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Importance of the lipid-related pathways in the association between statins, mortality and cardiovascular disease risk: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Purpose—Estimating how much of the impact of statins on coronary heart diseases (CHD), cardiovascular disease (CVD) and mortality risk is attributable to their effect on low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL) and triglycerides.

Methods—A semi-parametric g-formula estimator together with data from the Multi-Ethnic Study of Atherosclerosis (a prospective multi-center cohort study) were utilized to perform a mediation analysis. A total of 5,280 participants, men and women of various race/ethnicities from multiple sites across the United States, were considered in the current study.

Results—The adherence adjusted total relative reduction (RRR) estimate (95% confidence interval) of statins on CHD was 14% (−16%, 37%) and the indirect component through LDL was 23% (−4%, 58%). For CVD, the total RRR was 23% (2%, 40%) and the indirect component through LDL was 5% (−13%, 25%). The total RRR of mortality was 18% (−1%, 35%) and the indirect component through LDL was −4% (−17%, 12%). The estimated indirect components through HDL and triglycerides were close to zero with narrow confidence intervals for all three outcomes.

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Sharing: The R code utilized for conducting the analyses is available from the corresponding author upon request.

Conclusions—The estimated effect of statins on mortality, CVD and CHD appeared to be independent of their estimated effect on HDL and triglycerides. Our study provides evidence that the preventive effect of statins on CHD could be attributed in large part to their effect on LDL. Our g-formula estimator is a promising approach to elucidate pathways, even if it is hard to make firm conclusions for the LDL-pathway on mortality and CVD.

Keywords

Hydroxymethylglutaryl-CoA Reductase Inhibitors; Cholesterol; Cardiovascular diseases; Coronary disease; Mortality; Mediation analysis

INTRODUCTION

The effects of statins have been widely investigated, revealing their ability to reduce low-density lipoprotein cholesterol (LDL), triglycerides, the risks of coronary heart diseases (CHD), cardiovascular disease (CVD), and all-cause mortality, as well as to increase high-density lipoprotein cholesterol (HDL) ^{1, 2, 3, 4, 5, 6}. Statins have also been shown to have few adverse effects, relative to the size of their benefits ^{4, 5, 7}.

Although statins were initially developed as a lipid-lowering drug class ⁸, it has become evident that they also have pleiotropic effects ^{9, 10, 11, 12, 13, 14, 15, 16, 17}. Garnering a better understanding of the mechanisms relating statin treatment to improved outcomes has been recognized as important and might “help to elucidate the full therapeutic benefits of these agents” ¹⁴.

Numerous randomized trials have reported that a larger reduction in cholesterol following statin treatment correlates with a greater reduction of CHD, CVD and mortality risk ^{6, 18, 19, 20, 21, 22, 23}, thus suggesting a mediation effect. However, typical trials where only the treatment is randomized are susceptible to yield biased estimates of the importance of intermediate pathways, unless appropriate control is made for potential confounders and causal mediation analyses are conducted ²⁴. We are aware of only one study that used such causal mediation methods to quantify the importance of the cholesterol-pathway in the effect of statins ²⁵.

The aim of the current study is to provide further evidence concerning the importance of lipid-related pathways in the effect of statins on CHD, CVD and mortality risks using causal mediation methods. More specifically, we investigated how much of the total effect of statins on the five-year risk of CHD is attributable to their effect on 1) LDL, 2) HDL and 3) triglycerides, and similarly for five-year risk of CVD and all-cause mortality. This five-year period was chosen for comparability with previous studies whose average follow-up time is often approximately five years. To perform this mediation analysis, we propose a g-formula estimator that directly accounts for censored time to events and provides results on scales that are easy to interpret.

METHODS

Data

We used data from the Multi-Ethnic Study of Atherosclerosis (MESA), a population-based prospective cohort study that enrolled 6,814 men and women aged between 45 and 84 years at baseline who were initially free of clinical cardiovascular diseases. The cohort was recruited from six Field Centers across the United-States between July 2000 and August 2002 (Exam 1). Four follow-up examinations have taken place: Exam 2 (September 2002 – February 2004), Exam 3 (March 2004 – September 2005), Exam 4 (September 2005 – May 2007) and Exam 5 (April 2010 – January 2012). MESA was approved by the institutional review board at each site, subjects provided informed consent and ethics approval for the current study has been obtained from the CHU de Québec – Université Laval research center’s ethics committee. More details regarding MESA’s design have already been published ²⁶.

