Supplementary Material to

Relations of Change in Plasma Levels of LDL-C, non-HDL-C and apoB with Risk Reduction From Statin Therapy – A Meta-Analysis of Randomized Trials

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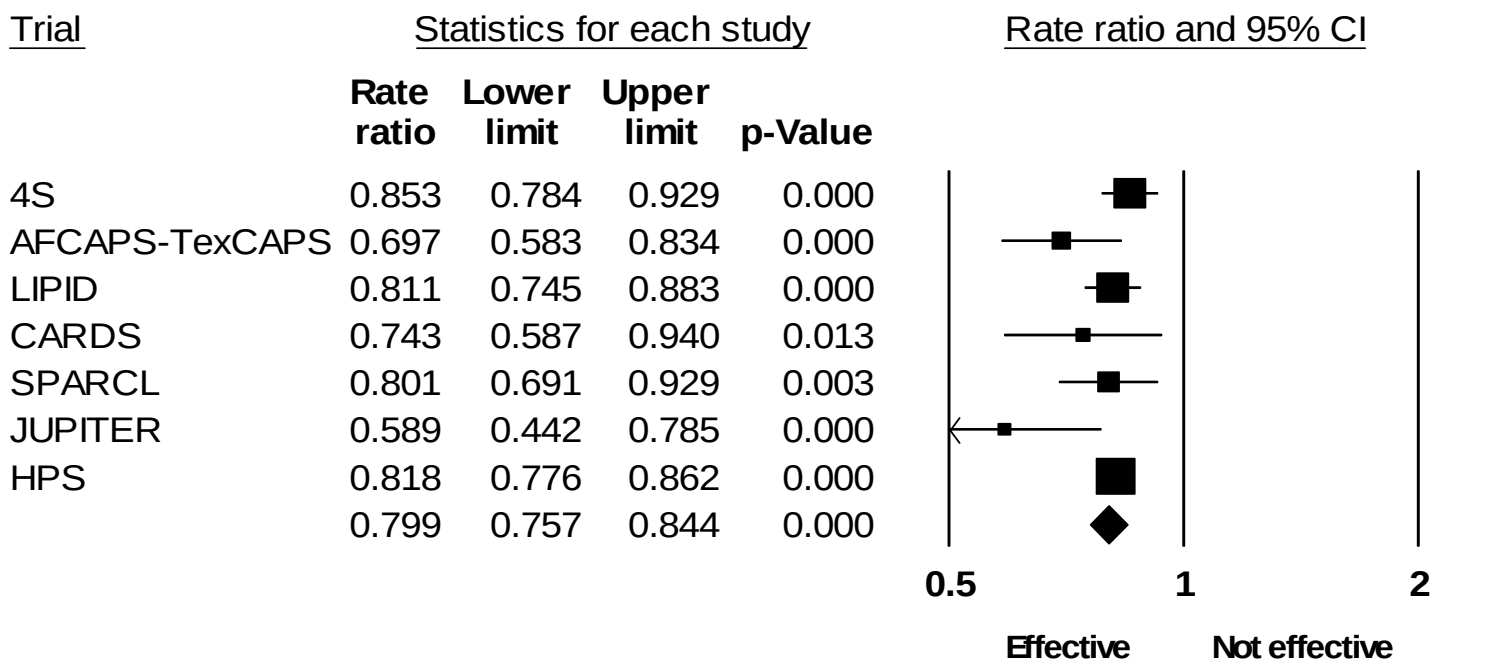
APPENDIX A - Detailed Frequentist Meta-Analysis Results

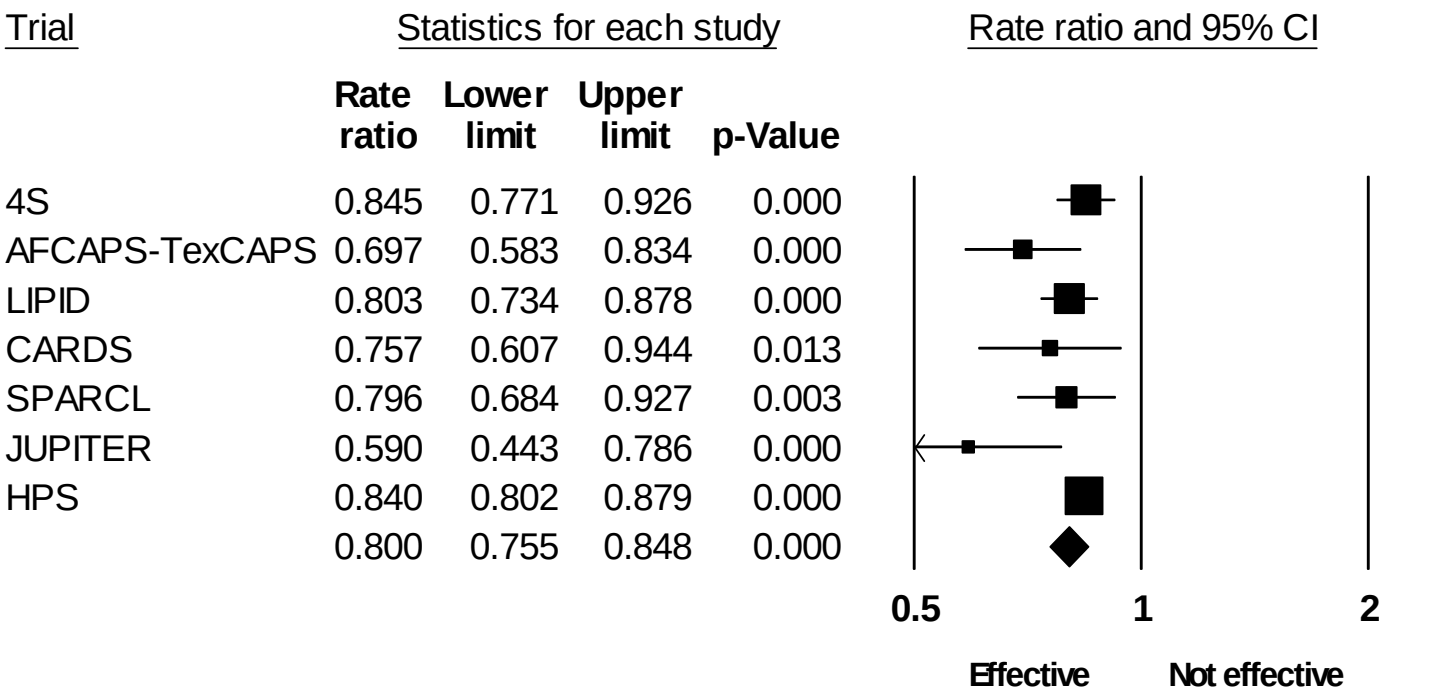
Figure A1. Random effects analysis of statin trial HRs per SD (32 mg/dl) LDL-C decrement



