24,980 experienced a first major coronary event. There were no significant differences in any non-lipid, 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 1).

INDEPENDENT ASSOCIATIONS OF LDL-C AND SBP

In the entire study sample, participants with LDL-C genetic scores above 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<0.001), as compared to participants with LDL-C scores equal to or below the median. This scaled to an OR of 0.46 (95%CI: 0.43-0.48) per 38.67 (1 mmol/L) lower LDL-C. The magnitude of this association was very similar among participants randomly divided into increasing quartiles of the SBP genetic score (p for heterogeneity = 0.81) (Figure 2A).

Similarly, in the entire study sample, participants with SBP genetic scores above the median had 2.9 mmHg lower SBP and an OR of 0.83 for major coronary events (95%CI: 0.81-0.86; p<0.001), as compared to participants with SBP scores equal to or below the median. This scaled to an OR of 0.55 (95%CI: 0.52-0.59) per 10 mmHg lower SBP. The magnitude of this association was very similar among participants randomly 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=0.92). 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 2x2 factorial analysis, as compared to the reference group, participants in the group with LDL-C scores above the median had 14.7 mg/dL lower LDL-C and an OR of 0.73 (95%CI:0.70-0.75, p<0.001) for major coronary events; and participants with SBP scores above the median had 2.9 mmHg lower SBP and an OR of 0.82 (95%CI:0.79-0.85, p<0.001) for MCE. Participants in the group with both LDL-C and SBP scores above the median had both 13.9 mg/dL lower LDL-C and 3.1 mmHg lower SBP and an OR of 0.61 (95%CI:0.59-0.64, p<0.001) for MCE. When scaled, combined exposure to 1 mmol/L lower LDL-C and 10 mmHg lower SBP was associated with an OR of 0.22 (95%CI:0.21-0.24) for major coronary events (Figure 3). The magnitude of the association in the combined exposure group was approximately equivalent to the log-additive associations with the risk of MCE in the groups with lower LDL-C and lower SBP, respectively (0.73*0.82=0.60).

The association between combined exposure to both lower LDL-C and lower SBP was similar for multiple different composite cardiovascular outcomes, and for the individual components of the composite outcomes including cardiovascular death (Figure 4). Combined exposure to 1 mmol/L lower LDL-C and 10 mmHg lower SBP was associated with an OR of 0.32 (95%CI:0.25-0.40, p<0.001) 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 similar among men and women, and among participants with and without diabetes (all p values for interaction > 0.05) (Figure 4). However, this association appeared to be attenuated among current smokers as compared to former and never smokers (p for interaction <0.001).

**ASSESSMENT OF DOSE-RESPONSE**

In a 4x4 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 5). In a meta-regression analysis of the associations between differences in LDL-C and SBP and the risk of MCE in each of these 16 groups, combined exposure to 1 mmol/L lower and 10 mmHg lower SBP was associated with an OR of 0.22 for major coronary events (95%CI: 0.17-0.26, p<0.001), which is very similar to the scaled odds ratios presented above (eTable 4).

**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). Furthermore, in analyses using generalized linear models to estimate relative risks using log-binomial regression and a log link function, the relative risk associated with lifetime exposure to 1 mmol/L lower LDL-C and 10 mmHg lower SBP was very similar to the odds ratio estimated using both logistic regression or a logit-binomial regression (RR: 0.24, 95%CI: 0.19-0.29, p<0.001). Finally, because the associations of LDL-C with cardiovascular disease may be mediated by changes in the concentration of circulating LDL particles as measured by apoB, rather than the concentration of cholesterol carried by those particles as measured by plasma LDL-C, all analyses were repeated using directly measured changes in apoB rather than changes in LDL-C.24 In these analyses, combined exposure to 30 mg/dL lower apoB and 10 mmHg lower SBP
was associated with an OR of 0.20 for major cardiovascular events (95%CI: 0.18-0.21, p<0.001) (eTable 6).

