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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

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Objectives The purpose of this study was to estimate the effect of long-term exposure to lower plasma low-density lipoprotein cholesterol (LDL-C) on the risk of coronary heart disease (CHD).

Background LDL-C is causally related to the risk of CHD. However, the association between long-term exposure to lower LDL-C beginning early in life and the risk of CHD has not been reliably quantified.

Methods We conducted a series of meta-analyses to estimate the effect of long-term exposure to lower LDL-C on the risk of CHD mediated by 9 polymorphisms in 6 different genes. We then combined these Mendelian randomization studies in a meta-analysis to obtain a more precise estimate of the effect of long-term exposure to lower LDL-C and compared it with the clinical benefit associated with the same magnitude of LDL-C reduction during treatment with a statin.

Results All 9 polymorphisms were associated with a highly consistent reduction in the risk of CHD per unit lower LDL-C, with no evidence of heterogeneity of effect ($I^2 = 0.0\%$). In a meta-analysis combining nonoverlapping data from 312,321 participants, naturally random allocation to long-term exposure to lower LDL-C was associated with a 54.5% (95% confidence interval: 48.8% to 59.5%) reduction in the risk of CHD for each mmol/l (38.7 mg/dl) lower LDL-C. This represents a 3-fold greater reduction in the risk of CHD per unit lower LDL-C than that observed during treatment with a statin started later in life ($p = 8.43 \times 10^{-19}$).

Conclusions Prolonged exposure to lower LDL-C beginning early in life is associated with a substantially greater reduction in the risk of CHD than the current practice of lowering LDL-C beginning later in life. (J Am Coll Cardiol 2012;60: 2631–9) © 2012 by the American College of Cardiology Foundation

The causal relationship between low-density lipoprotein cholesterol (LDL-C) and coronary atherosclerosis is well established. Multiple randomized trials have demonstrated that lowering LDL-C by treatment with a statin significantly reduces the risk of major coronary events (1). However, persons being treated with a statin continue to experience a substantial residual risk of events. Because coronary atherosclerosis is a chronic, progressive disease that begins early in life and develops slowly over several decades before becoming clinically manifest, it is intuitively appealing to hypothesize that lowering LDL-C beginning earlier in life may prevent or substantially delay the progression of coronary atherosclerosis and thereby significantly improve the clinical benefit of therapies that lower LDL-C (2–4).

See page 2640

Although intuitive, the clinical benefit of lowering LDL-C beginning early in life is unknown. Ideally, the effect of long-term exposure to lower LDL-C on the risk of coronary heart disease (CHD) would be evaluated in a randomized, controlled trial. Unfortunately, the cost and logistical complex-

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Abbreviations and Acronyms

CHD = coronary heart disease
HDL-C = high-density lipoprotein cholesterol
LDL-C = low-density lipoprotein cholesterol
MI = myocardial infarction
OR = odds ratio
SNP = single-nucleotide polymorphism

ity of following a very large number of young asymptomatic people over several decades within the context of a clinical trial may be impractical. However, in the absence of a randomized trial, it may still be possible to estimate the effect of random allocation to long-term exposure to lower LDL-C on the risk of CHD by appealing to the principle of Mendelian randomization.

Multiple single-nucleotide polymorphisms (SNPs) are associated with small differences in LDL-C (5). Each of these polymorphisms is allocated randomly at the time of conception in a process sometimes referred to as Mendelian randomization (6). Inheriting an allele associated with lower LDL-C is therefore analogous to being randomly allocated to a therapy that lowers LDL-C beginning at birth, whereas inheriting the other allele is analogous to being randomly allocated to usual care. If certain assumptions are satisfied (6), then the association between such a polymorphism and the risk of CHD should provide an unconfounded estimate of the effect of lifelong exposure to lower LDL-C on the risk of CHD in a manner analogous to a long-term randomized trial comparing a therapy that lowers LDL-C beginning early in life with usual care. For example, persons who inherit a 46L allele of the *PCSK9* gene have been reported to have both lower lifelong exposure to LDL-C and a much greater than expected reduced risk of CHD (7). Subsequent studies of this and other polymorphisms have reported generally similar, although less dramatic, results (8,9). However, the magnitude and consistency of the association between long-term exposure to lower LDL-C and the risk of CHD mediated by a variety of different polymorphism has not been reliably quantified. A reliable estimate of the association between long-term exposure to lower LDL-C and the risk of CHD would provide important information about whether the magnitude of this effect is sufficiently compelling to influence public health policy, professional guidelines, and individual treatment decisions. Therefore, we conducted a series of meta-analyses to estimate the association between lifelong exposure to lower LDL-C and the risk of CHD mediated by 9 SNPs in 6 different genes. We then meta-analyzed the results of these Mendelian randomization studies to reliably quantify the effect of long-term exposure to lower LDL-C on the risk of CHD and compared it with the effect of lowering LDL-C during treatment with a statin started later in life.