Meta Analysis

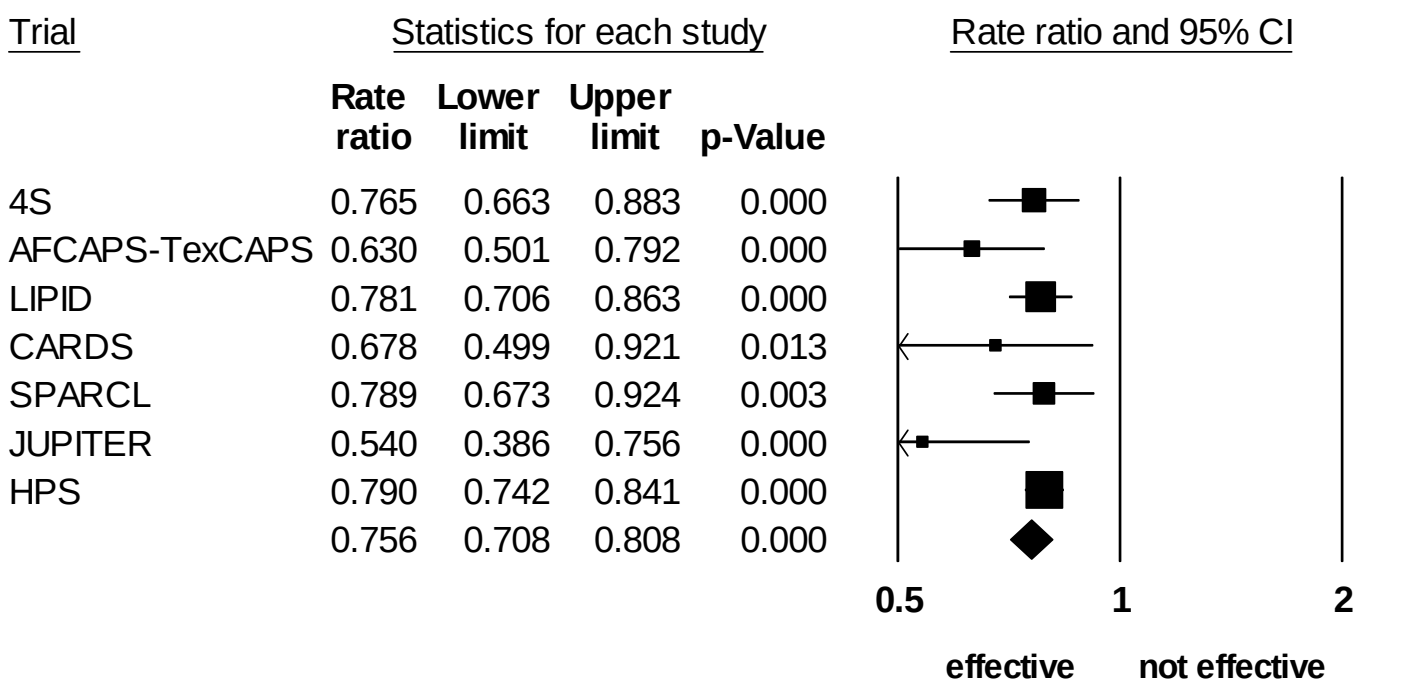
Reduction in risk per 1-SD reduction of LDL-C = 20.1% (15.6%, 24.3%)

Figure A2. Random effects analysis of statin trial HRs per SD (36 mg/dl) Non-HDL-C decrement



Reduction in risk per 1-SD reduction of non-HDL-C = 20.0% (15.2%, 24.7%)

Figure A3. Random effects analysis of statin trial HRs per SD (27 mg/dl) ApoB decrement



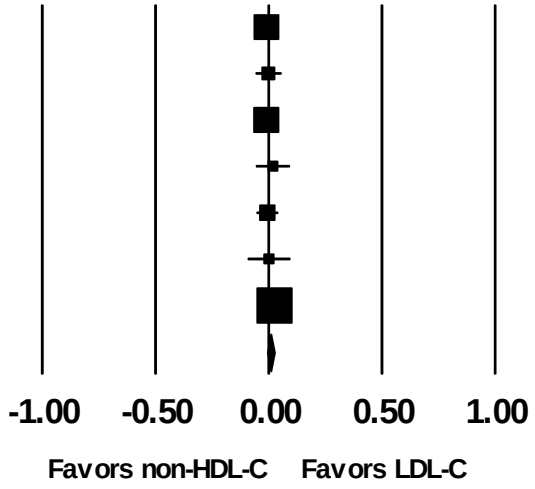
Reduction in risk per 1-SD reduction of apoB = 24.4% (19.2%, 29.2%)

Figure A4. Random effects analysis of Non-HDL-C - LDL-C Log HRs per SD

Trial	Point estimate	Lower limit	Upper limit	p-Value
4S	-0.010	-0.040	0.019	0.494
AFCAPS-TexCAPS	-0.001	-0.061	0.059	0.974
LIPID	-0.010	-0.040	0.019	0.487
CARDS	0.019	-0.059	0.096	0.638
SPARCL	-0.006	-0.056	0.045	0.824
JUPITER	0.001	-0.095	0.098	0.980
HPS	0.026	0.008	0.044	0.004
	0.006	-0.009	0.021	0.445