Study design

We analyzed the data from our observational cohort as if they arose from a sequence of four nonrandomized “trials”, where each subject could participate in more than one trial ²⁷. This approach seeks to emulate the randomized trial gold-standard utilizing observational data in the design of the study and thus offers greater comparability to the results of randomized trials. Figure 1 depicts the study design. The entry examination for Trial 1 was MESA’s Exam 2. Participants that had experienced a CVD event prior to the start of Trial 1 and those that were statin users at their pre-entry examination, at MESA’s Exam 1, were not eligible for inclusion in Trial 1. The latter exclusion criterion was imposed to avoid the potential confounding due to the unmeasured untreated pre-entry cholesterol values for participants already taking statins before Trial 1. Thus, Trial 1 consisted of all the MESA’s participants that didn’t meet the two aforementioned exclusion criteria. The statin usage exposure and the cholesterol mediators were measured at the entry examination, whereas the potential confounders were measured at the pre-entry examination. Although the cholesterol mediator and the statin exposure were measured simultaneously, the beginning of the statin exposure precedes the cholesterol measurement since it corresponds to medications that the subjects were taking prior to their entry examination. Follow-up for CHD, CVD and death events started at the date of entry into the trial. Trials 2, 3 and 4 were constructed similarly, respectively having their entry examination at MESA’s Exams 3, 4 and 5, and having their pre-entry examination at MESA’s Exams 2, 3 and 4. Note that already being a participant in a previous trial does not automatically preclude a subject from being eligible in another trial. Thus, for example, a given subject could simultaneously contribute follow-up information to all four trials if they remained CVD free and were not statin users throughout all pre-entry examinations.

CHD, CVD and All-Cause Mortality

All-cause mortality as well as CHD and CVD events have been monitored for all participants from cohort entry until the end of 2013 utilizing multiple sources of information. CHD included myocardial infarction, resuscitated cardiac arrest, definite angina, probable angina followed by revascularization and CHD death. In addition to any

CHD event, CVD also included stroke, stroke death, other atherosclerotic death, and other CVD death. For more information, see the Appendix of reference ²⁸.

LDL, HDL and Triglycerides

Blood samples were obtained at all examinations and were assayed for HDL and triglycerides. LDL was estimated using Friedewald equation ²⁹.

Statins

The use of statins was determined by questionnaire. The participants were also asked to bring containers for all medications used in the two weeks preceding each examination ³⁰.

Potential confounders

A rich set of 16 potential confounders was selected *a priori* (see Table 1). Fasting glucose was determined from blood samples and diabetes as fasting glucose >6.94 mmol/L. Two computed tomographies scanning of the chest of each participant were performed, the Agatston score was computed for each and the results were averaged ³¹. A BMI <25 kg/m² was categorized as normal, 25 BMI <30 kg/m² as overweight and BMI ≥ 30 kg/m² as obesity ³². Systolic and diastolic blood pressures were calculated as the average of the last two measures, of a series of three. Hypertension was defined as either having a systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure ≥ 90 mmHg or taking antihypertensive medication ³³.

Education, gender and race were only assessed at Exam 1. Family history of a premature cardiovascular event was determined once at Exam 2. Agatston score was assessed for all participants at Exam 1 and then up to three more times (average=1.5 times). All other covariates were measured at every examination.

Statistical analyses

We describe in more detail the analyses that were performed to decompose the estimated effect of statins on five-year CHD risk that is attributable to the effect of statins on LDL. The method used to decompose the estimated effect of statins on CHD associated with HDL or triglycerides, or to decompose the estimated effect of statins on CVD and all-cause mortality attributable to LDL, HDL or triglycerides, are analogous.

Let $A_{i,t}$ denote statin use of subject $i = 1, \dots, n_t$ at entry in Trial $t = 1, 2, 3, 4$, ($A_{i,t} = 1$ if subject i was taking statins, and $A_{i,t} = 0$ otherwise), where n_t is the number of subjects included in Trial t . Let $M_{i,t}$ be the LDL of subject i at entry in Trial t , and $Y_{i,t} = 1$ if subject i had their first CHD in the five years following entry and $Y_{i,t} = 0$ otherwise.

We consider the potential outcome framework to causal inference to define the quantities we targeted ³⁴. To simplify the presentation, we henceforth drop the subscripts i and t . We denote by Y_{am} the value that Y would have taken if $A = a$ and $M = m$, by M_a the value that M would have taken if $A = a$, and by $Y_{aM_a^*}$ the value that Y would have taken if $A = a$ and $M = M_a^*$. For instance, Y_{1M_0} represents the counterfactual five-year incidence of CHD for a

given subject if they had taken statins, but their LDL was the same as if they had not taken statins.

