A Meta-Analysis of Low-Density Lipoprotein Cholesterol, Non-High-Density Lipoprotein Cholesterol, and Apolipoprotein B as Markers of Cardiovascular Risk

Allan D. Sniderman, MD; Ken Williams, MSc; John H. Contois, PhD; Howard M. Monroe, PhD; Matthew J. McQueen, MBChB, PhD; Jacqueline de Graaf, MD, PhD; Curt D. Furberg, MD, PhD

Background—Whether apolipoprotein B (apoB) or non-high-density lipoprotein cholesterol (HDL-C) adds to the predictive power of low-density lipoprotein cholesterol (LDL-C) for cardiovascular risk remains controversial.

Methods and Results—This meta-analysis is based on all the published epidemiological studies that contained estimates of the relative risks of non-HDL-C and apoB of fatal or nonfatal ischemic cardiovascular events. Twelve independent reports, including 233 455 subjects and 22 950 events, were analyzed. All published risk estimates were converted to standardized relative risk ratios (RRRs) and analyzed by quantitative meta-analysis using a random-effects model. Whether analyzed individually or in head-to-head comparisons, apoB was the most potent marker of cardiovascular risk (RRR, 1.43; 95% CI, 1.35 to 1.51), LDL-C was the least (RRR, 1.25; 95% CI, 1.18 to 1.33), and non-HDL-C was intermediate (RRR, 1.34; 95% CI, 1.24 to 1.44). The overall comparisons of the within-study differences showed that apoB RRR was 5.7%>non-HDL-C ($P<0.001$) and 12.0%>LDL-C ($P<0.0001$) and that non-HDL-C RRR was 5.0%>LDL-C ($P=0.017$). Only HDL-C accounted for any substantial portion of the variance of the results among the studies. We calculated the number of clinical events prevented by a high-risk treatment regimen of all those >70th percentile of the US adult population using each of the 3 markers. Over a 10-year period, a non-HDL-C strategy would prevent 300 000 more events than an LDL-C strategy, whereas an apoB strategy would prevent 500 000 more events than a non-HDL-C strategy.

Conclusions—These results further validate the value of apoB in clinical care. **(*Circ Cardiovasc Qual Outcomes*. 2011;4:337-345.)**

Key Words: cholesterol LDL ■ cholesterol HDL ■ apolipoproteins B ■ cardiovascular diseases ■ risk ■ meta-analysis

Low-density lipoprotein cholesterol (LDL-C) is now so firmly entrenched in the professional and public consciousness that few remember the intense debate that attended its introduction into routine clinical care. On the one hand, total cholesterol (TC) was the accepted standard and could be measured accurately and inexpensively. On the other hand, LDL-C offered greater accuracy in the assessment of risk, particularly in the small number of individuals in whom TC would be misleading because of extreme values for high-density lipoprotein cholesterol (HDL-C). Moreover, LDL-C was a conceptual advance in that it identified more precisely the pathogenic mechanism that produced arterial injury. These advantages had to be balanced against the disadvantages of a more-complex and expensive technology that was not standardized, was not free of significant error, necessitated fasting, and required reeducation of the profession and the public. Notwithstanding that TC and LDL-C were highly correlated and that there was no evidence of a major increase in predictive accuracy in groups, LDL-C won out, although overall risk continued to be expressed as the TC/HDL-C ratio.

History repeats itself: There is now a similar debate about whether non-HDL-C and apolipoprotein B (apoB) should supplant LDL-C. Non-HDL-C is the sum of the masses of cholesterol in the atherogenic apoB lipoprotein particles. On average, approximately one quarter of this cholesterol is in very-low-density lipoprotein (VLDL) and three quarters in

Received September 24, 2010; accepted February 11, 2011.

From the Mike Rosenbloom Laboratory for Cardiovascular Research, Royal Victoria Hospital, McGill University Health Centre, Montreal, Quebec, Canada (A.D.S.); KenAnCo Biostatistics and University of Texas Health Science Center at San Antonio, San Antonio, TX (K.W.); Maine Standards Company, Windham, ME (J.H.C.); KenAnCo Biostatistics and Department of Mathematics, Our Lady of the Lake University, San Antonio, TX (H.M.M.); Population Health Research Institute and McMaster University, Hamilton, Ontario, Canada (M.J.M.); Department of General Internal Medicine, Division of Vascular Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands (J.G.); and Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC (C.D.F.).

The online-only Data Supplement is available at http://circoutcomes.ahajournals.org/cgi/content/full/CIRCOUTCOMES.110.959247/DC1.

Correspondence to Allan D. Sniderman, MD, Mike Rosenbloom Laboratory for Cardiovascular Research, Room H7.22, Royal Victoria Hospital-McGill University Health Centre, 687 Pine Ave W, Montreal, Quebec H3A 1A1, Canada. E-mail allansniderman@hotmail.com

LDL, although the actual proportion is highly variable.[1] ApoB is the number of atherogenic apoB lipoprotein particles because each of these contains 1 molecule of apoB. LDL particles account for 90% of the total apoB particles and VLDL the other 10%, with little change in this relation except for unusual conditions, such as familial dyslipoproteinemia.[2] Thus, apoB may be usefully considered a measure of LDL particle number (LDL-P) and is closely correlated to concentrations of LDL-P derived by NMR spectroscopy.[3]

Both non-HDL-C and apoB have been shown to be superior to LDL-C in a number of prospective epidemiological studies. The conventional explanation for the superiority of non-HDL-C over LDL-C is that it includes the cholesterol in VLDL. We tested this hypothesis and demonstrated that because there is almost always very much more cholesterol in LDL than in VLDL, the relative risk of VLDL cholesterol versus LDL-C would have to be unrealistically high for this to be the explanation.[4] Rather, non-HDL-C appears to be a more accurate index of vascular risk than LDL-C because it is a better surrogate for LDL-P assessed by either apoB or NMR measurement.[4,5] Given their very high degree of correlation, it is not surprising that in large groups the overall relations of non-HDL-C and apoB to ischemic risk are very similar.

WHAT IS KNOWN

- Both non-high-density lipoprotein cholesterol (Non-HDL-C) (the total mass of cholesterol within the very-low-density lipoprotein [LDL] and LDL particles) and apolipoprotein B (apoB) (the total number of atherogenic apoB lipoprotein particles) have been suggested to be more accurate markers than LDL cholesterol (LDL-C) of the risk of vascular disease.
- The results of individual published studies have not yielded a consistent result, particularly with regard to the relative predictive powers of non-HDL-C and apoB.

WHAT THE STUDY ADDS

- The present study is a meta-analysis of all the published studies reporting estimates of the relative risks of non-HDL-C and apoB of fatal and nonfatal ischemic vascular events.
- Whether analyzed individually or head to head, apoB was the most potent marker of risk, LDL-C was the least, and non-HDL-C was intermediate.
- This study indicates that apoB is superior to LDL-C and non-HDL-C as a predictor of cardiovascular risk.

Indeed, the Emerging Risk Factors Collaboration (ERFC) meta-analysis found the hazard ratios of apoB and non-HDL-C and of non-HDL-C and LDL-C to be indistinguishable.[6] The ERFC meta-analysis was based on patient-level data, which was one of its major strengths. Of the total of 68 studies included, apoB and non-HDL-C could be compared in 22. The authors' conclusion is that all 3 variables (LDL-C, non-HDL-C, and apoB) are interchangeable as markers of vascular risk, but this conclusion conflicts with the considerable published evidence (as discussed in this article) that apoB and non-HDL-C are superior to LDL-C for this purpose.

Of note, not all the published prospective studies were included in the ERFC meta-analysis, and 2 major case-control studies were specifically excluded. Accordingly, we have undertaken a meta-analysis of all published reports containing apoB and non-HDL-C cardiovascular relative risk ratios (RRRs). Our objectives were to determine the overall balance of the evidence comparing the standardized RRRs of all 3 markers and, if possible, to identify any factors associated with the variance among the studies.

Methods

Data Sources

We attempted to identify all published reports that reported risk estimates of non-HDL-C and apoB, relying on 4 sources: (1) the ERFC study,[6] (2) a literature search based on PubMed for articles published since 2005 containing both *apoB* and *non-HDL-C* as key words; (3) a meta-analysis by Thompson and Danesh[7] that included all published reports since 1997 containing apoB risk associations, and (4) narrative reviews by Sniderman et al[8] and the American Association for Clinical Chemistry Lipoproteins and Vascular Diseases Division Working Group on Best Practices.[9] From these sources, as shown in Figure 1, a total of 107 reports were identified. Of the 68 studies cited within the 56 reports noted in e-Appendix 1 of the ERFC study,[6] 45 lacked relevant data and are not included in either meta-analysis. One, the Framingham Offspring Study,[10] was cited by ERFC but, apparently, not included in the comparison of apoB with non-HDL-C and LDL-C. Thus, the ERFC comparison is based on 22 studies. On the other hand, the published versions of 19 studies included in the ERFC meta-analysis did not contain apoB and non-HDL-C risk associations, so they could not be included in the current meta-analysis. Three[11–13] of the original 56 reports cited in the ERFC and the Framingham Offspring Study[10] were included in the current meta-analysis. Of the 51 other reports identified either through PubMed or through the other reviews, 10 had published apoB and non-HDL-C RRRs. We used 2 of these reports[12,13] instead of ERFC-cited reports because the Copenhagen City Heart Study report cited by ERFC[14] did not contain the necessary risk associations, and the Women's Health Study report[15] excluded women taking hormone replacement therapy. The remaining 8 reports[16–23] with risk associations were included in the current analysis. Thus, 12 published reports containing both apoB and non-HDL-C vascular associations were identified for the present analysis.[10–13,16–23] Three studies[10,13,17] reported results stratified by sex, bringing the total number of analyses to 15 (Table).