EXTERNAL REPLICATION

Among 60,801 CAD cases and 123,504 controls in the CARDioGRAMplusC4D consortium studies, a 38.67 mg/dl (1 mmol/L) lower LDL-C was associated with an OR of 0.48 (95%CI: 0.43-0.54, p<0.001) for coronary artery disease and a 10 mmHg lower SBP was associated with an OR of 0.57 (95%CI: 0.50-0.65, p<0.001). 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=0.52) (eTable 7).


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 increasing combination of lower LDL-C and 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 confirm 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.25,26,27 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 helps 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 epidemiologic studies, Mendelian randomization studies and randomized controlled 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.\textsuperscript{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 the 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 epidemiologic studies and randomized trials.\textsuperscript{5,8,9,10} 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.\textsuperscript{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 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 SBP and lower levels of LDL-C 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.
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Dr Ference had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Reference group (both genetic scores ≤ median)</th>
<th>Group with genetically lower SBP (SBP genetic score &gt; median; LDL-C genetic score ≤ median)</th>
<th>Group with genetically lower LDL-C (LDL-C genetic score &gt; median; SBP genetic score ≤ median)</th>
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</tr>
<tr>
<td>Women, No. (%)</td>
<td>61,295 (54.1)</td>
<td>60,437 (54.4)</td>
<td>59,202 (54.3)</td>
<td>57,091 (54.1)</td>
</tr>
<tr>
<td>Men, No. (%)</td>
<td>52,005 (45.9)</td>
<td>50,660 (45.6)</td>
<td>49,825 (45.7)</td>
<td>48,437 (45.9)</td>
</tr>
<tr>
<td>Height, cm (SD)</td>
<td>168.6 (9.2)</td>
<td>168.6 (9.2)</td>
<td>168.7 (9.3)</td>
<td>168.8 (9.3)</td>
</tr>
<tr>
<td>Weight, kg (SD)</td>
<td>77.9 (15.8)</td>
<td>78.1 (15.9)</td>
<td>78.3 (15.9)</td>
<td>78.5 (16.0)</td>
</tr>
<tr>
<td>Body mass index (SD)</td>
<td>27.3 (4.7)</td>
<td>27.4 (4.7)</td>
<td>27.4 (4.8)</td>
<td>27.5 (4.8)</td>
</tr>
<tr>
<td>Hip, cm (SD)</td>
<td>103.2 (9.1)</td>
<td>103.4 (9.1)</td>
<td>103.4 (9.2)</td>
<td>103.6 (9.3)</td>
</tr>
<tr>
<td>Waist, cm (SD)</td>
<td>90.0 (13.4)</td>
<td>90.2 (13.5)</td>
<td>90.3 (13.5)</td>
<td>90.5 (13.5)</td>
</tr>
<tr>
<td>Waist-to-hip ratio, (SD)</td>
<td>0.87 (0.1)</td>
<td>0.87 (0.1)</td>
<td>0.87 (0.1)</td>
<td>0.87 (0.1)</td>
</tr>
<tr>
<td>Current smoker, No. (%)</td>
<td>8,044 (7.1)</td>
<td>7,888 (7.1)</td>
<td>8,068 (7.4)</td>
<td>7,492 (7.1)</td>
</tr>
<tr>
<td>Former smoker, No. (%)</td>
<td>27,192 (24.0)</td>
<td>26,885 (24.2)</td>
<td>26,385 (24.2)</td>
<td>25,432 (24.1)</td>
</tr>
<tr>
<td>Ever smoker, No. (%)</td>
<td>35,236 (31.1)</td>
<td>34,773 (31.3)</td>
<td>34,453 (31.7)</td>
<td>32,925 (31.2)</td>
</tr>
<tr>
<td>Creatinine, µmol/L (SD)</td>
<td>71.9 (17.8)</td>
<td>72.0 (18.8)</td>
<td>72.5 (17.4)</td>
<td>72.6 (17.6)</td>
</tr>
<tr>
<td>Cystatin-C, mg/L (SD)</td>
<td>0.91 (0.2)</td>
<td>0.91 (0.2)</td>
<td>0.91 (0.2)</td>
<td>0.91 (0.2)</td>
</tr>
<tr>
<td>LIPIDS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C, mg/dL (SD)</td>
<td>144.5 (34.4)</td>
<td>146.3 (34.5)</td>
<td>129.9 (30.9)</td>
<td>130.6 (30.8)</td>
</tr>
<tr>
<td>apoB, mg/dL (SD)</td>
<td>108.9 (23.9)</td>
<td>110.1 (24.0)</td>
<td>96.8 (21.9)</td>
<td>97.3 (21.9)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL (SD)</td>
<td>228.3 (45.5)</td>
<td>230.5 (45.5)</td>
<td>211.5 (41.0)</td>
<td>212.4 (40.9)</td>
</tr>
<tr>
<td>HDL-C, mg/dL, (SD)</td>
<td>55.8 (14.6)</td>
<td>55.8 (14.5)</td>
<td>56.6 (15.1)</td>
<td>56.6 (15.0)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL (IQR)</td>
<td>157.2 (94.6-193.0)</td>
<td>158.8 (95.2-195.3)</td>
<td>151.8 (91.2-186.3)</td>
<td>152.7 (91.5-188.0)</td>
</tr>
<tr>
<td>Non-HDL-C, mg/dL, (SD)</td>
<td>172.5 (42.4)</td>
<td>174.7 (42.6)</td>
<td>154.9 (38.6)</td>
<td>155.8 (38.6)</td>
</tr>
<tr>
<td>BLOOD PRESSURE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mmHg (SD)</td>
<td>139.2 (18.7)</td>
<td>136.3 (18.4)</td>
<td>139.2 (18.7)</td>
<td>136.2 (18.4)</td>
</tr>
<tr>
<td>DBP, mmHg (SD)</td>
<td>82.6 (10.1)</td>
<td>81.2 (10.0)</td>
<td>82.8 (10.2)</td>
<td>81.4 (10.1)</td>
</tr>
<tr>
<td>CURRENT TREATMENT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current lipid lowering therapy, No. (%)</td>
<td>24,532 (21.7)</td>
<td>21,921 (19.7)</td>
<td>15,796 (14.5)</td>
<td>13,799 (13.1)</td>
</tr>
<tr>
<td>Current BP lowering therapy, No. (%)</td>
<td>27,006 (23.8)</td>
<td>19,949 (18.0)</td>
<td>25,289 (23.2)</td>
<td>18,294 (17.3)</td>
</tr>
<tr>
<td>Both Current lipid and BP lowering therapy, No. (%)</td>
<td>15,950 (14.1)</td>
<td>12,296 (11.1)</td>
<td>11,304 (10.4)</td>
<td>8,711 (8.3)</td>
</tr>
</tbody>
</table>
Table 1 Legend: The baseline characteristics for each group of participants is given in the table.