The average total effect of statins on five-year risk of CHD is $E[Y_{1M_1}] - E[Y_{0M_0}]$, which can be interpreted as the difference between the proportion of individuals who would have had their first CHD in the following five years if everyone had received statins and the same proportion if no one had received statins. This effect can be decomposed into a direct component, not due to the effect of statins on LDL, and an indirect component, due to the effect of statins on LDL³⁵. The direct component is $E[Y_{1M_0}] - E[Y_{0M_0}]$, that is the difference between the proportion of subjects that would have had their first CHD in the following five years if everyone had received statins, but their LDL-level had been unaffected, and the same proportion if no one had received statins. The indirect component is the difference between the total effect and the direct effect.

We also considered the previous quantities on a relative risk reduction (RRR) scale, dividing by the negative of the baseline risk, $-E[Y_{0M_0}]$.

Intention to treat estimation—We first describe the analyses we conducted to obtain an observational study equivalent of intention to treat estimates where statins initiators are compared to non-initiators, regardless of whether they remained adherent to their initial treatment (taking statins or not taking statins) in follow-up visits.

We propose a semi-parametric g-formula estimator of the total effect and its components. Our estimator shares similarities with the approach of Imai et al³⁶. Details of the development of our estimator are provided in Appendix 1 and simulation studies investigating its performance are presented in Appendix 2.

Letting C be the potential confounders in Table 1 and $c_{i,t}$ be the observed values for subject i in trial t , we propose the following estimators of $E[Y_{aM_a^*}]$:

$$\hat{E}[Y_{aM_a}] = \frac{1}{N} \sum_{t=2}^5 \sum_{i=1}^{n_t} \hat{E}[Y|A=a, C=c_{i,t}],$$

when $a = a^*$ and

$$\hat{E}[Y_{aM_{a^*}}] = \frac{1}{N} \sum_{t=2}^5 \sum_{i=1}^{n_t} \int_M \hat{E}[Y|A=a, M=m, C=c_{i,t}] \hat{f}(m|A=a^*, C=c_{i,t}) dm,$$

when $a \neq a^*$, where $N = n_2 + n_3 + n_4 + n_5$.

To compute $\hat{E}[Y|A=a, C=c_{i,t}]$, we first fitted a Cox model for the time until a CHD event that included the statin use at entry and the pre-entry confounders. We have then computed the predicted 5-year risk employing Equation (5.5) from reference³⁷. This approach directly accounts for censored time-to-events due to loss to follow up or competing events through

the use of the Cox model. Age was entered utilizing restricted cubic splines. Agatston score was introduced as two variables: a dummy variable equal to one if the score is greater than zero, and equal to zero otherwise, as well as an interaction between this variable and the log of the Agatston score. Time to death (CVD/CHD) was considered as right censored at the end of follow-up. Time to CHD (CVD) was further considered as right censored if death from a non-CHD (non-CVD) cause occurred before the first CHD (CVD)³⁸. We did not censor follow-up time after five years of follow-up, since events occurring after this period could be informative in estimating the parameters of the Cox model. $E[Y|A = a, M = m, C = c_{i,t}]$ was estimated similarly, but also including LDL at entry and an interaction between statin use and LDL at entry (to simplify the methods, each mediator was investigated in a separate model).

To obtain $\hat{R}(m|A = a^*, C = c_{i,t})$, we have first fitted a linear regression where the outcome was $\log(M)$. This model included statin use at entry and all pre-entry potential confounders. The pre-entry values of LDL, HDL and triglycerides were all log-transformed. Age and Agatston score were included in the same manner as in the Cox model. The model further included an interaction between statin use at entry and pre-entry $\log(\text{LDL})$. We then took $\hat{R}(m|A = a^*, C = c_{i,t})$ as a log-normal distribution whose mean on the log-scale was the linear predictor from the model and whose variance was the residual variance. The integral over the M values was performed using the trapezoidal approximation.

Assumptions of the models were visually verified and appeared reasonable for most of the range of the data. Confidence intervals (CI) were obtained through the percentile method by performing non-parametric bootstrap with 2000 resamples³⁹. The bootstrap samples were taken from the original dataset to account for the within-subject correlation arising from the fact that each subject could participate in more than one trial.