Statistics for each study

Point estimate and 95% CI



Meta Analysis

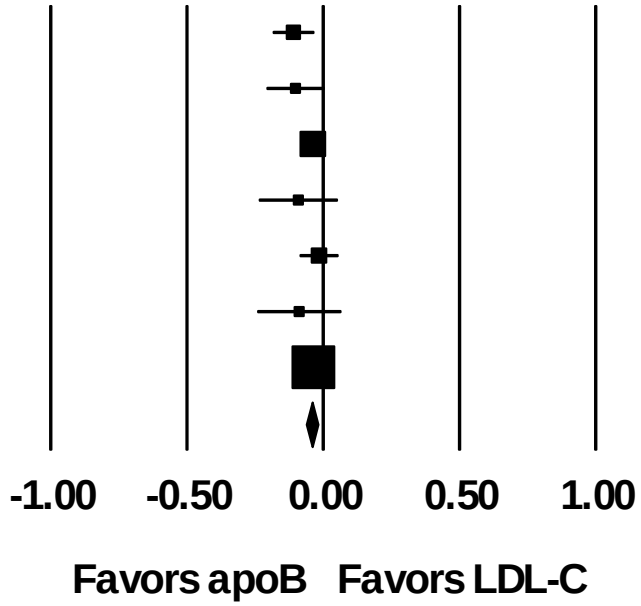
- Assumes correlation between non-HDL-C and LDL-C of r = 0.944 (calculated from NHANES 2005 – 2010 to be representative of the US adult population).
- Percentage difference in HRs = $e^{estimate} - 1$ so these estimates indicate the non-HDL-C HR is on average 0.6% higher than the LDL-C HR with the 95% confidence interval from 0.9% lower to 2.1% higher.
- Percentage difference in benefit: 2.4% (-3.6%, 8.4%) higher for LDL-C than for non-HDL-C. -3.6% “higher” means 3.6% lower.

Figure A5. Random effects analysis of ApoB - LDL-C Log HRs per SD

Trial	Point estimate	Lower limit	Upper limit	p-Value
4S	-0.109	-0.188	-0.030	0.007
AFCAPS-TexCAPS	-0.101	-0.210	0.007	0.068
LIPID	-0.038	-0.085	0.009	0.112
CARDS	-0.091	-0.238	0.056	0.224
SPARCL	-0.015	-0.089	0.059	0.690
JUPITER	-0.088	-0.244	0.068	0.270
HPS	-0.036	-0.064	-0.007	0.015
	-0.045	-0.066	-0.023	0.000

Statistics for each study

Point estimate and 95% CI



Meta Analysis

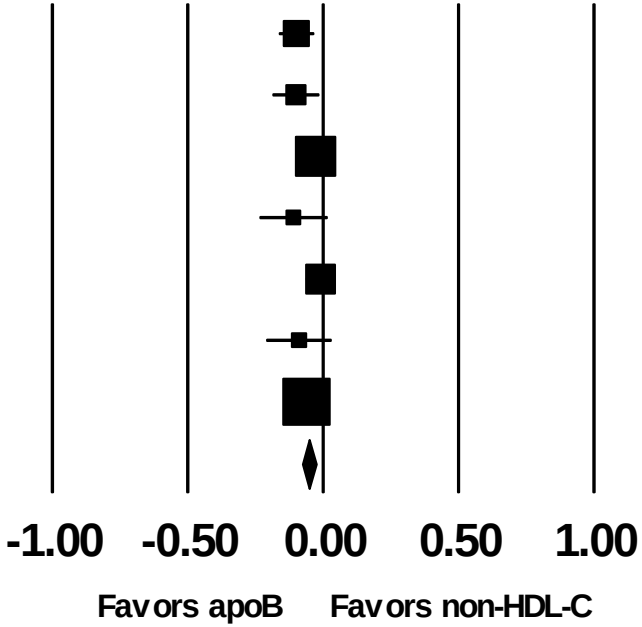
- Assumes correlation between apoB and LDL-C of r = 0.886 (calculated from NHANES 2005 – 2010 to represent the US adult residents).
- Overall the apoB HR is estimated to be 4.5% (2.3%, 6.4%) lower than the LDL-C HR.
- Estimated benefit (risk reduction) per 1-S reduction of apoB is 17.9% (9.1%, 25.4%) greater than for LDL-C

Figure A6.1 Random effects analysis of apoB - non-HDL-C Log HRs per SD

Trial	Point estimate	Lower limit	Upper limit	p-Value
4S	-0.099	-0.166	-0.031	0.004
AF/TexCAPS	-0.100	-0.189	-0.012	0.027
LIPID	-0.027	-0.064	0.009	0.137
CARDS	-0.110	-0.238	0.018	0.093
SPARCL	-0.009	-0.066	0.047	0.747
JUPITER	-0.089	-0.212	0.034	0.155
HPS	-0.062	-0.087	-0.036	0.000
	-0.055	-0.081	-0.030	0.000

Statistics for each study

Point estimate and 95% CI



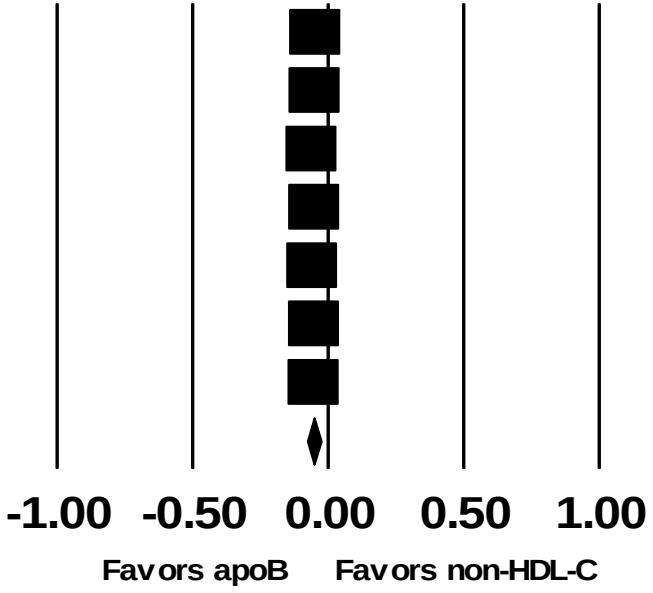
Meta Analysis

- Assumes correlation between apoB and non-HDL-C of r = 0.934 (calculated from NHANES 2005 – 2010 to represent US adult residents).
- Overall the apoB HR was lower than the non-HDL-C HR by 5.4% (3.0%, 7.8%).
- Estimated benefit (risk reduction) per 1-S reduction of apoB is 21.6% (12.0%, 31.2%) greater than for non-HDL-C.