Calculations

All published apoB, non-HDL-C, and LDL-C risk associations (odds ratios or hazard ratios) and 95% CIs were converted to RRRs per 1-SD increment in the study being examined. Accordingly, in all studies, risk was estimated as a continuous variable. If the risk associations were reported by quantiles, the increments were set equal to the difference between standard normal distribution mean values of the 2 quantiles compared (2.18 SDs for top versus bottom tertiles, 2.54 for quartiles, and 2.80 for quintiles). SEs for each log-RRR point estimate were calculated from the CIs. SEs for the difference between 2 measures were estimated using the reported correlation between the 2 measures or, if not reported, the correlation in the National Health and Nutrition Examination Survey 2005 to 2006 code book[24] (apoB correlation, $r=0.89$ with LDL-C and $r=0.95$ with non-HDL-C; non-HDL-C correlation with LDL-C, $r=0.94$). Estimates of the means and SDs of apoB, non-HDL-C, LDL-C, TC, HDL-C, and triglycerides were derived from reported statistics.

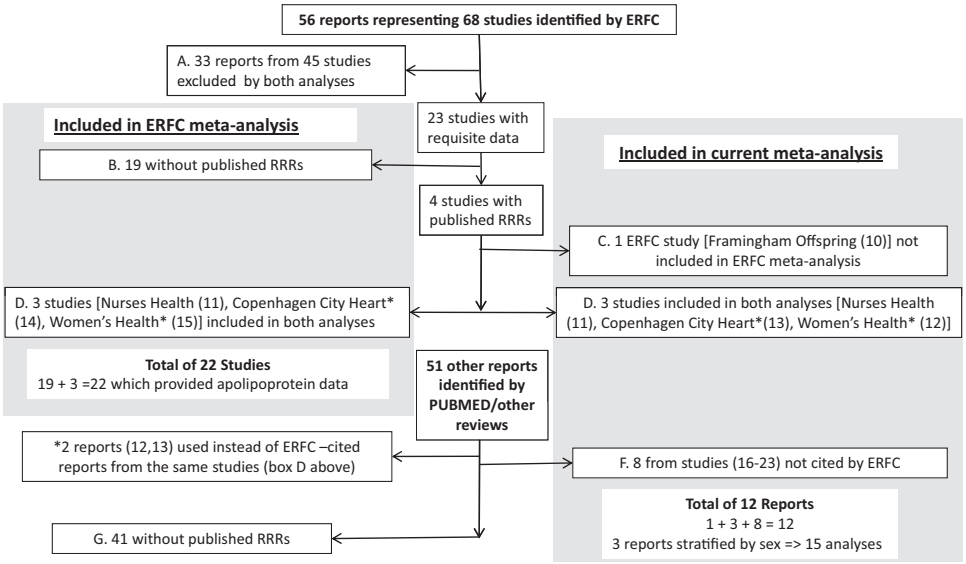


Figure 1. Comparison of reports and studies included in the current meta-analysis versus those included in the ERFC comparison of apoB and non-high-density lipoprotein cholesterol RRRs for cardiovascular events. The 107 candidate reports for the current meta-analysis are categorized A through E as indicated in the text and listed individually in online-only Data Supplement Table 1. The ERFC meta-analysis obtained patient-level data from all studies whether previously published or not, whereas the current meta-analysis was based on published statistics only. ERFC indicates Emerging Risk Factors Collaboration; RRR, relative risk ratio.

Meta-Analysis Model

Meta-analyses of these statistics were performed as recommended by Borenstein et al[25] with a random-effects model. We chose a random-effects rather than a fixed-effects model for a number of reasons, among which was the fact that not all studies had the same mixture of clinical ischemic events, as follows: The Casale Monferrato study[19] was based only on fatal ischemic events; the INTERHEART study[22] and International Studies of Infarct Survival (ISIS)[23] were based only on nonfatal ischemic events; and the remainder included both nonfatal and fatal events. By choosing a random-effects model, we do not assume that the atherogenic parameters being compared have exactly the same relation to fatal as to nonfatal ischemic events.

Subgroup analyses were conducted to assess the heterogeneity associated with the different attributes of the studies. Meta-regression also was performed using continuous measures. In addition, because this review was limited to published reports, we conducted analyses to assess the extent of publication bias.

Results

The 15 independent published analyses identified for this meta-analysis provided a total of 233 455 subjects and 22 950 events.

RRRs of Each Marker

The forest plots of the RRRs from these studies for each of the 3 indices (LDL-C, non-HDL-C, and apoB) are shown in Figure 2, and details are provided in online-only Data Supplement Figures 1 through 3.The overall geometric mean RRRs (95% CI) among these 15 analyses were as follows: apoB, 1.43 (1.35 to 1.51); non-HDL-C, 1.34 (1.24 to 1.44); and LDL-C, 1.25 (1.18 to 1.33) (all $P<0.001$). These results pointed to a hierarchy of accuracy among the 3 markers, with apoB having the highest RRR, LDL-C having the lowest RRR, and non-HDL-C an intermediate RRR. Each individual study RRRs were significantly ($P<0.05$) >1.0 except for non-HDL-C in the Casale Monferrato study ($P=0.22$)[19] and Copenhagen Heart women ($P=0.058$)[13] and for LDL-C in the health professionals with diabetes ($P=0.08$),[16] Casale Monferrato ($P=0.17$), Copenhagen Heart women ($P=0.13$), and Framingham Offspring ($P=0.13$ in men; $P=0.07$ in women; reported as significant when pooled, however) studies.

Percentage Differences Among RRRs

The meta-analysis of the percentage difference between the apoB and non-HDL-C RRRs is shown in Figure 3A. On average, across all studies, the apoB RRR was 5.7% higher than the non-HDL-C RRR (95% CI, 2.4% to 9.1%; $P<0.001$). Thus, apoB in head-to-head comparison was superior to non-HDL-C. The comparison of non-HDL-C to LDL-C is shown in Figure 3B. On average, the RRR of non-HDL-C was 5.0% greater than the LDL-C RRR (95% CI, 0.9% to 9.1%; $P=0.017$). Finally, Figure 3C shows the forest plot of the comparison of apoB and LDL-C. On average, the RRR of apoB was 12.0% greater than the RRR of LDL-C (95% CI, 8.5% to 15.4%; $P<0.0001$). These head-to-head analyses also rank order the 3 markers as follows: apoB>non-HDL-C>LDL-C. Additional details on the head-to-head comparisons are provided in online-only Data Supplement Figures 4 through 6. There was significant heterogeneity of each of these 3 comparisons across all the studies ($P<0.001$).

Heterogeneity and Meta-Regression Analysis

The studies comparing apoB to non-HDL-C can be divided into 2 groups: those that found the 2 markers to be equivalent and those that demonstrated apoB to be statistically superior. No study demonstrated non-HDL-C to be substantially better than apoB. To assess this heterogeneity in outcome, we conducted the subgroup analyses presented in online-only Data Supplement Figure 7. There was no evidence of any significant effect on the variance of within-study difference between the apoB RRR and the non-HDL-C RRR due to sex, age range, diabetes status, outcome measure, or documenta-

Table. Published Studies With Vascular Risk Associations for Both Apolipoprotein B and Non-HDL-C

								Relative Risk Reported		
Year	Study	Sex	Design	Assay*	Outcome	Adjust†	Per‡	ApoB	Non-HDL-C	LDL-C
2004	Health Professionals[16]	Male	Pros	Y Y Y	CVD	Demog	Quintile	2.31 (1.25–4.27)	2.25 (1.24–4.08)	1.63 (0.94–2.81)
2004	Nurses' Health[11]	Female	Pros CC	Y Y Y	CHD	+RFs	1 SD	1.80 (1.50–2.20)	1.60 (1.30–1.90)	1.40 (1.20–1.60)
2005	MONICA/KORA[17]	Male	Pros	N Y Y	CHD	+RFs	1 SD	1.49 (1.25–1.78)	1.49 (1.26–1.75)	Not reported
2005	MONICA/KORA[17]	Female	Pros	N Y Y	CHD	+RFs	1 SD	1.73 (1.32–2.27)	1.79 (1.40–2.30)	Not reported
2005	Health Professionals[18]	Male	Pros CC	Y Y Y	CHD	+RFs	Quintile	2.98 (1.76–5.06)	2.75 (1.62–4.67)	2.07 (1.24–3.45)
2005	Women's Health[15]	Female	Pros	Y Y Y	CVD	+RFs	Quintile	2.50 (1.68–3.72)	2.51 (1.69–3.72)	1.62 (1.17–2.25)
2006	Casale Monferrato[19]	Pooled	Pros	_ _ _	Fatal CVD	+RFs	Quartile	1.48 (1.02–2.14)	0.79 (0.54–1.15)	0.77 (0.53–1.12)
2007	Copenhagen Heart[13]	Female	Pros	N _ _	IHD	Demog	Tertile	1.51 (1.19–2.50)	1.28 (0.99–1.85)	1.27 (0.98–1.83)
2007	Copenhagen Heart[13]	Male	Pros	N _ _	IHD	Demog	Tertile	1.95 (1.49–2.55)	1.90 (1.45–2.50)	1.70 (1.24–2.24)
2007	Chin–Shan Cohort[20]	Pooled	Pros	Y Y Y	CHD	+RFs	Quintile	2.74 (1.45–5.19)	1.98 (1.00–3.92)	1.86 (1.00–3.46)
2007	Fram Offspring[10]	Female	Pros	Y Y Y	CHD	+RFs	1 SD	1.38 (1.15–1.67)	1.28 (1.06–1.56)	1.20 (0.99–1.46)
2007	Fram Offspring[10]	Male	Pros	Y Y Y	CHD	+RFs	1 SD	1.37 (1.20–1.57)	1.22 (1.06–1.40)	1.11 (0.97–1.27)
2008	AMORIS[21]	Pooled	Pros	Y Y Y	MI	Demog	1 SD	1.51 (1.47–1.55)	1.50 (1.46–1.53)	1.42 (1.36–1.45)
2008	INTERHEART[22]	Pooled	CC	Y Y Y	Nonfatal MI	Smoking	1 SD	1.32 (1.28–1.36)	1.21 (1.17–1.24)	1.28 (1.25–1.32)
2009	Women's Health[12]	Female	Pros	Y Y Y	CVD	+RFs	Quintile	2.57 (1.98–3.33)	2.52 (1.95–3.25)	1.74 (1.40–2.16)
2009	ISIS[23]	Pooled	CC	_ _ _	Nonfatal MI	Smoking	2 SDs	2.66 (2.37–2.99)	2.10 (1.89–2.33)	2.21 (1.96–2.48)

Data are presented as relative risk reduction (95% CI). AMORIS indicates Apolipoprotein Mortality Risk study; ApoB, apolipoprotein B; CC, case control; CHD, coronary heart disease; CVD, cardiovascular disease; Demog, demographics; Fram, Framingham; HDL-C, high-density lipoprotein cholesterol; IHD, ischemic heart disease; ISIS, International Studies of Infarct Survival; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; MONICA/KONA, Monitoring of Trends and Determinants in Cardiovascular Disease Augsburg project; Pros, prospective; RF, risk factor.