Methods

Design and rationale. Our study consisted of several interrelated components. First, we selected, a priori, 9 SNPs located in 6 different genes (Fig. 1). Each of these polymorphisms has been previously reported to be associated with LDL-C, but not to be reliably associated with other lipoproteins or nonlipid risk factors for coronary disease (5). We selected these SNPs specifically to minimize the poten-

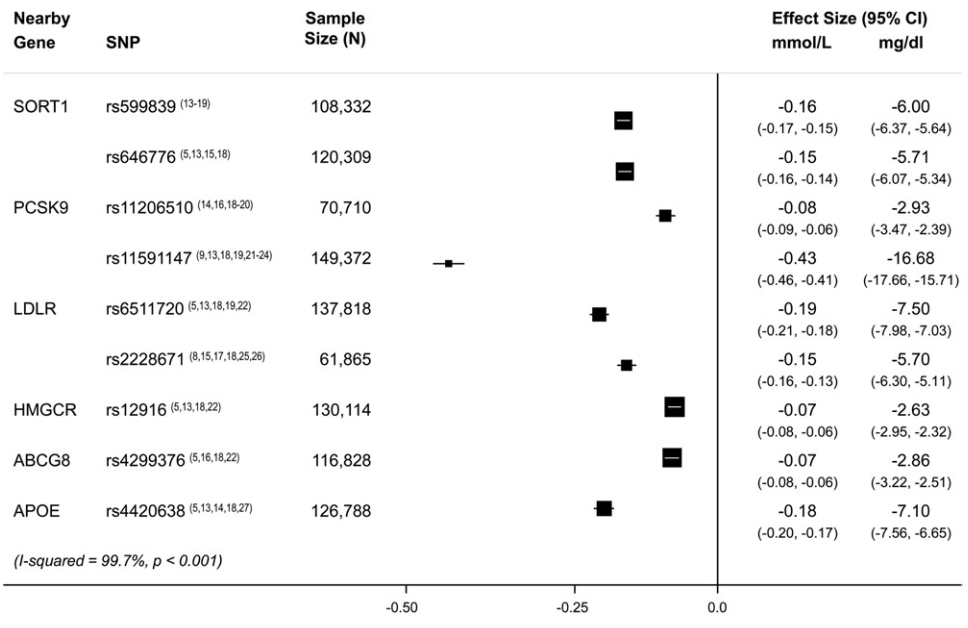

Figure 1 Association Between Exposure Alleles and LDL-C

Boxes represent the summary point estimate of effect for the association between each exposure allele and low-density lipoprotein cholesterol (LDL-C) measured in mmol/l. **Bars** represent 95% confidence interval (CI). SNP = single-nucleotide polymorphism.

tial for confounding by pleiotropy. For each SNP, we defined the exposure allele as the allele previously associated with lower LDL-C. Second, we conducted a series of meta-analyses to quantify the association between the exposure allele for each SNP and circulating levels of LDL-C. Third, we conducted a series of meta-analyses to quantify the association between the exposure allele for each SNP and the risk of CHD. Fourth, we standardized the association between the exposure allele for each SNP and the risk of CHD per unit lower LDL-C to directly compare the effect of long-term exposure to lower LDL-C on the risk of CHD mediated by a variety of different mechanisms. Fifth, we combined the effect estimates for each exposure allele on the risk of CHD adjusted per unit lower LDL-C in a meta-analysis to obtain a more precise overall summary estimate of the effect of long-term exposure to lower LDL-C on the risk of CHD. Sixth, we compared the risk reduction associated with long-term exposure to lower LDL-C estimated from the combined meta-analysis of the genetic studies with the risk reduction associated with the same magnitude of LDL-C reduction observed in a meta-analysis of statin trials.

Contributing studies and data. We searched PubMed, EMBASE, and Index of Science, as well as the supplementary materials, online data repositories, and references of selected articles to identify all published and unpublished data on the association between circulating levels of LDL-C and each of the 9 SNPs included in our study. We then conducted a similar search to identify all published and unpublished data on the association between the risk of CHD and each of the 9 SNPs. The primary outcome was CHD, defined as a composite of cardiovascular death, nonfatal myocardial infarction, or coronary revascularization as adopted by the CARDIoGRAM consortium (10), or where this convention was not followed (or could not be extracted from the available data), we used the individual study-specific primary outcome. To estimate the clinical benefit of lowering LDL-C beginning later in life, we relied on data from a meta-analysis of statin trials conducted by the Cholesterol Treatment Trialists' Collaboration (1).