Figure A6.2 Random effects analysis of apoB - non-HDL-C Log HRs per SD

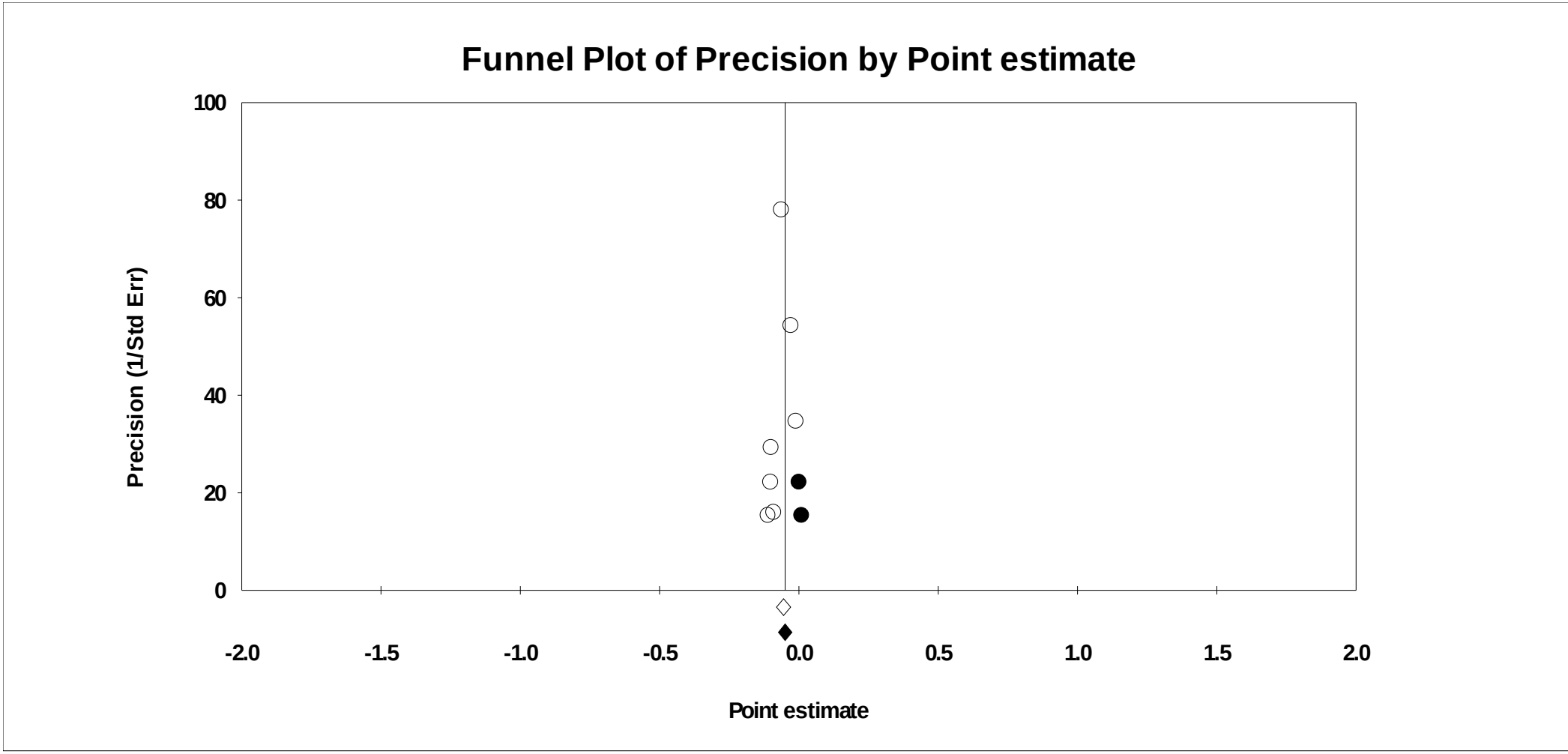
Trial	Statistics with study removed			
	Point	**Lower limit**	**Upper limit**	**p-Value**
4S	-0.049	-0.075	-0.024	0.000
AF/TexCAPS	-0.052	-0.078	-0.025	0.000
LIPID	-0.064	-0.090	-0.037	0.000
CARDS	-0.053	-0.080	-0.027	0.000
SPARCL	-0.061	-0.084	-0.037	0.000
JUPITER	-0.054	-0.082	-0.027	0.000
HPS	-0.056	-0.092	-0.019	0.003
	-0.055	-0.081	-0.030	0.000