Adherence-adjusted estimation—Intention to treat estimates can be problematic because they depend on the proportion of the subjects who adhere to their initial treatment²⁷. We thus consider an adherence-adjusted analysis as our primary analysis. Our approach for obtaining adherence-adjusted estimates essentially consisted in discarding information on follow-up visits once a subject discontinued their initial treatment and using inverse probability weighting to redistribute the weights of such subjects onto similar subjects that pursued their initial treatment. More details are provided in Appendix 3.

Sensitivity analyses—We conducted an adherence-adjusted analysis comparing Atorvastatin (the most commonly used statin in our data) users to non-statin users to investigate if the decomposition of the effect might vary according to type of statins. We have also performed two sensitivity analyses where alcohol consumption (yes or no) and self-reported walking pace (in 5 categories ranging from very slow to brisk), as a measure of physical activity⁴⁰, were considered as additional confounders. These are considered as sensitivity rather than main analyses because of the amount of missing data on these variables ($\approx 10\%$ for alcohol, walking pace was not collected at Exam 4). Sensitivity analyses yielded similar results to those presented below (see Appendix 4).

Missing data—A single Expectation-Maximization imputation of missing Agatston scores was performed (correlations between 0.86 and 0.99 were observed between measures taken at Exam 1 and measures taken at other Exams, not presented). Otherwise, only rows without any missing data were considered. Available data is described in Figure 2.

RESULTS

Pre-entry characteristics of the participants in the trials are reported in Table 1 (characteristics by trial are reported in Appendix 5). A total of 5,280 subjects participated in at least one of our trials, of which 336 experienced a CHD event, 509 a CVD event and 638 died before the end of follow-up. A total of 4402 subjects participated in multiple trials; the average number of trials to which subjects participated was 2.9. The average follow-up times for trials 1, 2, 3 and 4 were respectively 8.3, 7.5, 6.8 and 2.9 years, after censoring observations that discontinued their initial treatment. The adherence proportion after 1, 2 and 3 follow-up visits were respectively of 86%, 85% and 81%.

Below, we summarize the adherence-adjusted estimates for the decomposition of the effect of statins on all-cause mortality, CVD and CHD. The complete results are presented in Table 2. The intention to treat estimates are reported in Appendix 6.

The total adherence-adjusted association between statin use and CHD was -0.4% (95% CI = -1.1% , 0.4%) on the risk difference (RD) scale and 14% (-16% , 37%) on the RRR scale. A large portion, if not all, of this association might be due to the LDL-lowering properties of statins (RD = -0.7% , 95% CI = -1.7% , 0.1% ; RRR = 23% , 95% CI = -4% , 58%). The total association between statins and CVD was -1.0% (-1.8% , -0.1%) on the RD scale and 23% (2% , 40%) on the RRR scale. A small portion of this association was estimated to be attributable to the LDL pathway, but wide confidence intervals were obtained (RD = -0.2% , 95% CI = -1.1% , 0.5% ; RRR = 5% , 95% CI = -13% , 25%). The total association between statin use and mortality was -0.9% (95% CI = -1.8% , 0.0%) on a RD scale and 18% (-1% , 35%) on the RRR scale. Results were inconclusive regarding the importance of the LDL-pathway (RD = 0.2% , 95% CI = -0.6% , 0.8% ; RRR = -4% , 95% CI = -17% , 12%). For all three outcomes, the portion attributable to the HDL or triglycerides pathways was estimated to be negligible.

DISCUSSION

Our results provide evidence of the importance of the LDL-lowering properties of statins on reducing the risk of CHD. In fact, our indirect effect estimate is larger than the total effect estimate. This suggests that statins decrease the risk of CHD because of their LDL-lowering properties, but slightly increase the risk through other pathways; the net effect remaining beneficial. Our study also provides evidence that the HDL- and triglycerides-pathways play a minor role in the effect of statins on CHD, CVD and mortality. Regarding the importance of the LDL-pathway on CVD or mortality, our study is somewhat inconclusive: small indirect associations were observed, but wide confidence intervals were obtained. An expanded discussion of the substantive results is provided in Appendix 7.

It is important to take into account a number of potential limitations when interpreting our results. First, because we considered observational data, any causal inference made rests upon the assumptions of no unmeasured confounding. Since we considered a rich set of potential confounders, which was built based on substantive knowledge, it appears reasonable to assume that the most important confounding factors were accounted for. Moreover, our total effect estimates are consistent with those produced by large meta-analyses of randomized controlled trials ^{2, 5}.