There were no differences in non-lipid or non-blood pressure related baseline characteristics thus demonstrating that partition into each group was consistent with being random. Baseline characteristics are given as means or proportion (%), except plasma triglycerides which are given as median values. SD is standard deviation, IQR is interquartile range.
**Figure 1:** Randomization scheme and baseline characteristics

**Figure 1 Legend:** All participants in the study were first randomly divided into two groups based on whether their LDL-C genetic score was equal to or below, or above the median. Participants in each of these two groups were then further randomized into two more groups based on whether their SBP genetic score was equal to or below, or above the median. This process produced four groups: a reference group, a group randomized to lower LDL-C, a group randomized to lower SBP, and a group randomized to both lower LDL-C and lower SBP.
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 the risk of major coronary events stratified by quartiles of the SBP score

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

Figure 2 Legend: In part A of the Figure, participants were randomly divided into four groups based on the quartile value of their SBP genetic score. Among participants within each of these SBP score quartiles, participants were randomly divided into two groups based on whether their LDL-C genetic score was equal to or below, or above the median; and the differences in directly measured LDL-C and number of major coronary events were compared between these two groups (within each quartile of the SBP genetic score separately). The results are presented both as the associations with the risk of major coronary events for the observed differences in LDL-C between the groups, and for the risk of major coronary events scaled for 38.67 mg/dl (1 mmol/L) lower LDL-C. In part B of the Figure, participants were randomly divided into four groups based on the quartile value of their LDL-C genetic score. Among participants within each of these LDL-C score quartiles, participants were randomly divided into two groups based on whether their SBP genetic score was equal to or below, or above the median; and the differences in measured SBP and number of major coronary events were compared between these two groups (within each quartile of the LDL-C genetic score separately). The results are presented both for the associations with risk of major coronary events for the observed difference in SBP between the groups, and for the risk with major coronary events scaled for a 10 mmHg lower SBP. The boxes represent estimated odds ratios and the bars represent 95% confidence intervals.
**Figure 3:** Associations of exposure to lower LDL-C, lower SBP or both with risk of major coronary events