Statistical analysis. All meta-analyses were performed using inverse-variance weighted fixed-effect models (sensitivity analyses were performed using random-effects models). For each SNP, we standardized the estimate of the association between the exposure allele and the risk of CHD per unit lower LDL-C by dividing the natural log of the summary odds ratio (OR) and its SE by the effect estimate for the association between that allele and LDL-C (using the usual ratio of effect estimates method). We then combined the adjusted summary OR for each SNP in a meta-analysis to more precisely estimate the effect of long-term exposure to lower LDL-C. Each SNP was prioritized for inclusion in this meta-analysis by the inverse of the SE of its summary point estimate of effect, adjusted per unit lower LDL-C. Nonoverlapping data from studies evaluating each SNP were successively added to the meta-analysis in order of the inverse SE ranking of the SNPs. We performed multiple sensitivity analyses by including nonoverlapping data from multiple different combinations of

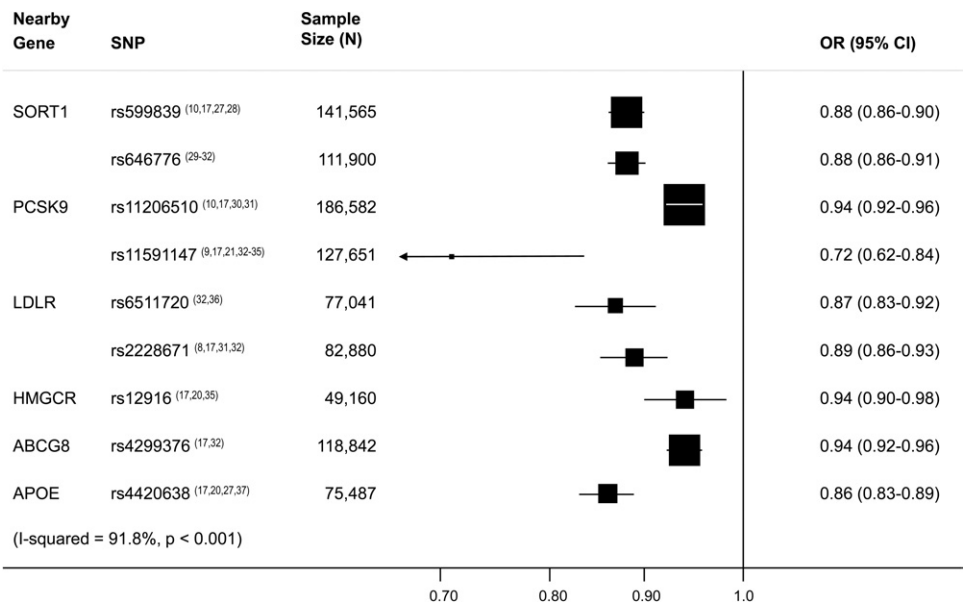

Figure 2 Association Between Exposure Alleles and Risk of CHD

Boxes represent the summary point estimate of odds ratio (OR) for the association between each exposure allele and risk of coronary heart disease (CHD). **Bars** represent 95% CI. (Unlike the other SNPs, the APOE-C1-C2 SNP rs4420638 is associated with LDL-C, HDL-C, triglycerides, and C-reactive protein. We included this SNP specifically to assess for heterogeneity of effect on the risk of CHD.) Abbreviations as in Figure 1.

SNPs in the meta-analysis. To further investigate the effect of long-term exposure to lower LDL-C on the risk of CHD, we also constructed a weighted LDL-C genetic score. As described elsewhere, regression on the risk score can be reconstructed from the regressions of the individual SNPs without access to individual level data (11). Further details of this analysis are provided in Online Table 1.

Next, we standardized the results of each of the statin trials per unit reduction in LDL-C using the same methods as described for the genetic studies. We then compared the risk reduction associated with long-term exposure to lower LDL-C with the risk reduction associated with the same magnitude of LDL-C reduction during treatment with a statin using a z-test. Heterogeneity was assessed using Cochran's Q, and the I^2 metric (12). To minimize the potential for population stratification bias, we restricted all analyses to persons of European ancestry, and we used genomic-control or principal component–adjusted measures of effect where provided. Care was taken to avoid double-counting data from studies that were included in >1 report. All statistical tests used a 2-sided $\alpha < 0.05$ as the threshold for statistical significance, and all analyses were performed using STATA (version 10.1, StataCorp, College Station, Texas).

Results

In separate meta-analyses involving sample sizes of up to 149,000 participants, the exposure allele for each SNP was associated with a lower LDL-C level that varied significantly between 2.6 and 16.7 mg/dl among the included polymorphism (Fig. 1) (5,8,13–27). Detailed results of these 9 meta-analyses are presented in Online Figures 1a to 1i. In separate meta-analyses involving sample sizes of up to 186,000 participants, the exposure allele for each SNP was also associated with a correspondingly lower risk of CHD (Fig. 2) (8–10,17,20,21,27–37). Detailed results of these 9 meta-analyses are presented in Online Figures 2a to 2i. There was a substantial amount of heterogeneity of effect on the risk of CHD among the included polymorphisms. The exposure alleles of the included SNPs were associated with a reduction in the risk CHD that varied significantly between 6% and 28% ($I^2 = 91.8\%$).