*Our consensus assessment of the assurances reported regarding apoB assay quality: Y indicates yes; N, no; _, unknown (not reported); first assessment, whether the assay used was World Health Organization-International Federation of Clinical Chemistry and Laboratory Medicine standardized; second assessment, whether the assay was robust (quality assay with documented performance); third assessment, whether sample integrity was maintained.

†Adjust indicates extent of adjustments as follows: demographics, age, sex, and ethnicity/region; smoking, demographics+smoking only; +RFs, demographics+conventional risk factors. A complete list of all covariates is provided in online-only Data Supplement Table 1.

‡Per indicates the increment for reported risk associations (highest vs lowest quantile).

tion of assay quality. However, heterogeneity was significant ($P<0.001$) by type of outcome as follows: the Casale Monferrato study[19] with an apoB RRR 28.0% (95% CI, 10.3% to 48.6%; $P<0.001$) higher than that for non-HDL-C, included only fatal outcomes; ISIS and INTERHEART combined (10.7%; 95% CI, 6.4% to 15.3%; $P<0.001$) included only nonfatal outcomes; and all the other studies that included both fatal and nonfatal outcomes favored apoB by 3.5% (95% CI, 1.1% to 5.9%; $P<0.01$). ISIS and INTERHEART, on the basis of their size, yielded the most precise estimates of effect size. However, even if both are excluded from the analysis, apoB remains superior to non-HDL-C as a marker of risk ($P<0.01$).

We used meta-regression to search for a potential explanation of the dispersion of the results. By the method of moments (appropriate given our assumption of random effects), no significant impact was observed for year of publication ($P=0.49$), mean age of subjects ($P=0.60$), or the range of apoB estimated as the SD divided by the mean ($P=0.48$). By contrast, as shown in Figure 4, the results of the meta-regression of mean HDL-C levels were of interest. Studies with higher mean HDL-C concentrations were associated with smaller differences between the RRR for non-HDL-C and apoB, whereas studies with lower HDL-C levels were associated with greater differences. Including all studies resulted in an overall association between HDL-C and the difference in RRR between apoB and non-HDL-C that almost reached statistical significance ($P=0.064$), and the R^2 of 0.565 indicated that the variance in HDL-C explained more than half of the overall variance in the differences in RRR between non-HDL-C and apoB. If the Casale Monferrato study[19] were to be excluded from the regression as an outlier (Figure 4), the association became significant with an even higher R^2 (0.613, $P=0.034$). It is noteworthy that the correlation between apoB and non-HDL-C in the Casale Monferrato study was substantially less than usual, and the point estimates of both non-HDL-C and LDL-C RRRs were <1.0.

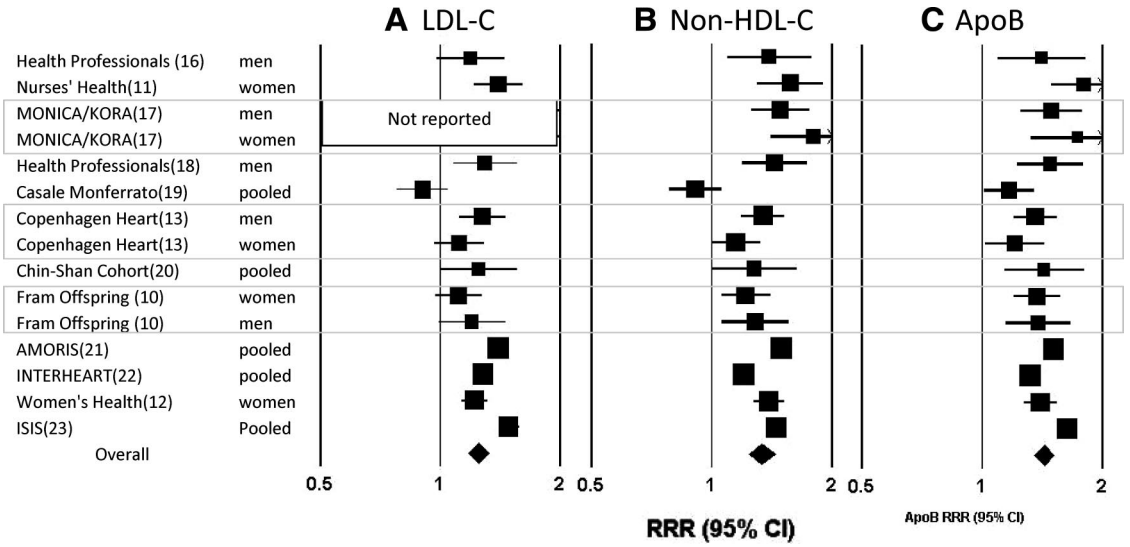


Figure 2. Forest plots of standardized vascular RRRs and 95% CIs for LDL-C (**A**), non-HDL-C (**B**), and apoB (**C**) from 12 independent epidemiological studies reporting RRRs for both apoB and non-HDL-C. The area of each marker is proportional to the weight (1/variance of the estimate) of the study in the meta-analysis. The diamond represents the estimated mean (95% CI) of all studies' effects as follows: apoB, 1.43 (1.35 to 1.51); non-HDL-C, 1.34 (1.24 to 1.44); and LDL-C, 1.25 (1.18 to 1.33). The overall effect and heterogeneity were highly significant ($P<0.001$) for each marker. An earlier Women's Health Study report[15] was excluded because its data were a subset of the data analyzed for the subsequent Women's Health Study report.[12] AMORIS indicates Apolipoprotein Mortality Risk study; ApoB, apolipoprotein B; Fram, Framingham; ISIS, International Studies of Infarct Survival; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MONICA/KORA, Monitoring of Trends and Determinants in Cardiovascular Disease Augsburg project; RRR, relative risk ratio.

All are consistent with the non-HDL-C result in Casale Monferrato being an outlier.

Publication Bias

The analyses to assess the potential for publication bias[25] revealed no significant evidence that our principal findings herein would be significantly altered by the inclusion of other reports (online-only Data Supplement Figure 8).

Discussion

This meta-analysis indicates that apoB is a more accurate marker of cardiovascular risk than non-HDL-C and that non-HDL-C is a more accurate marker of cardiovascular risk than LDL-C. There is a hierarchy among the markers, with apoB as the best, LDL-C as the worst, and non-HDL-C as intermediate between apoB and LDL-C. Moreover, the advantage of apoB over LDL-C was much greater than the

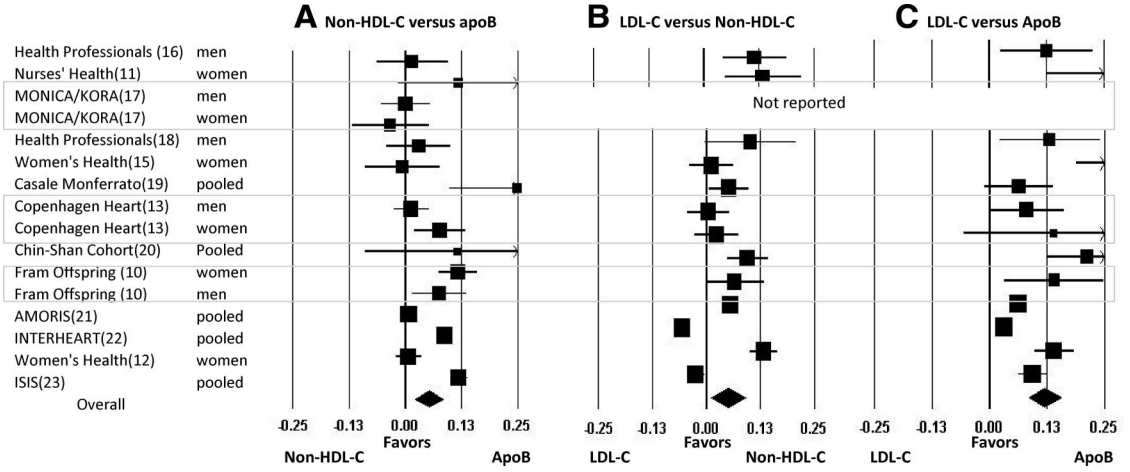


Figure 3. Forest plots of the differences between the logarithm of standardized RRRs of non-HDL-C (**A**), LDL-C (**B**), and apoB (**C**) from 12 independent epidemiological studies reporting RRRs for both apoB and non-HDL-C. The marker for each study represents the point estimate of the difference, and lines represent the 95% CIs. The area of each marker is proportional to the weight (1/variance of the estimate) of the study in the meta-analysis. The diamond represents the estimated mean difference (95% CI) across all studies. These differences were converted to percentages ($e^{\text{difference in log RRRs}}-1$) as follows: apoB RRR is 5.7% (2.4% to 9.1%) higher than non-HDL-C RRR ($P=0.001$) and 12.0% (8.5% to 15.4%) higher than LDL-C RRR ($P<0.001$) and non-HDL-C RRR is 5.0% (0.9% to 9.1%) higher than LDL-C RRR ($P=0.017$). AMORIS indicates Apolipoprotein Mortality Risk study; ApoB, apolipoprotein B; Fram, Framingham; ISIS, International Studies of Infarct Survival; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MONICA/KORA, Monitoring of Trends and Determinants in Cardiovascular Disease Augsburg project; RRR, relative risk ratio.