Point estimate (95% CI) with study removed



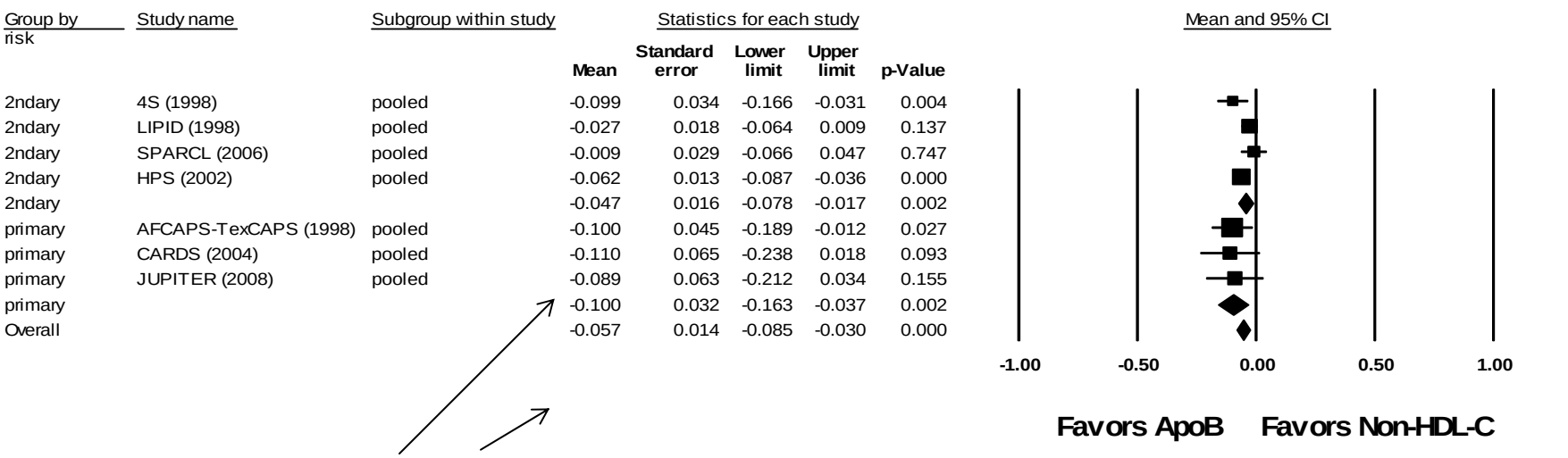
Meta Analysis

Figure A6.3 Funnel plot by point estimate of apoB – non-HDL-C log HRs to assess publication bias



- Overall average including "imputed studies" to balance the distribution from observed studies: 0.049 (-0.74, -0.025) versus -0.055 (-0.081, -0.030).

Figure A6.4 Mixed effects subgroup analysis by baseline risk of apoB – non-HDL-C log HRs per SD



Meta Analysis p = 0.141

- Transformed to the percentage by which the HR is lower (indicating a greater reduction in risk associated with a 1-SD decrement) for apoB than for non-HDL-C , these point estimates (95% confidence intervals) equate to an overall average among secondary trials of 4.6% (1.7%, 7.5%) versus 9.5% (3.6%, 15.0%) among primary trials.
- Overall difference in benefits favoring apoB among secondary trials is 18.4% (6.8%, 30.0%) versus 38% (14.4%, 60.0%), p = 0.141.

Appendix B. Bayesian Analysis for the difference of Log HR/SD between apoB and non-HDL-C

1 Introduction

In this report, we use Bayesian analysis to investigate the differences of the means between the ln*HR* of apoB, of non-HDL-C, and of LDL-C, incorporating prior information about the correlations between these variables.

2 Model Setup and Prior Settings

Notations: For each pair,

- (μ_x, μ_y): the true mean values of the ln*HR* of the first and second variables, respectively.
- (X, Y): The observed (estimated) values of the ln*HR* of the first and second variables, respectively.
- (σ_x, σ_y): The true standard deviations of the ln*HR* of the first and second variables, respectively.[2]
- ρ: The correlation between the ln*HR* of the first and second variables.
- (s_x, s_y): The observed (estimated) standard deviations of the ln*HR* of the first and second variables, respectively.

The model of ln*HR* of the first and second variables can be defined as follows as follows:

$$\begin{pmatrix} X \\ Y \end{pmatrix} \sim N_2\left(\begin{pmatrix} \mu_x \\ \mu_y \end{pmatrix}, \begin{pmatrix} \sigma_x^2 & \rho\sigma_x\sigma_y \\ \rho\sigma_x\sigma_y & \sigma_y^2 \end{pmatrix}\right), \qquad (1)$$

where N_2stands for a bivariate normal distribution. Using the meta-analysis results, we will plug-in the estimators for the standard deviations in (1). In the analysis, seven studies are used and the data are given in Table B.1.

Due to different standard deviations on those ln*HR*s for different trials, we modify the model (1) as the following.

$$\begin{pmatrix} X_i \\ Y_i \end{pmatrix} \sim N_2\left(\begin{pmatrix} \mu_x \\ \mu_y \end{pmatrix}, \begin{pmatrix} s_{xi}^2 & \rho s_{xi}s_{yi} \\ \rho s_{xi}s_{yi} & s_{yi}^2 \end{pmatrix}\right), \text{ for } i = 1,\ldots, 7. \qquad (2)$$

Here s_{xi} and s_{yi} in model (2) are the estimated standard deviations for X_i and Y_i, respectively.

Table S1: The mean and standard deviation estimates for the ln*HR* of apoB, non-HDL-C, and LDL-C.

	ApoB		Non-HDL-C		LDL-C	
Trial	Mean	S.E.	Mean	S.E.	Mean	S.E.
4S	0.765	0.073	0.845	0.046	0.853	0.043
AFCAPS-TexCAPS	0.630	0.117	0.697	0.091	0.697	0.091
LIPID	0.781	0.051	0.803	0.046	0.811	0.044
CARDS	0.678	0.156	0.757	0.112	0.743	0.120
SPARCL	0.789	0.081	0.796	0.078	0.801	0.076
JUPITER	0.540	0.172	0.590	0.147	0.589	0.147
HPS	0.790	0.032	0.840	0.023	0.818	0.027

3 Analysis

First we assign priors on three parameters (μ_x,μ_y,ρ). For the mean parameters (μ_x,μ_y), we use flat priors on them (both having normal priors with 0 as the mean and very large variances) so that we do not pose any subjective information. On the other hand, we consider different scenarios in Section 3.1 on the prior information of ρ, the correlation between the X and Y . The Bayesian computation uses the Markov chain Monte Carlo (MCMC) simulation with 5,000 burn-ins and 50,000 generated posterior deviates.