In a plot of the proportional risk reduction against the magnitude of lower LDL-C associated with each exposure allele, the relationship between long-term exposure to lower LDL-C and the risk of CHD was approximately log-linear (Fig. 3). After standardizing the effect of each exposure allele per unit lower LDL-C, each SNP was associated with a highly consistent effect on the risk of CHD (Table 1). Indeed, after adjusting the effect of each SNP per unit lower LDL-C, there was no evidence of any heterogeneity of effect on the risk CHD among the included SNPs, with the I^2 metric being reduced from 91.8% to 0.0% (Fig. 4, Online Fig. 3). In a meta-analysis of nonoverlapping data from 312,321 participants involving multiple different SNPs, each mmol/l (38.7 mg/dl) lower long-term exposure to LDL-C was associated with a 54.5% (OR: 0.46, 95% CI: 0.41 to 0.51; $p = 2.15 \times 10^{-45}$) reduction in the risk of CHD (Fig. 5). Detailed results of this meta-analysis are

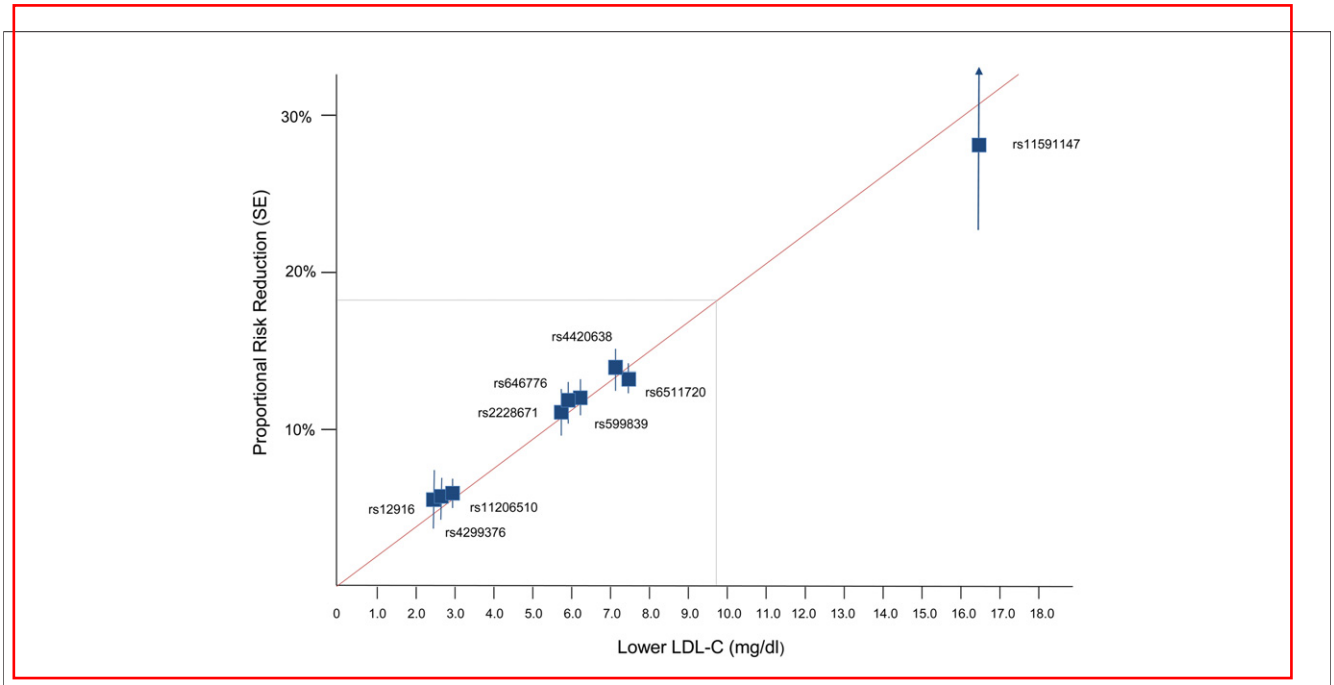

Figure 3 Log-Linear Effect of Each Unit Long-Term Exposure to Lower LDL-C on Risk of CHD

Boxes represent the proportional risk reduction (1 − OR) of CHD for each exposure allele plotted against the absolute magnitude of lower LDL-C associated with that allele (measured in mg/dl). **Vertical lines** represent 1 SE above and below the point estimate of proportional risk reduction. SNPs are plotted in order of increasing absolute magnitude of associations with lower LDL-C. The **line** (which is forced to pass through the origin) represents the increase in proportional risk reduction of CHD per unit lower long-term exposure to LDL-C. Abbreviations as in Figure 2.