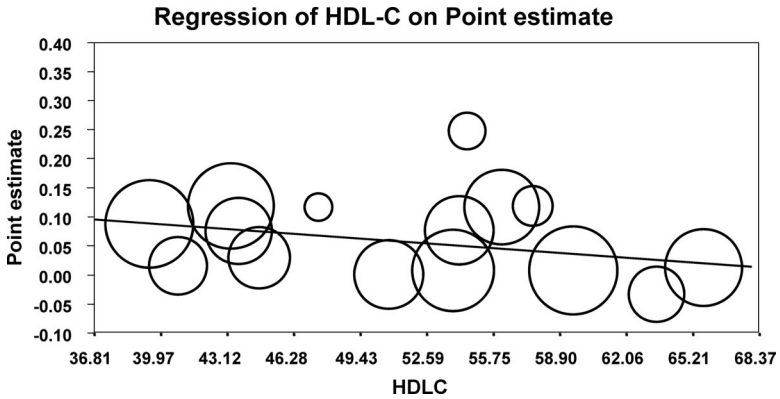


Figure 4. Plot of the meta-regression of the studies' mean HDL-C levels on the difference between apoB and non-HDL-C log-RRRs. The weight given each study by the method of moments is indicated by the area within each circle. The estimated slope of this curve represents a decrease in the difference of 0.0026 per milligram/deciliter increase in mean HDL-C ($P=0.064$). The R^2 index is 0.565, indicating more than half of the variance among studies may be explained by the variance in the studies' mean HDL-C level. If the Casale Monferrato study is excluded as an outlier, the method of moments estimate of the slope is −0.0028 ($R^2=0.613$, $P=0.034$). AMORIS indicates Apolipoprotein Mortality Risk study; ApoB, apolipoprotein B; Fram, Framingham; ISIS, International Studies of Infarct Survival; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MONICA/KORA, Monitoring of Trends and Determinants in Cardiovascular Disease Augsburg project; RRR, relative risk ratio.

advantage of non-HDL-C over LDL-C. Our findings differ, therefore, from those of the ERFC, which found apoB, LDL-C, and non-HDL-C to be of equivalent value as markers of cardiovascular risk.[6]

Comparison of Present Study With the ERFC Study

A major strength of the ERFC study is that the analyses are patient based and not study based as in the present analysis. Moreover, ERFC included only prospective epidemiological studies, although many were not originally designed as such. The apoB versus non-HDL-C comparisons in the ERFC study are based on 22 studies that included 91 307 subjects and 4449 events, whereas the present results are based on 12 reports that included 233 455 subjects and 22 950 events. Because we have relied on published materials, only 3 of the 22 studies used in the ERFC could be incorporated in the present analysis. Conversely, 9 of the studies included in this analysis were not incorporated in the ERFC study.

ERFC specifically excluded 2 major case-control studies—INTERHEART[22] and ISIS[23]—whereas we included them in the present analysis. There are arguments on both sides. Correct matching of controls to cases and the possibility that consequences of the event might alter the risk profile of the cases are potential weaknesses of the case-control design. By contrast, the massive number of cases that can be compared to controls, a strength that is particularly relevant in the present instance where closely correlated variables are being compared, is an indisputable strength of the case-control design. It is noteworthy that the effect sizes of INTERHEART and ISIS fit within the range of the other studies that make up the present analysis. The very large number of events, however, does result in much greater precision in the estimate of the effect size. No evidence of bias due to sampling time or other relevant biases was found in either study. Finally, omitting these studies does not change the overall results. ERFC also omitted the AMORIS (Apolipoprotein Mortality Risk) study on the basis that HDL-C was calculated, not measured by conventional methods.[21] However, the investigators validated this approach. AMORIS,[21] unlike INTERHEART[22] and ISIS,[23] showed non-HDL-C and apoB to be virtually the same in predictive value.

Nineteen out of the 22 studies included in the ERFC[6] have not published their results, particularly their event rates and lipid and apoB values, which limits assessment of the completeness of the follow-up, definition of events, adequacy of sample preservation, and assay quality. The last points are of particular relevance because it is clear that a number of the reports included in the ERFC were not either initially designed as prospective studies or intended to measure apoB. Moreover, whereas the present study pointed to a hierarchy of efficacy among the major markers for the atherogenic lipoproteins, a result that is consistent with the results of individual published studies, ERFC, which had 5 times fewer events, reported no significant gradient of efficacy among the 3 markers, a finding that is at variance with the published literature. It is also noteworthy that in the ERFC analysis, triglycerides had no independent predictive power, whereas in a prior study[26] and subsequent meta-analysis[27] by some of the same investigators, triglycerides were independent significant predictors of risk.

The results of the published studies that make up the present meta-analysis fall into 2 categories: those that show non-HDL-C and apoB to be equivalent as markers of risk and those that show apoB to be superior. We could not identify any published study that showed non-HDL- C to be substantially superior to apoB, and there was no evidence of publication bias. It is worth noting that even if the risk of non-HDL-C and apoB were equal overall in predictive power within groups, this finding would not be the case for large numbers of individuals within those groups.[28] VLDL and LDL particles differ in composition on the basis of differences in cholesterol content. These compositional differences often produce differences in the concentration of non-HDL-C and apoB that are sufficiently different as to produce clinically significant differences in risk assessments.

It is worth noting that the INTERHEART study demonstrated that all the major modifiable risk factors, including apoB, had similar associations in all the major peoples of the world.[29] Accordingly, our choice of a random-effects model rather than a fixed-effects model represents a conservative approach to the analysis of the interactions.

Pathophysiological Basis for Non-HDL-C as a Marker of Vascular Risk

That non-HDL-C and apoB should be close in performance as markers of risk should not be surprising given the very high correlation (generally >0.9) that exists between them. Non-HDL-C includes all the cholesterol in the apoB lipoproteins, whereas apoB reflects the total number of apoB-containing particles, the great majority of which are LDL. The present analysis indicates that non-HDL-C is superior to LDL-C as a marker of cardiovascular risk. The conventional explanation would be that the gain in predictive power is due to the cholesterol in VLDL. However, as we have outlined here, this cannot be the case. The superiority of non-HDL-C over LDL-C is due to the fact that non-HDL-C is a better marker of LDL-P than LDL-C.[4,5] It is not surprising, therefore, that non-HDL-C falls intermediately between apoB or LDL-P and LDL-C as a marker of cardiovascular risk, whereas apoB and LDL-P appear to be equivalent as predictors of risk.

The Impact of HDL-C on the Relative Predictive Powers of Non-HDL-C and ApoB

With the exception of HDL-C, we were unable to identify any factor that could materially affect the variance in the comparisons of the predictive power between non-HDL-C and apoB among the studies. LDL-C and HDL-C are independent variables. By contrast, there is evidence of a significant inverse relation between HDL-C and apoB or LDL-P such that lower levels of HDL-C tend to be associated with higher levels of apoB.[30] The inverse relation between apoB and HDL-C likely relates to the fact that HDL, as well as LDL, can participate in cholesteryl ester transfer protein-mediated core lipid exchange with the VLDL or LDL, with cholesteryl ester moving to the apoB particles in exchange for triglyceride moving to the HDL particles. A higher HDL-C points to less core lipid exchange and, therefore, greater concordance between non-HDL-C and apoB. A lower HDL-C points to more core lipid exchange and, therefore, greater discordance between non-HDL-C and apoB. When apoB and non-HDL-C are concordant, they will predict risk equally, whereas when they are discordant, apoB will be superior. Thus, one explanation consistent with our meta-regression findings is that compositional changes from core lipid exchange explain much of the variance in the predictive power of non-HDL-C and apoB. As discussed in this article, however, the predictive power of non-HDL-C appears to be related more to LDL-P than to inclusion of VLDL cholesterol along with LDL-C.[4]

Our findings add to the urgency to better understand the relation of HDL to the risk of vascular disease. Is HDL as important as we previously thought, and if so, which marker of HDL is most appropriate: HDL-C or HDL particle number? Alternatively, is the risk associated with HDL related more directly to one of the very large molecules that are associated with it?

Population Implications

To help readers to assess the potential clinical significance of this report's statistical conclusions, we estimated the differences in outcome using the different markers of LDL-associated risk. These estimates of benefit are possible because the National Health and Nutrition Examination Survey 2005 to 2006 is designed to be representative of the entire nonpregnant, noninstitutionalized, civilian American population.[24] Targeting the different markers in the same National Cholesterol Education Program Adult Treatment Panel III-based preventive treatment strategy[31–33] reveals that selecting non-HDL-C rather than LDL-C could potentially reduce the number of incident cases among adult US residents by an additional 300 000 (1.8 million versus 1.5 million) over 10 years, whereas targeting apoB rather than non-HDL-C would prevent another 500 000 patients (2.3 million versus 1.8 million) from experiencing a coronary event. These differences in effectiveness result from the higher average absolute risk among patients eligible for treatment and the greater RRRs associated with the measures with higher RRRs. It must be noted that these calculations are principally intended to illustrate the clinical implications and should not be taken as advocating the particular strategy assumed for the comparisons. Comparing more-complex, and potentially more effective, strategies is beyond the scope of this article. However, comparisons of scenarios with different targets using the realistic strategy chosen demonstrate that the differences in overall average standardized relative risks are clearly clinically as well as statistically significant.