The validity of our results also relies on the assumptions of the models that were used to construct our g-formula estimator, such as the proportional hazard assumption of the Cox model. These assumptions were visually verified and appeared to be reasonable.

Some bias could have been introduced by our treatment of missing data. A better alternative might have been to perform multiple imputations ⁴¹. However, this option was thought to be impractical to implement, due to the computational burden of combining bootstrapping with multiple imputations.

Although we know that the initiation of our statin exposure precedes the measure of the cholesterol mediators, we do not know the precise time when initiation occurred. Some bias could arise if the delay between initiation and measurement of the cholesterol mediator is too short in some cases for the full impact of statin treatment on cholesterol to be realized. However, the mean LDL-reduction associated with statin treatment we observed was very close to the one reported in a large meta-analysis of randomized trials (0.93 mmol/L vs 1.00 mmol/L – analysis not presented) ⁵, which suggests that this bias might be small.

Our adherence-adjusted analysis attempted to correct for the misclassification that occurs when a user becomes a non-user or vice-versa. However, the exact time where switching occurs is unknown. Therefore, some individuals have contributed follow-up time for outcome events in the wrong exposure group before being censored, which is likely to have biased our effect estimates towards the null. Because the adherence proportion after one visit is high (84%) and because our total effect point estimates are consistent with previous findings, we hypothesize that this misclassification bias may be small. Moreover, our analysis only investigated the contribution of statins through short-term changes in cholesterol, not accounting for how cholesterol varies over time. This is similar to the approach used in many clinical trials where the reduction in cardiovascular events is correlated with the reduction in cholesterol after one or two years ^{6, 20, 23}. It is nonetheless possible that the indirect effect of statins on cardiovascular outcomes through cholesterol depends both on short- and long-term effects on cholesterol. Recently, a parametric and a semi-parametric g-formula approach have been proposed to perform mediation analysis with time-varying exposures and mediators and could be considered to provide further insights on the mechanism relating statin to better cardiovascular outcomes ^{42, 43}. However, accounting for the time-varying nature of the variables comes at the cost of adding further complexities to the analysis. For instance, the parametric g-formula approach of Lin et al ⁴² depends on more stringent assumptions than ours, such as the correct parametric specification of the joint distribution of the exposure and confounders at each time-point whereas our method uses a non-parametric estimator for the joint distribution of the confounders. While the semi-

parametric method of VanderWeele and Tchetgen Tchetgen⁴³ avoids making such assumptions, it is potentially unstable in certain circumstances⁴². Our study also has a number of noteworthy strengths. The generalizability of the results to the American population is improved by the fact that we used data from a multi-ethnic population-based cohort with participants from multiple centers across the United States. The large number of participants, the length of the follow-up period and the relatively small number of losses-to-follow-up for a study of that length should also be noted. From a methodological perspective, we believe that our semi-parametric g-formula estimator is a promising approach to help elucidate intermediate pathways, since it has the ability of directly accounting for censored time to events through the use of the Cox model and avoids relying on stringent parametric assumptions. It also provides estimates on risk difference or relative risk reduction scales that are easy to interpret. Our approach is of particular interest for investigating exposure effects attributable to intermediate pathways in a relatively specific time-frame, such as short-term effects on the mediator.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

1. Few previous studies have attempted quantifying the relative importance of the lipid pathways in the effect of statins on coronary heart diseases, cardiovascular diseases and mortality using appropriate causal mediation approaches.
2. In this study, the effect of statins on coronary heart disease, cardiovascular disease and mortality appeared to be independent of their effect on high-density lipoprotein cholesterol and triglycerides.
3. The preventive effect of statins on coronary heart diseases could be attributed in large part to their effect on LDL.
4. The g-formula estimator we proposed is a promising approach to elucidate intermediate pathways for other drug classes

Figure 1.
Schematic representation of the study design

Figure 2.
Flowchart of the available data

Table 1

Pre-entry Characteristics of Participants in the Trials According to Statin Usage at the Entry Examination