Table 1 Associations of Exposure Alleles With CHD Adjusted per Unit of Change in LDL-C

SNP	Exposure Allele Frequency	LDL Effect, mmol/l (mg/dl)	Sample Size	OR_{CHD} (95% CI)	OR_{CHD} (95% CI) Adjusted per Unit Lower LDL: 0.125 mmol/l (4.83 mg/dl)	0.25 mmol/l (9.67 mg/dl)	0.50 mmol/l (19.33 mg/dl)	1.00 mmol/l (38.67 mg/dl)
rs599839	0.22	−0.16 (−6.00)	141,565	0.88 (0.86–0.90)	0.90 (0.89–0.92)	0.82 (0.79–0.85)	0.66 (0.62–0.72)	0.44 (0.38–0.52)
rs646776	0.21	−0.15 (−5.71)	111,900	0.88 (0.86–0.91)	0.90 (0.88–0.93)	0.81 (0.77–0.86)	0.66 (0.59–0.74)	0.43 (0.35–0.54)
rs11206510	0.19	−0.08 (−2.93)	186,582	0.94 (0.92–0.96)	0.90 (0.87–0.93)	0.81 (0.76–0.86)	0.66 (0.58–0.74)	0.43 (0.34–0.54)
rs11591147	0.02	−0.43 (−16.68)	127,651	0.72 (0.62–0.84)	0.91 (0.87–0.95)	0.83 (0.76–0.91)	0.69 (0.58–0.82)	0.47 (0.33–0.67)
rs6511720	0.11	−0.19 (−7.50)	77,041	0.87 (0.83–0.92)	0.92 (0.89–0.95)	0.84 (0.78–0.90)	0.70 (0.61–0.81)	0.49 (0.38–0.65)
rs2228671	0.12	−0.15 (−5.70)	82,880	0.89 (0.86–0.93)	0.91 (0.88–0.94)	0.83 (0.77–0.89)	0.69 (0.60–0.79)	0.47 (0.36–0.62)
rs12916	0.61	−0.07 (−2.63)	49,160	0.94 (0.90–0.98)	0.90 (0.83–0.97)	0.80 (0.69–0.93)	0.64 (0.47–0.87)	0.41 (0.22–0.76)
rs4299376	0.70	−0.07 (−2.86)	118,842	0.94 (0.92–0.96)	0.90 (0.86–0.94)	0.81 (0.75–0.88)	0.65 (0.56–0.77)	0.43 (0.31–0.59)
rs4420638	0.83	−0.18 (−7.10)	75,487	0.86 (0.83–0.89)	0.90 (0.88–0.93)	0.82 (0.78–0.86)	0.67 (0.60–0.74)	0.44 (0.36–0.54)

Point estimates of effect adjusted per unit lower LDL-C obtained by dividing the natural logarithm of the unadjusted OR (and its SE) for each exposure allele by the LDL-C effect size associated with that exposure allele measured in reference units (0.125, 0.25, 0.50, and 1.0 mmol/l, respectively), using the ratio of effect estimates method.

CHD = coronary heart disease; CI = confidence interval; LDL-C = low-density lipoprotein cholesterol; SNP = single-nucleotide polymorphism; OR = odds ratio.

presented in Online Figure 4. In multiple sensitivity analyses, this result did not change appreciably regardless of which SNPs were included in the meta-analysis of nonoverlapping data (Online Fig. 5). Furthermore, in a common sample of up to 83,873 participants, a weighted LDL-C genetic score composed of 6 SNPs (1 at each gene) was associated with a similar 53.2% reduction in the risk of CHD (OR: 0.47, 95% CI: 0.41 to 0.53; $p = 2.42 \times 10^{-32}$) for each mmol/l lower LDL-C (Online Table 1).

In a meta-analysis of 169,138 participants enrolled in 26 statin trials, treatment with a statin was associated with a 24% reduction in the risk of CHD (OR: 0.76, 95% CI: 0.74 to 0.78) per mmol/l (38.7 mg/dl) reduction in LDL-C (Online Table 2). Compared to treatment with a statin started later in life, prolonged exposure to lower LDL-C beginning early in life was associated with a 3-fold greater reduction in the risk of CHD (on the log scale) for each unit lower LDL-C (Fig. 5). This difference in risk reduction per unit lower LDL was highly numerically stable ($p = 8.4 \times 10^{-19}$).