Individual Patient Implications

We believe that the present results add to the already strong case that apoB be monitored routinely in the care of individual patients. We would note 4 points in particular. First, measurement of apoB identifies major abnormalities in LDL that are not evident when LDL-C is relied on, including in many patients with type 2 diabetes and the metabolic syndrome in whom LDL-C level is normal but apoB level is elevated.[8] Importantly, not all hypertriglyceridemic patients have elevated apoB, and not all normotriglyceridemic normocholesterolemic patients have a normal apoB.[8] As well, a substantially increased LDL-P will not be recognized in other patients who present with low HDL-C and otherwise normal lipids if apoB level is not measured.[34,35] On the other hand, apoB also allows a more accurate assessment of risk in individuals with elevated LDL-C but normal apoB levels.[36]

Second, measurement of apoB along with TC and triglyceride levels makes diagnosis of all the atherogenic dyslipoproteinemias possible in individual patients.[37] This includes identification of familial combined hyperlipidemia, the most common familial dyslipoproteinemia associated with vascular disease, and familial dysbetalipoproteinemia, an unusual but not rare dyslipoproteinemia associated with major vascular risk that cannot be diagnosed accurately at the present time in most lipid clinics.

Third, successful diagnosis and therapy in individual patients demands that the diagnostic biomarker be measured accurately and precisely. When LDL-C was introduced into clinical practice, great effort was expended to ensure that the laboratory determination was as reliable as possible. Particular attention was paid to the measurement of HDL-C, a component of the Friedewald equation. Although never fully standardized, the chemical precipitation methods were reasonably reliable and robust. Unfortunately, that is less true with newer, homogeneous HDL-C methods, and errors in the measurement of HDL-C can affect the accuracy of non-HDL-C measurement. The clinical assays for apoB, on the other hand, have become reliable and robust, and apoB can be measured on nonfasting samples at low cost.[9] Accordingly, apoB is superior to LDL-C and non-HDL-C as a laboratory analyte, and reducing laboratory error will reduce clinical error in individual patient care.

Fourth, although within statin trials non-HDL-C and apoB are generally equivalent risk markers,[8] apoB is a better marker of the individual who can benefit from an increased dose of statins in that apoB level identifies more individuals with LDL-P that remain elevated above reasonable percentile target levels of the population.[38]

The Canadian guidelines determined that levels of apoB ≥120 mg/dL identify patients at high risk of vascular disease due to atherogenic lipoproteins and selected a single target of <80 mg/dL.[39] No very-high-risk target was selected, but based on the most recent statin clinical trials, we would suggest that it be <70 mg/dL. Thus, 120 mg/dL, 80 mg/dL, and 70 mg/dL for apoB would correspond to values of 160 mg/dL, 100 mg/dL, and 70 mg/dL for LDL-C and 190 mg/dL, 130 mg/dL, and 100 mg/dL for non-HDL-C.

Summary

The present meta-analysis indicates that apoB is superior to non-HDL-C and that non-HDL-C is superior to LDL-C as a predictor of cardiovascular risk. Moreover, we have shown that if apoB measurement is introduced into routine care, many more events would be prevented than if diagnosis and therapy were based on either LDL-C or non-HDL-C levels. Thus, at a population level, apoB is a superior analytic tool to LDL-C or non-HDL-C. The issue is complicated, however, because the advantage of apoB is not constant. In patients in whom LDL composition is normal, the cholesterol markers and apoB are equivalent markers of risk.[5,8] The critical difference is when the markers are discordant, that is, when LDL-C is normal but LDL-P is high or, alternatively, when LDL-C is high but LDL-P is normal. Here, the evidence-indicated risk follows apoB and LDL-P, not LDL-C.[5,8,38]

Significant discordance in LDL composition is common. Hypertriglyceridemic hyperapoB is characterized by increased cholesterol-depleted LDL-P.[5] Hypertriglyceridemic hyperapoB is the hallmark dyslipoproteinemia associated with diabetes mellitus and the metabolic syndrome[40] and the most common dyslipoproteinemia associated with premature coronary artery disease.[8] Indeed, it is only because discordant LDL is so common in the general population that apoB becomes a more accurate overall marker of cardiovascular risk than LDL-C or non-HDL-C.

Entry and trapping of apoB lipoprotein particles within the arterial wall is the prime cause of atherosclerosis, the signal event that initiates, sustains, and collaborates in completing the long complex cycle that results in the acute arterial injury that produces a clinical event. Given this fundamental pathophysiological reality, it makes clinical sense to measure the parameter that matters most to this process—the number of atherogenic apoB particles in plasma, apoB—rather than the concentration of a constituent of these atherogenic particles—cholesterol.

This dispute about markers is a dispute with consequence. If measures of atherogenic particle number are not introduced into clinical care and if the apoB model is valid, we have shown that the price in terms of lives lost that could have been saved and infarcts that occurred that could have been prevented would be substantial. Accordingly, not introducing the apoB model into clinical care demands a high degree of certainty that the evidence in favor of apoB is not correct, a degree of certainty we submit is not reasonable given the array of available evidence.

We believe that history does repeat itself. LDL-C allowed us to move from plasma lipids to lipoprotein lipids, a change that at the time was hotly disputed, but a change that with time led to improvement in diagnosis and therapy. Similarly, apoB will allow us to move from lipoprotein lipids to lipoprotein particles, and this will lead to further improvement in diagnosis, therapy, and prevention of cardiovascular events.

Sources of Funding

This research was funded entirely by the Mike Rosenbloom Laboratory for Cardiovascular Research, Royal Victoria Hospital, McGill University Health Centre, Montreal, Quebec, Canada.

Disclosures

None.

References

1. Sniderman AD, Hogue JC, Bergeron J, Gagné C, Couture P. Non-HDL cholesterol and apoB in dyslipidaemia. *Clin Sci (Lond)*. 2008;114:149–155.
2. Barter PJ, Ballantyne CM, Carmena R, Castro Cabezas M, Chapman MJ, Couture P, deGraaf J, Durrington PN, Faergeman O, Frohlich J, Furberg CD, Gagne C, Haffner SM, Humphries SE, Jungner I, Krauss RM, Kwiterovich P, Marcovina S, Packard CJ, Pearson TA, Reddy KS, Rosenson R, Sarrafzadegan N, Sniderman AD, Stalenhoef AF, Stein E, Talmud PJ, Tonkin AM, Walldius G, Williams KMS. ApoB versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person/ten-country panel. *J Intern Med*. 2006;259:247–258.
3. Jeyarajah EJ, Cromwell WC, Otvos JD. Lipoprotein particle analysis by nuclear magnetic resonance spectroscopy. *Clin Lab Med*. 2006;26:847–870.
4. Sniderman AD, McQueen MJ, Contois JH, Williams K, Couture P, Furberg CD. Why is non-HDL-cholesterol a better marker of cardiovascular risk than LDL-cholesterol? *J Clin Lipidol*. 2010;4:152–155.
5. Cromwell WC, Otvos JD, Keyes MJ, Pencina MJ, Sullivan L, Vasan RS, Wilson PWF, D'Agostino RB. LDL particle number and risk of future cardiovascular disease in the Framingham Offspring Study—implications for LDL management. *J Clin Lipidol*. 2007;1:583–592.
6. Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, Wood AM, Lewington S, Sattar N, Packard CJ, Collins R, Thompson SG, Danesh J; Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA*. 2009;302:1993–2000.
7. Thompson A, Danesh J. Associations between apolipoprotein B, apolipoprotein AI, the apolipoprotein B/AI ratio and coronary heart disease:

a literature-based meta-analysis of prospective studies. *J Intern Med*. 2006;259:481–492.
8. Sniderman AD, de Graaf J, Couture P. ApoB and the atherogenic apoB dyslipoproteinemias. In: Kwiterovich PO Jr. ed. *The Johns Hopkins Textbook of Dyslipidemia*. Philadelphia, PA: Lippincott Williams & Wilkins; 2009:196–210.
9. Contois JH, McConnell JP, Sethi AA, Csako G, Devaraj S, Hoefner DM, Warnick GR. Apolipoprotein B and cardiovascular disease risk: position statement from AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices. *Clin Chem*. 2009;55:407–419.
10. Ingelsson E, Schaefer EJ, Contois JH, McNamara JR, Sullivan L, Keyes MJ, Pencina MJ, Schoonmaker C, Wilson PW, D'Agostino RB, Vasan RS. Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. *JAMA*. 2007;298:776–785.
11. Shai I, Rimm EB, Hankinson SE, Curhan G, Manson JE, Rifai N, Stampfer MJ, Ma J. Multivariate assessment of lipid parameters as predictors of coronary heart disease among postmenopausal women: potential implications for clinical guidelines. *Circulation*. 2004;110:2824–2830.
12. Mora S, Otvos JD, Rifai N, Rosenson RS, Buring JE, Ridker PM. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. *Circulation*. 2009;119:931–939.
13. Benn M, Nordestgaard BG, Jensen GB, Tybjaerg-Hansen. Improving prediction of ischemic cardiovascular disease in the general population using apolipoprotein B: the Copenhagen City Heart Study. *Arterioscler Thromb Vasc Biol*. 2007;27:661–670.
14. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. *JAMA*. 2007;298:299–308.
15. Ridker PM, Rifai N, Cook NR, Bradwin G, Buring JE. Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. *JAMA*. 2005;294:326–333.
16. Jiang R, Schulze MB, Li T, Rifai N, Stampfer MJ, Rimm EB, Hu FB. Non-HDL cholesterol and apolipoprotein B predict cardiovascular disease events among men with type 2 diabetes. *Diabetes Care*. 2004;27:1991–1997.
17. Meisinger C, Loewel H, Mraz W, Koenig W. Prognostic value of apolipoprotein B and A-I in the prediction of myocardial infarction in middle-aged men and women: results from the MONICA/KORA Augsburg cohort study. *Eur Heart J*. 2005;26:271–278.
18. Pischon T, Girman CJ, Sacks FM, Rifai N, Stampfer MJ, Rimm EB. Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. *Circulation*. 2005;112:3375–3783.
19. Bruno G, Merletti F, Biggeri A, Bargero G, Prina-Cerai S. Pagano G, Cavallo-Perin P. Effect of age on the association of non-high-density-lipoprotein cholesterol and apolipoprotein B with cardiovascular mortality in a Mediterranean population with type 2 diabetes: the Casale Monferrato study. *Diabetalogia*. 2006;49:937–944.
20. Chien KL, Hsu HC, Su TC, Chen MF, Lee TY, Hu FB. Apolipoprotein B and non-high density lipoprotein cholesterol and the risk of coronary heart disease in Chinese. *J Lipid Res*. 2007;48:2499–2505.
21. Holme E, Aastveit AH, Jungner I, Walldius G. Relationships between lipoprotein components and risk of myocardial infarction: age, gender and short versus longer follow-up periods in the Apolipoprotein MOrtalityRISk study (AMORIS). *J Intern Med*. 2008;264:30–38.
22. McQueen M, Hawken S, Wang X, Ounpuu S, Sniderman A, Probstfield J, Steyn K, Sanderson JE, Hasani M, Volkova E, Kazmi K, Yusuf S; INTERHEART Study Investigators. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. *Lancet*. 2008;372:224–233.
23. Parish S, Peto R, Palmer A, Clarke R, Lewington S, Offer A, Whitlock G, Clark S, Youngman L, Sleight P, Collins R; International Studies of Infarct Survival Collaborators. The joint effects of apolipoprotein B, apolipoprotein A1, LDL-cholesterol, and HDL cholesterol on risk: 3510 cases of acute myocardial infarction and 9805 controls. *Eur Heart J*. 2009;30:2137–2146.
24. NHANES Investigators. National Health and Nutrition Examination Survey. http://www.cdc.gov/nchs/data/nhanes/nhanes_05_06/nhanes_2005_2006_codebook_description.pdf. Accessed February 16, 2009.
25. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. *Introduction to Meta-Analysis*. Chichester, UK; 2009.
26. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, Boekholdt SM, Khaw KT, Gudnason V. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. *Circulation*. 2007;115:450–458.
27. Sarwar N, Sandhu MS, Ricketts SL, Butterworth AS, Di Angelantonio E, Boekholdt SM, Ouwehand W, Watkins H, Samani NJ, Saleheen D, Lawlor D, Reilly MP, Hingorani AD, Talmud PJ, Danesh J; Triglyceride Coronary Disease Genetics Consortium and Emerging Risk Factors Collaboration. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. *Lancet*. 2010;375:1634–1639.
28. Sniderman AD, Williams K, McQueen MJ, Furberg CD. When is equal not equal? *J Clin Lipidol*. 2010;4:83–88.
29. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–952.
30. El Harchaoui K, Arsenault BJ, Franssen R, Després JP, Hovingh GK, Stroes ES, Otvos JD, Wareham NJ, Kastelein JJ, Khaw KT, Boekholdt SM. High-density lipoprotein particle size and concentration and coronary risk. *Ann Intern Med*. 2009;150:84–93.
31. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110:227–239.
32. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97:1837–1847.
33. D'Agostino RB, Russell MW, Huse DM, Ellison RC, Silbershatz H, Wilson PW, Hartz SC. Primary and subsequent coronary risk appraisal: new results from the Framingham study. *Am Heart J*. 2000;139:272–281.
34. Genest J Jr, Bard JM, Fruchart JC, Ordovas JM, Schaefer EJ. Familial hypoalphalipoproteinemia in premature coronary artery disease. *Arterioscler Thromb*. 1993;13:1728–1737.
35. Sniderman AD, Dagenais GR, Cantin B, Després JP, Lamarche B. High apolipoprotein B with low high-density lipoprotein cholesterol and normal plasma triglycerides and cholesterol. *Am J Cardiol*. 2001;87:792–793.
36. St-Pierre AC, Cantin B, Dagenais GR, Després JP, Lamarche B. Apolipoprotein-B, low-density lipoprotein cholesterol, and the long-term risk of coronary heart disease in men. *Am J Cardiol*. 2006;97:997–1001.
37. Sniderman A, Couture P, de Graaf J. Diagnosis and treatment of apolipoprotein B dyslipoproteinemias. *Nat Rev Endocrinol*. 2010;6:335–346.
38. Sniderman A. Targets for LDL-lowering therapy. *Curr Opin Lipidol*. 2009;20:282–287.
39. Genest J, McPherson R, Frohlich J, Anderson T, Campbell N, Carpentier A, Couture P, Dufour R, Fodor G, Francis GA, Grover S, Gupta M, Hegele RA, Lau DC, Leiter L, Lewis GF, Lonn E, Mancini GB, Ng D, Pearson GJ, Sniderman A, Stone JA, Ur E. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult—2009 recommendations. *Can J Cardiol*. 2009;25:567–579.
40. Sniderman AD, Scantlebury T, Cianflone K. Hypertriglyceridemic hyperapob: the unappreciated atherogenic dyslipoproteinemia in type 2 diabetes mellitus. *Ann Internal Med*. 2001;135:447–459.

SUPPLEMENTAL MATERIAL

A Meta-analysis of LDL-C, non-HDL-C, and apoB as markers of cardiovascular risk.

Note: Citations throughout this appendix refer to the reference list of the main article.

Table A1. List of candidate reports by inclusion/exclusion categories
#A: ERFC-identified report without the requisite non-HDL-C and apoB data
B: ERFC-identified study with requisite data but without published non-HDL-C and apoB relative risk ratios (RRRs)
C: ERFC-identified report with published RRRs not included in ERFC meta-analysis
D: Reports from ERFC-cited studies included in both analyses
E: Reports from studies not cited by ERFC with RRRs
F: Reports not cited by ERFC without RRRs

Ref	#	meta-analyses	Study	citation
1	A	Neither	*Air Force/Texas Coronary Atherosclerosis Prevention Study	Circulation 2000; 101(5):477-484.
2	A	Neither	*Antihypertensive and Lipid-Lowering to prevent Heart Attacks	JAMA 2002; 288(23):2998-3007.
3	A	Neither	*British Regional Heart Study	BMJ 1989; 298(6679):998-1002.
4	A	Neither	*British Women's Heart and Health Study	J Epidemiol Community Health 2003; 57(2):134-140.
5	A	Neither	*Busselton population health	J Epidemiol Community Health 1997; 51(5):515-519.
6	A	Neither	*Caerphilly and Speedwell Collaborative Heart Disease	Br Heart J 1992; 68(1):60-66.
7	A	Neither	*Cardiovascular Health Study	J Am Geriatr Soc 2004; 52(10):1639-1647.
8	A	Neither	*Edinburgh Artery Study	Am J Epidemiol 1992; 135(4):331-340.
9	A	Neither	*Epidemiologische Studie zu Chancen der Verhütung, …	Pharmacoepidemiol Drug Saf 2008; 17(5):485-494.
10	A	Neither	*Finish Risk Cohort Study	Int J Epidemiol 2000; 29(1):49-56.
11	A	Neither	*Finland, Italy and Netherlands Elderly Study	Eur Heart J 2001;22(7):573-579.
12	A	Neither	*GOTMONICA	J Intern Med 1997; 242(3):199-211.
13	A	Neither	*Glostrup Study	Int J Epidemiol 1991; 20(1):105-113.
14	A	Neither	*Göteborg 1943 Study	J Intern Med 2000; 247(1):111-118.
15	A	Neither	*Honolulu Heart Program	Am J Cardiol 2000; 86(4):412-416.
16	A	Neither	*Hoorn Study	Diabetologia 2003; 46(7):910-916.
17	A	Neither	*Israeli IHD/Glucose Intolerance, Obesity, Hypertension	Preventive Medicine 2005; 41(1):85-91.
18	A	Neither	*Japanese	Am J Epidemiol 2001; 153(5):490-499.
19	A	Neither	*Lower Extremity Arterial Disease Event Reduction Trial	Curr Control Trials Cardiovasc Med 2001; 2(4):195
20	A	Neither	*Multiple Risk Factor Intervention Trial 1	Am J Cardiol 1986; 57(8):538-545.
21	A	Neither	*Northwick Park Heart Study II	Atherosclerosis 2005; 181(1):93-100.

***Report cited by ERFC as providing data on triglycerides, HDL-C and non-HDL-C, and other risk factors**

Table A1. List of candidate reports by inclusion/exclusion categories
#A: ERFC-identified report without the requisite non-HDL-C and apoB data
B: ERFC-identified study with requisite data but without published non-HDL-C and apoB relative risk ratios (RRRs)
C: ERFC-identified report with published RRRs not included in ERFC meta-analysis
D: Reports from ERFC-cited studies included in both analyses
E: Reports from studies not cited by ERFC with RRRs
F: Reports not cited by ERFC without RRRs

Ref	#	meta-analyses	Study	citation
22	A	Neither	*Population Study of Women in Göteborg, Sweden	Circulation 2004; 109(5):601-606.
23	A	Neither	*Progetto CUORE	Eur J Cardiovasc Prev Rehabil 2006; 13(4):562-570
24	A	Neither	*Rancho Bernardo Study	Am J Cardiol 2003; 91(11):1311-1315.
25	A	Neither	*Reykjavik Study	J Cardiovasc Risk 2002; 9(2):67-76.
26	A	Neither	*Risk Factors and Life Expectancy Pooling Project	Eur J Epidemiol 1993; 9(5):459-476.
27	A	Neither	*Scottish Heart Health Extended Cohort	Heart 2007; 93(2):172-176.
28	A	Neither	*Established Populations for Epidemiologic Study of Elderly	Aging (Milano) 1993; 5(1):27-37.
29	A	Neither	*Tromsø Study	Lancet 1977; 1(8019):965-968.
30	A	Neither	*West of Scotland Coronary Prevention Study	Circulation 1998; 97(15):1440-1445.
31	A	Neither	*Yao city Japan	J Clin Epidemiol 1994; 47(9):961-969.
32	A	Neither	*Zaragosa study	BMC Public Health 2006; 6:38.
33	A	Neither	*Zutphen Elderly Study	Am J Epidemiol 1996; 143(2):151-158.
34	B	ERFC	*Atherosclerosis Risk in Communities Study	Circulation 104(10):1108-1113.
35	B	ERFC	*BUPA Study	Lancet. 1994;343:75–79
36	B	ERFC	*Bruneck Study	Arterioscler Thromb Vasc Biol 1999; 19(6):1484-14
37	B	ERFC	*Cardiovascular Study in the Elderly	J Hum Hypertens 1998; 12(9):575-581.
38	B	ERFC	*Diet and Risk of Cardiovascular Disease in Spain	Annals of Nutrition and Metabolism 2000; 44(3):10
39	B	ERFC	*Dubbo Study of the Elderly	Am J Cardiol 2002; 89(1):69-72.
40	B	ERFC	*EPIC Norfolk Study	Ann Intern Med 2007; 146(9):640-648.
41	B	ERFC	*Göttingen Risk Incidence and Prevalence Study	Atherosclerosis 1997; 129(2):221-230.
42	B	ERFC	*Kuopio Ischaemic Heart Disease Study	Circulation 1991; 84(1):129-139.