3.1 Analysis of the difference in ln*HR* between apoB and Non-HDL-C

In this section we investigate the Bayesian analysis of the between the ln*HR* of apoB and non-HDL-C. Three priors on the correlation, ρ, are considered

(a)$\rho \sim N(0.87,0.17^2)I(0.5,1)$: a normal prior on ρ with mean 0.87 and standard deviation 0.17, truncated between (0.5,1). The posterior analysis yields the results in Table B.2.
(b) $\rho \sim U(0.5,1)$: a flat prior of ρ is given on interval (0.5,1). The posterior analysis yields the results in Table B.3.
(c)$\rho \sim U(-1,1)$: flat prior for ρ is given on interval (-1,1). The posterior analysis yields the results in Table B.4.
(d) The posterior distributions of ρ for the three different priors are shown in Figure B.1.

Table S2: Posterior Analysis using truncated normal $N(0.87,0.17^2)$ on (0.5,1) for ρ.

Parameter	Mean	Median	Standard Deviation	95% Bayesian Interval
μ_x	0.7828	0.7827	0.0233	(0.7371,0.8290)
μ_y	0.8288	0.8288	0.0179	(0.7937,0.8640)
ρ	0.8505	0.8691	0.0837	(0.6410,0.9592)
μ_x-μ_y	-0.0460	-0.0457	0.0123	(-0.0712,-0.0224)
$P(\mu_x$-$\mu_{y>0})$	0.000420	0.0	0.020490	(0.0,0.0)
Bayes factor of μ_x-$\mu_y \leq 0$ against μ_x-$\mu_y > 0$				2380 favoring apoB

Table S3: Posterior Analysis using flat prior for ρ on (0.5, 1).

Parameter	Mean	Median	Standard Deviation	95% Bayesian Interval
μ_x	0.7825	0.7824	0.0237	(0.7364,0.8295)
μ_y	0.8286	0.8285	0.0181	(0.7935,0.8646)
ρ	0.8318	0.8617	0.1063	(0.558,0.9602)
μ_x-μ_y	-0.0461	-0.0457	0.0130	(-0.0728,-0.0212)
$P(\mu_x$-$\mu_{y>0})$	0.000900	0.0	0.029987	(0.0,0.0)
Bayes factor of μ_x-$\mu_y \leq 0$ against μ_x-$\mu_y > 0$				1110 favoring apoB

Table S4: Posterior Analysis using flat prior for ρ on (-1; 1).

Parameter	Mean	Median	Standard Deviation	95% Bayesian Interval
μ_x	0.7819	0.7817	0.0247	(0.7355,0.8283)
μ_y	0.8281	0.8281	0.0181	(0.7927,0.8638)
ρ	0.7948	0.8517	0.1778	(0.2751,0.9596)
μ_x-μ_y	-0.0462	-0.0457	0.0141	(-0.0756,-0.0193)
$P(\mu_x$-$\mu_{y>0})$	0.002060	0.0000	0.045341	(0.0,0.0)
Bayes factor of μ_x-$\mu_y \leq 0$ against μ_x-$\mu_y > 0$				484 favoring apoB

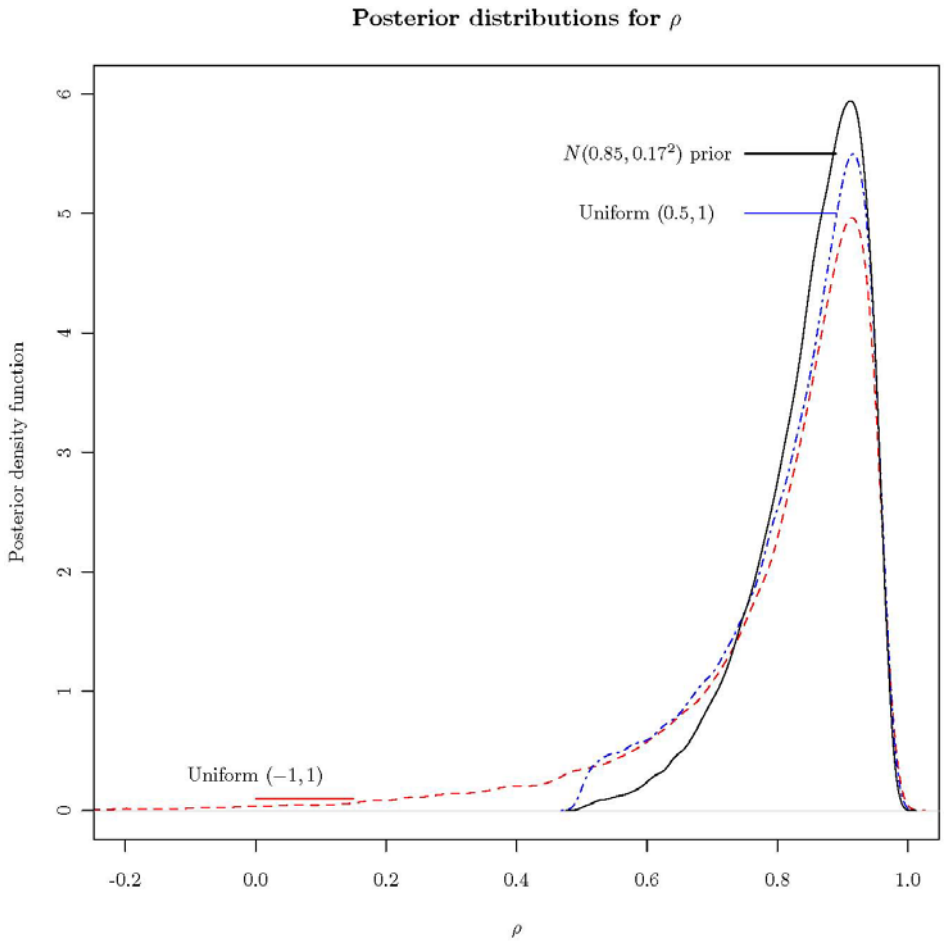


Figure S7: In comparing the *lnHR* between apoB and non-HDL-C, the posterior distributions of ρ, by using three different prior distributions on ρ.