Discussion

We sought to reliably quantify the effect of long-term exposure to lower LDL-C beginning early in life on the risk of CHD. To do this, we conducted a series of meta-analyses

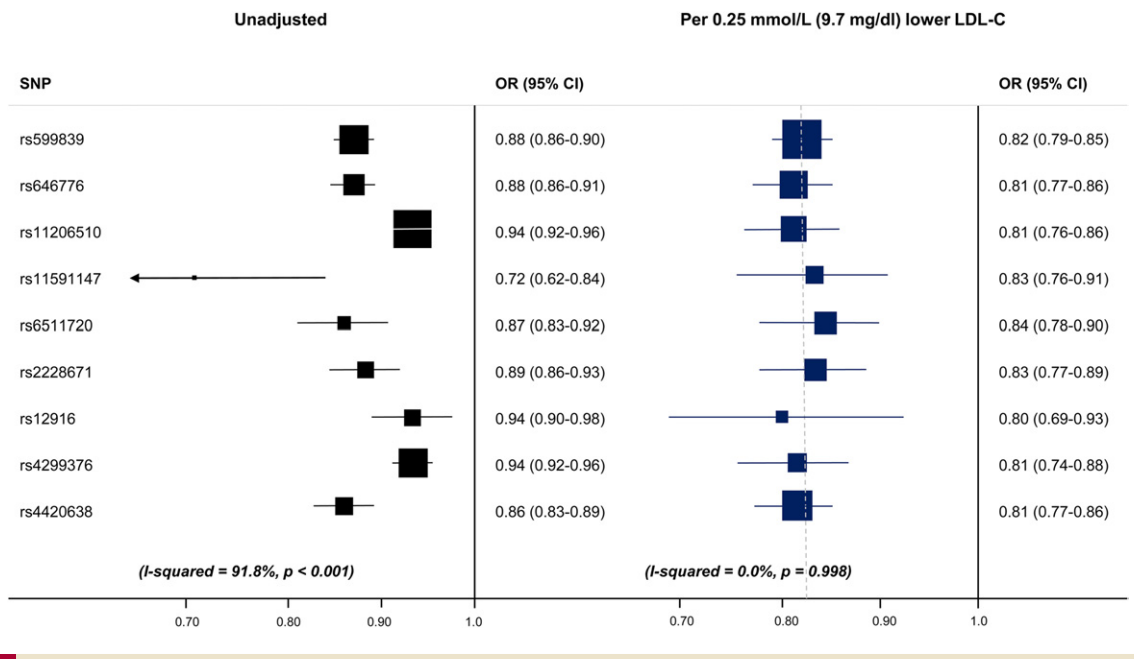

Figure 4 Association of Exposure Alleles With Risk of CHD per Unit Lower LDL-C

Unadjusted OR for the association between each exposure allele and the risk of CHD as described in Figure 2, and after adjustment per 0.125 mmol/l lower LDL-C. Abbreviations as in Figures 1 and 2.

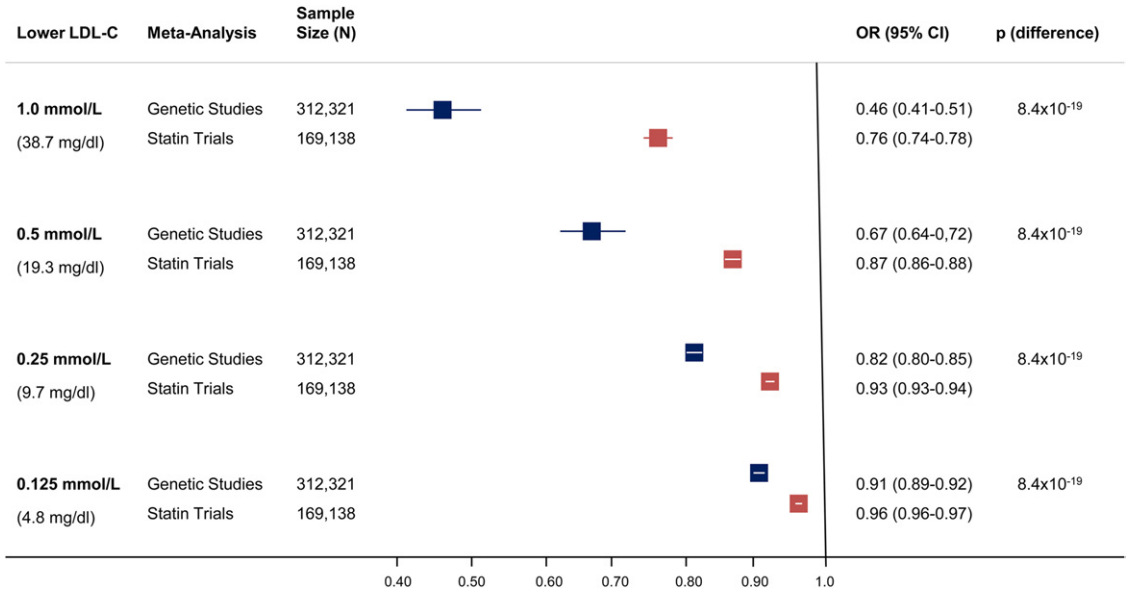

Figure 5 **Comparative CHD Risk Reduction of Earlier and Later LDL-C Lowering**

Boxes represent the summary point estimate of the OR for the association between each unit lower LDL-C and the risk of CHD, for both meta-analyses combining data from Mendelian randomization studies adjusted per unit lower LDL-C and meta-analyses of statin trials adjusted per unit lower LDL-C. Bars represent 95% CI. See Online Appendix for details. Abbreviations as in Figures 1 and 2