***Report cited by ERFC as providing data on triglycerides, HDL-C and non-HDL-C, and other risk factors**

Table A1. List of candidate reports by inclusion/exclusion categories
#A: ERFC-identified report without the requisite non-HDL-C and apoB data
B: ERFC-identified study with requisite data but without published non-HDL-C and apoB relative risk ratios (RRRs)
C: ERFC-identified report with published RRRs not included in ERFC meta-analysis
D: Reports from ERFC-cited studies included in both analyses
E: Reports from studies not cited by ERFC with RRRs
F: Reports not cited by ERFC without RRRs

Ref	#	meta-analyses	Study	citation
43	B	ERFC	*National Health and Nutrition Examination Survey III	Am J Cardiol 2000; 86(3):299-304.
44	B	ERFC	*Prospective Cardiovascular Münster Study	Am J Cardiol 1992; 70(7):733-737.
45	B	ERFC	*Prospective Epidemiological Study of Myocardial Infarction	Arterioscler Thromb Vasc Biol 2002; 22(7):1155-11
46	B	ERFC	*Prospective Study of Pravastatin in the Elderly at Risk	Circulation 2005; 112(20):3058-3065.
47	B	ERFC	*Quebec Cardiovascular Study	Atherosclerosis 2000; 153(2):263-272.
48	B	ERFC	*Strong Heart Study	Diabetes 1992; 41 Suppl 2:4-11.:4-11.
49	B	ERFC	*Turkish Adult Risk Factor Study	J Epidemiol Community Health 1992; 46(5):470-476.
50	B	ERFC	*Uppsala	Arterioscler Thromb Vasc Biol 2006; 26(2):406-410
51	B	ERFC	*VIP/MONICA	J Intern Med 1998; 244(5):425-430.
52	B	ERFC	*Whitehall II Study	Arterioscler Thromb Vasc Biol 2008; 28(8):1556-15
53	C	Current	*Framingham Offspring Study	JAMA. 2007;298:776–785
54	D	ERFC	*Copenhagen City Heart Study	JAMA 2007; 298(3):299-308.
55	D	Current	Copenhagen City Heart Study	Arterioscler Thromb Vasc Biol. 2007;27:661–670
56	D	Both	*Nurses' Health Study (11)	Circulation.2004;110:2824–2830
57	D	ERFC	*Women's Health Study (15)	JAMA. 2005;294:326–3633
58	D	Current	Women's Health Study (12)	Circulation. 2009;119:931-939.
59	E	Current	Apolipoprotein Related Mortality Risk Study (21)	J Intern Med. 2008;264:30–38
60	E	Current	Casale Monferrato Study (19)	Diabetologia. 2006;49:937–944
61	E	Current	Chin-Shan Cohort (20)	J Lipid Res. 2007;48:2499–2505
62	E	Current	Health Professionals Follow-up Study (16)	Diabetes Care. 2004;27: 1991–1997
63	E	Current	Health Professionals Follow-up Study (18)	Circulation. 2005;1112:3375–3583

***Report cited by ERFC as providing data on triglycerides, HDL-C and non-HDL-C, and other risk factors**

Table A1. List of candidate reports by inclusion/exclusion categories
#A: ERFC-identified report without the requisite non-HDL-C and apoB data
B: ERFC-identified study with requisite data but without published non-HDL-C and apoB relative risk ratios (RRRs)
C: ERFC-identified report with published RRRs not included in ERFC meta-analysis
D: Reports from ERFC-cited studies included in both analyses
E: Reports from studies not cited by ERFC with RRRs
F: Reports not cited by ERFC without RRRs

Ref	#	meta-analyses	Study	citation
64	E	Current	INTERHEART Study (22)	Lancet 2008; 372: 224–33
65	E	Current	International Studies of Infarct Survival (23)	Euro Heart J (2009) 30, 2137–2146
66	E	Current	Monitoring of Trends and Determinants in CVD (17)	EurHeart J. 2005;26:271–278
67	F	Neither	4S Placebo Wing clinical trial	Circulation. 1998;97:1453–1460
68	F	Neither	Air Force/Texas Coronary Atherosclerosis Prevention Study	Circulation. 2000;101:477–484
69	F	Neither	Angina Prognosis Study in Stockholm	Atherosclerosis. 1997;135:109–118
70	F	Neither	ApoB and Type 1 Diabetes	J Immunol Methods. 2006;260: 272–280
71	F	Neither	Apolipoprotein Related Mortality Risk Study	Clin Chem Lab Med 2004; 42: 1355–63.
72	F	Neither	Apolipoprotein Related Mortality Risk Study	Lancet. 2001;358:2026–2033
73	F	Neither	Apolipoprotein Related Mortality Risk Study	Lancet. 2003;361: 777–780
74	F	Neither	Bezafibrate Coronary Atherosclerosis Intervention Trial	J Am Coll Cardiol. 1998;32:1648–1656
75	F	Neither	Bugalusu Heart Study	Pediatrics. 2008;121:924–929
76	F	Neither	Caerphilly Prospective Study	Eur J Clin Invest 2000; 30: 947–56.
77	F	Neither	Cardiovascular Health Study	Arterioscler Thromb Vasc Biol.2002;22:1175–1180
78	F	Neither	Cardiovascular risk in Young Finns Study	J Am CollCardiol. 2008;1:1–2
79	F	Neither	Diabetes Atherosclerosis Intervention Study	Circulation. 2003;107:1733–1737
80	F	Neither	Dubbo Study of the Elderly	Atherosclerosis 2001; 159: 201–8.
81	F	Neither	EPIC Norfolk Study	J Am Coll Cardiol.2007;49:547–553
82	F	Neither	Eastern Finland Heart Survey	Am J Cardiol. 1985;56:228–231
83	F	Neither	Fenofibrate Intervention and Event Lowering in Diabetes	Diabetologia 2010 53:1846-1855
84	F	Neither	Framingham Offspring Study	J Clin Lipidol. 2007;1:583–592

****Report cited by ERFC as providing data on triglycerides, HDL-C and non-HDL-C, and other risk factors***

Table A1. List of candidate reports by inclusion/exclusion categories
#A: ERFC-identified report without the requisite non-HDL-C and apoB data
B: ERFC-identified study with requisite data but without published non-HDL-C and apoB relative risk ratios (RRRs)
C: ERFC-identified report with published RRRs not included in ERFC meta-analysis
D: Reports from ERFC-cited studies included in both analyses
E: Reports from studies not cited by ERFC with RRRs
F: Reports not cited by ERFC without RRRs

Ref	#	meta-analyses	Study	citation
85	F	Neither	Glostrup Study	Atherosclerosis 1997; 132: 77–84.
86	F	Neither	Guernsey	Atherosclerosis 1992; 92: 177–85.
87	F	Neither	Incremental Decrease in End points Through Aggressive Lipid-lowering	Ann Med. 2008:1–9
88	F	Neither	Kuopio Ischaemic Heart Disease Study	Circulation 1992; 86: 803–11.
89	F	Neither	Kuopio Ischaemic Heart Disease Study	Arterioscler Thromb Vasc Biol 1999; 19: 2742–8.
90	F	Neither	Leiden Heart Study.	Arterioscler Thromb Vasc Biol. 2000;20: 2408–2413
91	F	Neither	Long-term Intervention with Pravastatin in Ischaemic Disease	Circulation. 2002;105: 1162–1169
92	F	Neither	Monitoring of Trends and Determinants in CVD	Eur Heart J 2005;26: 271–8.
93	F	Neither	National Health and Nutrition Examination Survey	Am J Cardiol. 2006;98:1047–1052
94	F	Neither	Northwick Park Heart Study	Arterioscler Thromb Vasc Biol.2002;22:1918–1923
95	F	Neither	Quebec Cardiovascular Study	Arterioscler Thromb Vasc Biol 2005; 25:553–9.
96	F	Neither	Quebec Cardiovascular Study	Circulation. 1996;94:273–278
97	F	Neither	Quebec Cardiovascular Study	Am J Cardiol. 2006;97:997–1001
98	F	Neither	Reykjavik Study	Am J Cardiol 1992; 69: 1251–4.
99	F	Neither	Simon et al	Atherosclerosis.2005;179:339–344
100	F	Neither	TEKHARF Survey	Anadolu Kardiyol Derg. 2007;2:128–133
101	F	Neither	THROMBO Metabolic Syndrome	Atherosclerosis. 2004;177:367–373
102	F	Neither	TNT/IDEAL	Circulation. 2008; 117:3002–3009
103	F	Neither	Thrombosis Prevention Trial	Circulation. 1999;99:2517–2522
104	F	Neither	U.S. Physicians Health Study	N Engl J Med 1991; 325: 373–81.