Discussion

- When we look at Tables B.2 through B.4, there is almost no difference in the inference on μ_x-μ_y, which is the logarithm of the ratio of the *HR*s between apoB and non-HDL-C. At a 0.05 level of significance, all conclude that the ln*HR* of apoB is significantly smaller than that of non-HDL-C.
- The posterior probability that $P(\mu_x$-$\mu_y > 0)$, which is the inferential probability that ln*HR* of apoB is larger than that of non-HDL-C, is almost closed to zero, confirms the conclusion that ln*HR* of apoB is significantly smaller than that of non-HDL-C.
- Since almost flat priors on μ_x and μ_y are used with the mean of the difference being 0, the prior odds is 1 between μ_x-$\mu_y \leq 0$ and μ_x-$\mu_y > 0$. Hence in Tables B.2 through B.4, we can see that the Bayes factor of the hypothesis μ_x-$\mu_y \leq 0$ against μ_x-$\mu_y > 0$ are all very large, indicating the data are in favor of μ_x-$\mu_y \leq 0$.
- Although the 95% Bayesian intervals for those three priors show different ranges, there is little change in the posterior means, especially the median estimations of ρ. This indicates that the correlation ρ being a high positive value is confirmed.
- Figure B.1 shows the posterior densities of ρ. Most of the posterior probability mass falls within high-positive-value ranges.

3.2 Analysis of the ln*HR* between apoB and LDL-C

In this section, we consider the comparison of the ln*HR* between apoB and LDL-C. The prior distribution on ρ is set as truncated normal on (0.5,1), with mean 0.84 and a standard deviation of 0.11. The analysis result is shown in Table B.5.

Table S5: Posterior Analysis of the ln*HR* between apoB and LDL-C using truncated normal $N(0.84,0.11^2)$ on (0.5,1) for ρ.

Parameter	Mean	Median	Standard Deviation	95% Bayesian Interval
ρ	0.8040	0.8305	0.1109	(0.5424,0.9507)
μ_x-μ_y	-0.0373	-0.0370	0.0138	(-0.0659;-0.0105)
$P(\mu_x$-$\mu_{y>0})$	0.005280	0.0	0.072470	(0.0,0.0)
Bayes factor of μ_x-$\mu_y \leq 0$ against μ_x-$\mu_y > 0$				188 favoring apoB

Discussion

Most of the discussions in Section 3.1 can be applied here. It is significant that the ln*HR* of apoB is smaller than that of LDL-C.

3.3 Analysis of the ln*HR* between non-HDL-C and LDL-C

The third analysis is to compare the ln*HR* between non-HDL-C and LDL-C. The prior on ρ is truncated normal on (0.5,1) with mean 0.89 and standard deviation 0.06. The analysis results are shown in Table B.6.

Table S6: Posterior Analysis of the ln*HR* between non-HDL-C and LDL-C using truncated normal $N(0.89,0.06^2)$ on (0.5,1) for ρ.

Parameter	Mean	Median	Standard Deviation	95% Bayesian Interval
ρ	0.8777	0.9074	0.0923	(0.6126,0.9743)
μ_x-μ_y	0.008825	0.008702	0.0138	(-0:0093,0.02741)
$P(\mu_x$-$\mu_{y>0})$	0.861620	1.0	0.345302	(0.0,1.0)
Bayes factor of μ_x-$\mu_y \leq 0$ against μ_x-$\mu_y > 0$				0.161 favoring non-HDL-C (equivalent to 6.21 favoring LDL-C)

Discussion

In this case, we also learn that the correlation of the ln*HR* between non-HDL-C and LDL-C is high (close to 90%). However, although the Bayes factor seems more in favor of $\mu_{\text{non-HDL-C}}$-$\mu_{\text{LDL-C}} > 0$, the 95% Bayesian interval states that the difference may not be significant.

4. Comparison of results to Bayesian meta-analysis by Robinson and colleagues (2012)

On the surface, our results also contrast with a recent Bayesian meta-analysis by Robinson (2012) and colleagues. We say "on the surface" because the two analyses differed in several important respects suggesting the two sets of results should be interpreted differently.

4.1 Studies included

Robinson *et al.* included a total of 25 different trials (24 with CHD outcomes) and performed subgroup analysis in 12 "statin" trials compared to our 7. The 5 statin trials they included, but we did not, had low-dose rather than placebo control groups. We excluded all trials with any treatment other than statin in an attempt to isolate the benefit of LDL-lowering from other potentially risk reducing treatments. For example one trial they included compared aggressive versus standard cholesterol and blood pressure targets. Thus we thought it would be inaccurate to attribute the entire reduction in risk to LDL-lowering.