to estimate the association between lifelong exposure to lower LDL-C and the risk of CHD mediated by 9 SNPs in 6 different genes. For each SNP, we used the allele associated with lower LDL-C as a proxy for a treatment that lowers LDL-C beginning at birth to estimate the effect of lowering LDL-C beginning early in life. Because each SNP is allocated randomly at the time of conception, the results of these Mendelian randomization studies should be unconfounded by other lipid and nonlipid risk factors for CHD, and therefore they can be thought of as approximately analogous to a series of natural randomized trials evaluating the effect of long-term exposure to lower LDL on the risk of CHD. We then combined these Mendelian randomization studies in a meta-analysis to obtain a more precise estimate of the effect of long-term exposure to lower LDL-C on the risk of CHD and compared it with the effect of lowering LDL-C during treatment with a statin.

In a meta-analysis involving >312,00 participants, we found that naturally random allocation to long-term exposure to lower LDL-C beginning early in life was associated with a 3-fold greater reduction in the risk of CHD for each unit lower LDL-C than that observed during treatment with a statin started later in life. For example, long-term exposure to 1 mmol/l (38.7 mg/dl) lower LDL-C was associated with a 55% reduction in the risk of CHD (OR: 0.45). By contrast, treatment with a statin started later in life would require a 3-fold greater reduction in LDL-C of 3 mmol/l (116 mg/dl) to achieve this same magnitude of risk reduction (OR: $0.44 = 0.76 \cdot 0.76 \cdot 0.76$).

Furthermore, we found that the association between long-term exposure to lower LDL-C and the risk of CHD was approximately log-linear, just as the association between the magnitude of LDL-C reduction and the clinical benefit of statin therapy is approximately log-linear (38). Therefore, if this log-linear relationship extends beyond the observed range of data in our study, as it does for the association between LDL-C and the risk of CHD in both epidemiological studies (39) and in the statin trials, then prolonged exposure to very low levels of LDL-C beginning early in life could potentially result in dramatic reductions in the risk of CHD. Indeed, the results of our study are consistent with the observation that CHD appears to be rare in societies that maintain very low levels of LDL-C throughout adulthood (40).

The magnitude of the effect of prolonged exposure to lower LDL-C on the risk of CHD observed in our study was also substantially greater than predicted based on the results of observational epidemiological studies. For example, the 55% reduction in the risk of CHD per mmol/l lower long-term exposure to LDL-C observed in our study is more than 2-fold greater (on the log scale) than the 31% (OR: 0.69, 95% CI: 0.65 to 0.74) risk reduction per mmol/l lower non-HDL cholesterol (and directly measured LDL-C) observed in a large meta-analysis (39) of prospective cohort studies (p for difference $= 7.4 \times 10^{-10}$). This finding suggests that genetically mediated changes in LDL-C are likely to be a better reflection of the cumulative effect of lifelong exposure to differences in circulating

LDL-C as compared with measurements made in adulthood, even when those measurements are corrected for regression dilution bias.

Importantly, we evaluated 9 polymorphisms located in 6 different genes, including polymorphisms in the genes that encode for the targets of both statins and monoclonal antibodies directed against PCSK9. Although each of these polymorphisms presumably affects circulating LDL-C levels by a different mechanism, and the per-allele effect of these SNPs on LDL-C levels varied by more than 6-fold; all 9 polymorphisms were associated with a highly consistent reduction in the risk of CHD when measured per unit lower LDL-C. This finding suggests that the effect of long-term exposure to lower LDL-C on the risk of CHD appears to be independent of the mechanism by which LDL-C is lowered. Therefore, the method of lowering LDL-C is likely to be less important than the magnitude and timing of LDL-C reduction. As a result, diet and exercise are probably as effective at reducing the risk of CHD as are statins or other treatments that lower LDL-C when started early in life (and when measured per unit lower LDL-C).