**Figure 3 Legend:** The number of participants randomly partitioned into each group, and the number of major coronary events that occurred in each group are listed in the Figure. The $\Delta$ LDL-C represents the difference in the mean directly measured plasma LDL-C level for each group relative to the reference group; and the $\Delta$ SBP represents the difference in the mean measured SBP level for each group relative to the reference group. The left side of the Figure gives the observed odds ratios for major coronary events as compared to the reference group; and the right side of the Figure gives the odds ratios scaled for a difference of 38.67 mg/dl (1 mmol/L) lower LDL-C (for the group allocated to lower LDL-C), 10 mmHg lower SBP (for the group allocated to lower SBP), and combined difference of both 38.67 mg/dl (1 mmol/L) lower LDL-C and 10 mmHg lower SBP (for the group allocated to both lower LDL-C and lower SBP) as compared to the reference group. The boxes represent estimated odds ratios and the bars represent 95% confidence intervals.
**Figure 4:** Association of combined exposure to both lower LDL-C and lower SBP on various cardiovascular outcomes and within subgroups

A. Association of combined exposure to lower LDL-C and lower SBP with the risk of various cardiovascular outcomes

b. Association of combined exposure to lower LDL-C and lower SBP with the risk of major coronary events within subgroups

**Figure 4 Legend:** Part A of the Figure reports the association of combined exposure to 13.9 mg/dl lower LDL-C and 3.1 mmHg lower SBP on the risk of various cardiovascular outcomes derived by comparing the group with both LDL-C and SBP genetic scores above the median with the reference group. The right side of the Figure 3A reports the same associations scaled for the combined exposure to 38.67 mg/dl (1 mmol/L) lower LDL-C and 10 mmHg lower SBP. Part B of the Figure reports the associations between combined exposure to 13.9 mg/dl lower LDL-C and 3.1 mmHg lower SBP on the risk of major coronary events as compared to the reference group, among various subgroups. The right side of Figure 3B reports the same associations scaled for 38.67 mg/dl (1 mmol/L) lower LDL-C and 10 mmHg lower SBP within each subgroup. There were no significant differences in the associations of combined exposure to lower LDL-C and lower SBP and the risk of major coronary events in any subgroups, except for an attenuation of the odds ratio among current smokers as compared to former and never smokers (p for interaction < 0.001). A Z test was used to assess for interactions between pairs of subgroups, and Cochran’s Q test was used when comparing more than two subgroups. The boxes represent estimated odds ratios and the bars represent 95% confidence intervals.
**Figure 5:** Dose-dependent associations and meta-regression analysis for combinations of increasingly lower LDL-C and lower SBP on the risk of major coronary events

**Figure 5 Legend:** For this analysis, all participants in the study were first randomly divided into four (4) groups based on quartile value of their LDL-C genetic score. Participants in each of these four groups were then further randomized into four additional groups based on the quartile value of their SBP genetic score. This process produced sixteen (16) groups with exposure to increasingly greater combinations of lower LDL-C and lower SBP as compared to 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 in the Figure and expressed as a proportional risk reduction (calculated as [1-odds ratio] multiplied by 100). The groups are ordered on the X-axis by the sum of their LDL-C and SBP genetic score quartile values. The differences in directly measured LDL-C and SBP for each group compared to the reference group is reported next to the corresponding box. The dashed line is the multivariable meta-regression line derived by regressing the association with major coronary events for each of the 15 groups in the 4x4 factorial analysis by the differences in LDL-C and SBP for each group as compared to the reference group. The boxes represent estimated odds ratios and the bars represent 95% confidence intervals. The tabular data for these analyses is presented in the Supplement.