4.2 Dependent variable relative risk versus HR

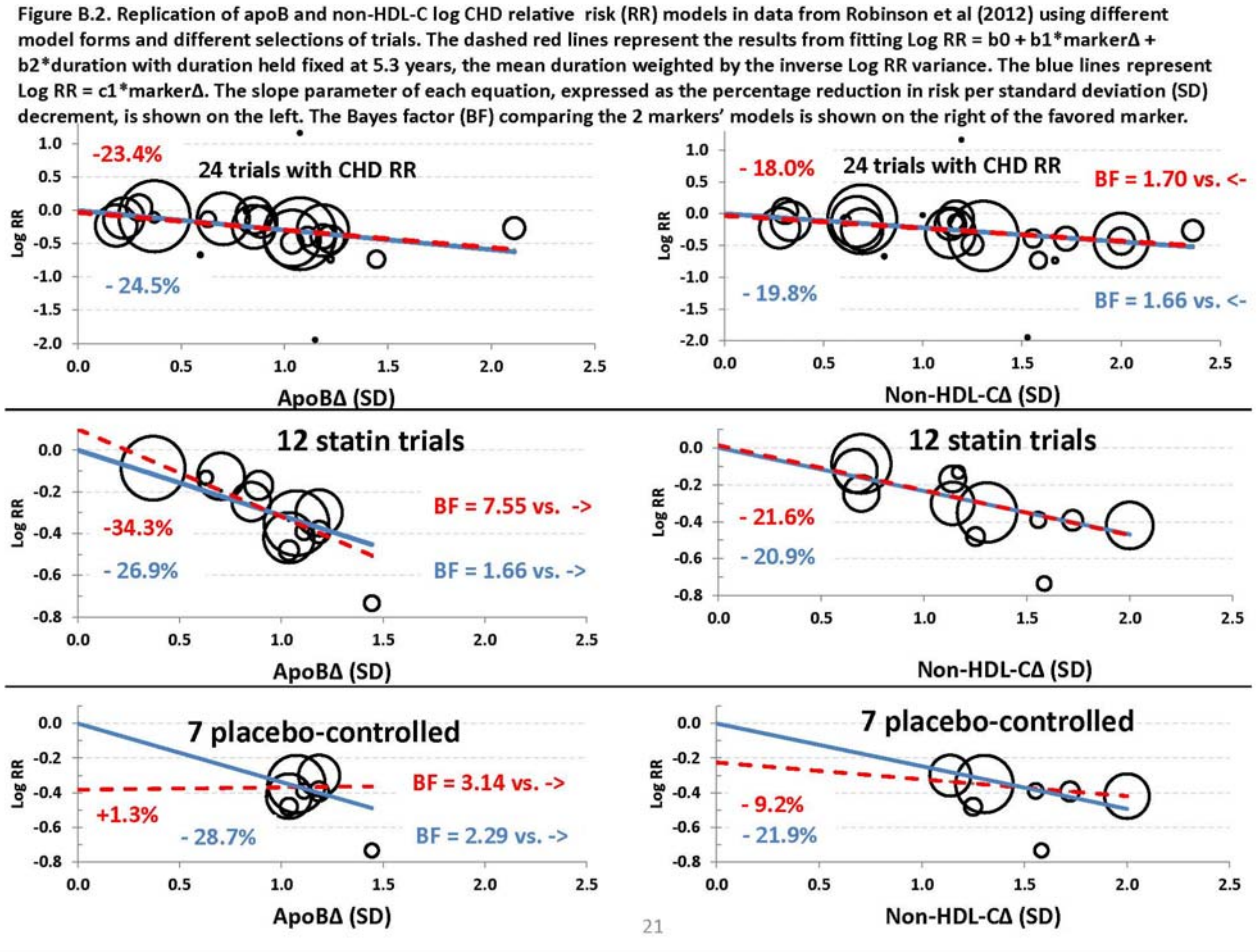
In the Robinson *et a*l report, the choice of dependent variable was the relative risk calculated from each treatment group's sample size and number of events while ours was based on the published HRs and 95% confidence intervals. While these variables are similar, HRs take into account any differences in censoring which existed between the groups.

4.3 Compared models versus effect sizes

Robinson *et al* compared how well the data supported two different models, one for each marker. Each model contained an intercept, the decrease in the marker, and the duration for each trial while we compared specific parameter estimates, the HRs per SD decrement. We believe the estimated HR per SD decrement of a marker is a better indicator of how effectively lowering a particular marker reduces risk. The assumption that the risk ratio is a function of the trial duration is counter the basic proportional hazards assumption of Cox regression which was used in the vast majority of the trials. They included an intercept term while we used no intercept assuming instead that a trial with no LDL-lowering would have no risk reduction attributable to either marker. With the

authors' cooperation, we were able to replicate their Bayesian meta-analyses using the data from their report on all trials. This reproduced their reported 9% reduction in CHD risk per 10 mg/dl decrease in apoB and a produced a 5% risk reduction per 10 mg/dl decrease in non-HDL-C which Robinson et al did not report. While it may be unusual for a model with a greater slope parameter estimate to not be supported as strongly by the data as a model with a lesser slope, it is possible as it was in this case. From their description of methods one can conclude that the finding stated in the abstract that the non-HDL-C "decrease modestly outperformed apoB decrease for prediction of coronary heart disease (Bayes factor [BF] 1.45)" might be more precisely stated that the data supported the non-HDL-C model better than the apoB model to an extent "barely worth mentioning". Since they were comparing models instead of parameters, the decrement chosen did not matter but in our comparison it did.

Figure S8. Replication of apoB and non-HDL-C CHD Relative Risk Models Using Data from Robinson et al.



To illustrate how significant the differences in approach can be, we replicated their Bayesian analysis comparing the model they used to the model we used in all 24 trials with CHD outcomes and in two subsets: 12 statin trials and 7 placebo-controlled statin trials. The results of these analyses are presented in Figure B.2. With one exception the mean marker slope expressed as risk reduction per SD

decrement of apoB was greater than per SD decrement of non-HDL-C; using their model form in the 7 placebo-controlled trials produced an estimated 1.3% increase in risk per SD reduction of apoB. According to this fit, a placebo-controlled statin trial with no apoB lowering and duration of 5.3 years would have an estimated Log RR of −0.383 equating to a 31.8% risk reduction. We believe this estimate was an aberrant result from including intercept and duration terms in the model. Note also the Bayes factor for this model 3.14 providing substantial support favoring the apoB model because it fits the data better even though the parameter estimate of interest to us was substantially weaker. Note also in all 24 trials with CHD outcomes the BF ~ 1.7 in both models modestly favors the non-HDL-C model although the slope estimate comparison favors apoB. In our replication of their approach using their model, the 95% confidence interval for each parameter included zero for both models though in opposite directions (negative in the apoB model and positive in the non-HDL-C model). Thus the possibility exists that in the 24 CHD trials non-HDL-C model was more overfit to the data than was the apoB model.

4.4 **Accounting for the lack of independence in the estimates**

Robinson et al apparently treated the models as though they were independent in the simulations for each model whereas both our frequentist and Bayesian analyses accounted for the covariance structure evident in the data, as well as the literature, allowing for the correlation between the markers within each trial and between the HRs and marker decreases across trials. Their approach was analogous to doing across-the-board independent t-tests while our approach is analogous to doing paired t-tests within individuals and within each trial. While the point estimates are similar with either approach, the statistical power to find more extreme Bayes factors is greater when the co-variances are modeled. We believe this difference explains why their BFs were in the "barely worth mentioning" range (BF 1 to 3) while our BFs are well above the 3 to 15 "substantial support" range.