	Non-Users (n = 13,702)	Users (n = 1,651)
Age, mean (SD)	62.5 (10.1)	64.8 (9.3)
Education (highest level reached)		
- Less than high school	15.3	18.1
- High school	16.6	19.1
- More than high school	67.8	62.8
Gender female	53.8	54.7
Health insurance	92.2	95.1
Race/ethnicity		
- White, Caucasian	38.4	38.2
- Chinese American	12.4	10.1
- Black, African-American	27.2	28.1
- Hispanic	21.9	23.6
Site		
- WFU	15.3	16.6
- COL	17.2	16.5
- JHU	13.6	15.4
- UMN	15.9	16.1
- NWU	19.3	15.5
- UCLA	19.3	15.5
LDL in mmol/L, mean (SD)	3.0 (0.8)	3.5 (0.9)
HDL in mmol/L, mean (SD)	1.4 (0.4)	1.3 (0.4)
Triglycerides in mmol/L, mean (SD)	1.3 (0.7)	1.6 (0.8)
Agatston score > 0	41.3	53.5
Ln of Agatston score when > 0, mean (SD)	4.1 (1.8)	4.4 (1.8)
BMI		
- Normal	32.0	24.5
- Overweight	38.0	38.2
- Obesity	30.0	37.3
Cigarette smoking		
- Never	48.3	48.0
- Former	40.0	42.9
- Current	11.7	9.2
Diabetes	9.0	22.4
Family history of CVD	25.9	28.9
Hypertension	39.9	57.1
Number of medications, mean (SD)	4.0 (3.6)	4.9 (3.6)

Results are expressed as percentage unless otherwise indicated

Table 2

Decomposition of the Adherence-adjusted Effect Estimate of Statins on Coronary Heart Disease, Cardiovascular Disease and Mortality (95% confidence intervals in parenthesis)

	Measure	Total effect of statins	Direct effect of statins	Indirect effect of statins (via the mediator)
CHD				
LDL	RD	-0.4% (-1.1%, 0.4%)	0.3% (-0.9%, 1.7%)	-0.7% (-1.7%, 0.1%)
	RRR	14% (-16%, 37%)	-9% (-59%, 29%)	23% (-4%, 58%)
HDL	RD	-0.4% (-1.1%, 0.4%)	-0.4% (-1.1%, 0.4%)	0.0% (-0.1%, 0.0%)
	RRR	14% (-16%, 37%)	13% (-16%, 36%)	1% (-1%, 3%)
Trig.	RD	-0.4% (-1.1%, 0.4%)	-0.4% (-1.2%, 0.4%)	0.0% (-0.1%, 0.1%)
	RRR	14% (-16%, 37%)	14% (-15%, 37%)	0% (-4%, 3%)
CVD				
LDL	RD	-1.0% (-1.8%, -0.1%)	-0.7% (-1.9%, 0.6%)	-0.2% (-1.1%, 0.5%)
	RRR	23% (2%, 40%)	17% (-14%, 42%)	5% (-13%, 25%)
HDL	RD	-1.0% (-1.8%, -0.1%)	-0.9% (-1.8%, 0.0%)	0.0% (-0.1%, 0.0%)
	RRR	23% (2%, 40%)	22% (0%, 40%)	1% (0%, 3%)
Trig.	RD	-1.0% (-1.8%, -0.1%)	-1.0% (-1.8%, 0.0%)	0.0% (-0.1%, 0.1%)
	RRR	23% (2%, 40%)	22% (1%, 40%)	0% (-2%, 2%)
Mortality				
LDL	RD	-0.9% (-1.8%, 0.0%)	-1.1% (-2.1%, 0.0%)	0.2% (-0.6%, 0.8%)
	RRR	18% (1%, 35%)	23% (0%, 44%)	-4% (-17%, 12%)
HDL	RD	-0.9% (-1.8%, 0.0%)	-0.8% (-1.7%, 0.1%)	-0.1% (-0.2%, 0.0%)
	RRR	18% (-1%, 35%)	17% (-3%, 34%)	2% (0%, 4%)
Trig.	RD	-0.9% (-1.8%, 0.0%)	-0.9% (-1.8%, 0.0%)	0.0% (-0.1%, 0.1%)
	RRR	18% (-1%, 35%)	19% (0%, 35%)	-1% (-3%, 1%)

The total estimated effect is decomposed in an indirect effect, due to the effect of statins on a given mediator, and a direct component, not due to the effect of statins on that given mediator. LDL = low-density lipoprotein, HDL = high-density lipoprotein, Trig. = triglycerides, RD = risk difference, RRR = relative risk reduction, CHD = coronary heart diseases, CVD = cardiovascular diseases.

Estimates are adjusted for age, education, gender, health insurance, race/ethnicity, Field Center, previous LDL, previous HDL, previous triglycerides, Agatston score, BMI, cigarette smoking, diabetes, family history of CVD, hypertension and total number of medication.