The results of our study support the hypothesis that lowering LDL-C beginning early in life, or approximately equivalently maintaining low levels of LDL-C throughout life, may prevent or substantially delay the development of atherosclerosis. Indeed, our study demonstrates that prolonged exposure to lower LDL-C beginning early in life, before the development of atherosclerosis, is associated with a substantially greater reduction in the risk of CHD than the current practice of lowering LDL-C beginning later in life after atherosclerosis has already developed. This finding may explain much of the residual risk of coronary events experienced by persons being treated with a statin or other lipid-lowering therapy. Lowering LDL-C beginning later in life after the development of atherosclerosis may serve merely to stabilize existing atherosclerotic plaques that can still progress to cause symptoms or disrupt to cause acute coronary syndromes, thus resulting in a high residual risk of events. By contrast, prolonged exposure to lower LDL-C beginning early in life is associated with a substantially greater reduction in the risk of CHD and therefore a substantially lower corresponding residual risk of coronary events.

The results of our study also suggest that lowering LDL-C is likely to be a much more effective strategy for the primary prevention of CHD than is currently recognized. Current estimates of the effectiveness of lowering LDL-C as a strategy for the primary prevention of CHD are based largely on data from the statin trials. However, the mean age at the time of randomization in the statin trials was 63 years (1), which means that persons enrolled in these trials had already been exposed to a lifetime of circulating LDL-C. Our study demonstrates that both the magnitude of exposure to LDL-C and the length of time exposed to LDL-C each have an important effect on the risk of CHD. Therefore, the effectiveness of lowering LDL-C as a strategy for the primary prevention of CHD can potentially be substantially improved by initiating therapies to lower LDL-C beginning much earlier in life than is currently recommended.

It is important to note that our study is not a substitute for a randomized trial. Although our study provides an estimate of the potential risk reduction that can be achieved with long-term exposure to lower LDL-C, it cannot estimate the potential risks of long-term exposure to a lipid-lowering therapy. Only a randomized trial can adequately compare the benefits and risks of long-term exposure to a lipid-lowering therapy.

Until such a long-term trial is conducted, however, the results of our study suggest that an effective primary prevention strategy may be to place greater emphasis on a healthy diet and regular exercise beginning early in life, with the aim of maintaining low levels of LDL-C. For persons who cannot maintain a low level of LDL-C with diet and exercise alone, it may be reasonable to consider adding a treatment to lower LDL-C beginning in early adulthood, before the development of significant atherosclerosis. A primary prevention strategy that encourages maintaining low levels of LDL-C throughout the whole of one's lifetime has the potential to dramatically reduce the risk of CHD. In future, it may be possible to further personalize this strategy by focusing more intensely on persons who inherit 1 or more polymorphisms that increase their vulnerability to LDL-C (41).

Study limitations. Our study has several limitations, including inherent limitations with making causal inferences using the principle of Mendelian randomization (6,42) and the fact that we measured the associations of the included SNPs with LDL-C and CHD, respectively, in different populations. In addition, although our study relies on the principle of Mendelian randomization, our use of summary data did not allow us to perform an instrumental variables analysis.

Recognizing these limitations in our study design, we tested the assumptions of Mendelian randomization by evaluating multiple different polymorphisms and assessing for consistency of effect. We found no evidence of any heterogeneity of effect on the risk of CHD per unit lower LDL-C among any of the polymorphisms included in our study. This lack of heterogeneity of effect strongly suggests that the results of our study are unlikely to be significantly confounded by pleiotropy or linkage disequilibrium because it is unlikely that each of the included polymorphisms are acting through similar pleiotropic effects or have similar linkage disequilibrium patterns.

Indeed, the results of our study appear to have been independently, although indirectly, confirmed in a recent study evaluating the effect of polymorphisms that influence HDL-C (43). In that study, a weighted LDL-C genetic score including 13 polymorphisms associated with LDL-C (only 2 of which overlapped with the polymorphism included in our study) was associated with 2.13-fold increased risk of MI (95% CI: 1.69 to 2.69) for each SD (34.1 mg/dl)

increase in long-term exposure to LDL-C. Although not reported in that study, the reciprocal of this estimate is 0.47 (95% CI: 0.37 to 0.59), representing a 53.0% proportional reduction in risk per 34.1 mg/dl lower long-term exposure to LDL-C. The magnitude of this effect agrees closely with the results reported here and therefore provides external validation of our study results.

Conclusions

In summary, we conducted a series of meta-analyses involving 9 polymorphisms in 6 different genes to reliably quantify the effect of long-term exposure to lower LDL-C on the risk of CHD. We found that prolonged exposure to lower LDL-C beginning early in life is associated with a 3-fold greater reduction in the risk of CHD for each unit lower LDL-C than treatment with a statin started later in life and that this effect appears to be independent of the mechanism by which LDL-C is lowered.

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Key Words: cardiovascular disease ■ genetic polymorphism ■ low-density lipoprotein cholesterol ■ myocardial infarction ■ prevention.

APPENDIX

For supplemental tables and figures, please see the online version of this article.