***Report cited by ERFC as providing data on triglycerides, HDL-C and non-HDL-C, and other risk factors**

Table A1. List of candidate reports by inclusion/exclusion categories
#A: ERFC-identified report without the requisite non-HDL-C and apoB data
B: ERFC-identified study with requisite data but without published non-HDL-C and apoB relative risk ratios (RRRs)
C: ERFC-identified report with published RRRs not included in ERFC meta-analysis
D: Reports from ERFC-cited studies included in both analyses
E: Reports from studies not cited by ERFC with RRRs
F: Reports not cited by ERFC without RRRs

Ref	#	meta-analyses	Study	citation
105	F	Neither	Uppsala Longitudinal Study of Adult Men	Am Heart J 2004; 148: 596–601.
106	F	Neither	VA_HIT	Circulation. 2006;113: 1556–1563
107	F	Neither	Women's Health Study	Circulation.2002;106:1930–1937

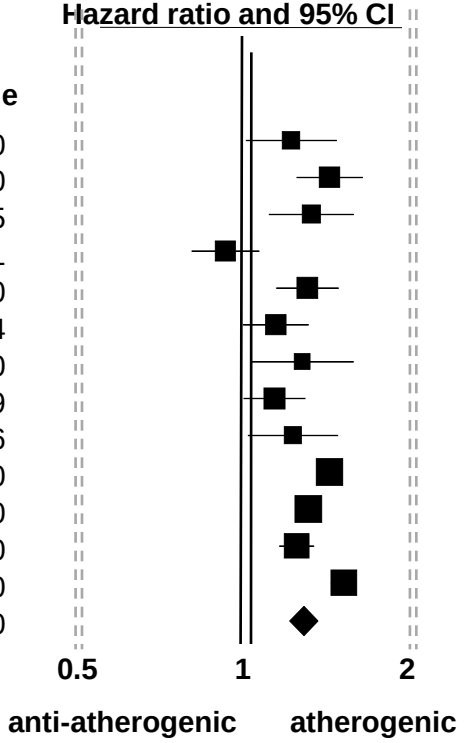
***Report cited by ERFC as providing data on triglycerides, HDL-C and non-HDL-C, and other risk factors**

Table A2. List of covariates/model adjustments

Study abbreviation	ADJUSTMENTS
Health Professionals (16)	age, BMI, family history of MI, physical activity, smoking (never, past, or current), alcohol consumption, fasting status, history of hypertension, aspirin use, HbA1c
Nurses' Health(11)	age, smoking, fasting status, CRP, homocysteine, BMI, family history, hypertension, diabetes, hormone use, physical activity, alcohol intake, blood draw parameters
MONICA/KORA(17)	age, diabetes, regular smoking, BMI, alcohol intake
Health Professionals(18)	age, smoking, blood draw, BMI, parent MI < 60, hypertension, alcohol intake, physical activity
Women's Health(15)	age, Framingham BP category, BMI, diabetes, current smoking
Casale Monferrato(19)	age, sex, hypertension, smoking, CHD, AER, fibrinogen, cumulative average HbA1c, referring physician
Copenhagen Heart(13)	age
Chin-Shan Cohort(20)	age group, gender, BMI, smoking, alcohol, marital status, education, occupation, exercise, family CHD history, hypertension, diabetes
Fram Offspring (10)	age, SBP, antihypertensive treatment, diabetes, smoking
AMORIS(21)	age sex
INTERHEART(22)	age, sex, smoking, geographic region
Women's Health(12)	age, randomized treatment assignment, smoking status, postmenopausal hormone use, blood pressure, diabetes, BMI
ISIS(23)	age, sex, smoking, BMI

LDL C relative risk ratio (RRR)

Study name	Subgroup within study	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Health Professionals (16)	men	1.191	0.979	1.448	1.749	0.080
Nurses' Health(11)	women	1.400	1.212	1.617	4.585	0.000
Health Professionals (18)	men	1.297	1.080	1.557	2.787	0.005
Casale Monferrato(19)	pooled	0.902	0.779	1.045	-1.369	0.171
Copenhagen Heart(13)	men	1.276	1.114	1.461	3.517	0.000
Copenhagen Heart(13)	women	1.116	0.967	1.288	1.500	0.134
Chin-Shan Cohort(20)	pooled	1.248	1.000	1.558	1.960	0.050
Fram Offspring (10)	men	1.110	0.970	1.270	1.518	0.129
Fram Offspring (10)	women	1.200	0.988	1.457	1.840	0.066
AMORIS(21)	pooled	1.400	1.356	1.446	20.583	0.000
INTERHEART(22)	pooled	1.280	1.246	1.315	17.759	0.000
Women's Health(12)	women	1.219	1.128	1.317	5.007	0.000
ISIS(23)	pooled	1.487	1.402	1.577	13.210	0.000
Overall		1.249	1.177	1.326	7.311	0.000

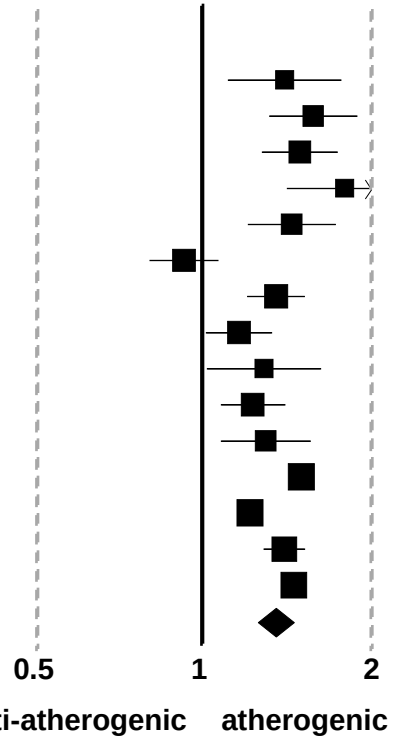


Meta Analysis

Figure A1. Forest plot of LDL-C relative risk ratios among 13 studies in 11 reports with both apoB and non-HDL-C relative risk ratios. The relative risk ratio was significantly greater ($p<0.05$) than 1.0 within 9 of the 13 studies and highly significant ($p<0.001$) overall. Heterogeneity was also highly significant ($p <0.001$).

Non-HDL C relative risk ratio (RRR)

Study name	Subgroup within study	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Health Professionals (16)	men	1.393	1.092	1.778	2.668	0.008
Nurses' Health(11)	women	1.572	1.300	1.900	4.670	0.000
MONICA/KORA(17)	men	1.485	1.260	1.750	4.718	0.000
MONICA/KORA(17)	women	1.794	1.400	2.300	4.617	0.000
Health Professionals (18)	men	1.435	1.188	1.734	3.746	0.000
Casale Monferrato(19)	pooled	0.910	0.785	1.057	-1.235	0.217
Copenhagen Heart(13)	men	1.344	1.186	1.522	4.634	0.000
Copenhagen Heart(13)	women	1.149	0.995	1.326	1.897	0.058
Chin-Shan Cohort(20)	pooled	1.276	1.000	1.629	1.960	0.050
Fram Offspring (10)	men	1.218	1.060	1.400	2.781	0.005
Fram Offspring (10)	women	1.286	1.060	1.560	2.551	0.011
AMORIS(21)	pooled	1.495	1.460	1.530	33.636	0.000
INTERHEART(22)	pooled	1.204	1.170	1.240	12.551	0.000
Women's Health(12)	women	1.391	1.269	1.523	7.085	0.000
ISIS(23)	pooled	1.449	1.375	1.526	13.883	0.000
Overall		1.337	1.239	1.442	7.508	0.000

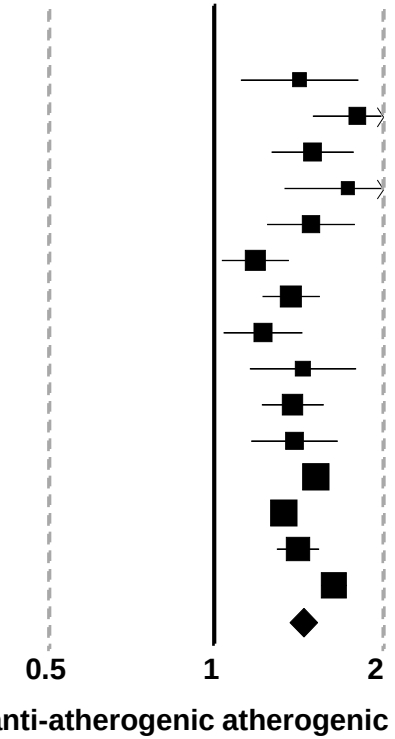


Meta Analysis

Figure A2. Forest plot of non-HDL-C relative risk ratios among 15 independent studies in 12 reports with both apoB and non-HDL-C relative risk ratios. The relative risk ratio was significantly greater ($p<0.05$) than 1.0 within 12 of the 15 studies and highly significant ($p<0.001$) overall. Heterogeneity was also highly significant ($p <0.001$).

ApoB relative risk ratio (RRR)

Study name	Subgroup within study	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Health Professionals (16)	men	1.410	1.096	1.814	2.675	0.007
Nurses' Health(11)	women	1.800	1.486	2.180	6.016	0.000
MONICA/KORA(17)	men	1.490	1.249	1.778	4.422	0.000
MONICA/KORA(17)	women	1.730	1.319	2.269	3.963	0.000
Health Professionals (18)	men	1.480	1.225	1.788	4.068	0.000
Casale Monferrato(19)	pooled	1.170	1.012	1.353	2.121	0.034
Copenhagen Heart(13)	men	1.360	1.201	1.541	4.832	0.000
Copenhagen Heart(13)	women	1.208	1.019	1.432	2.176	0.030
Chin-Shan Cohort(20)	pooled	1.430	1.138	1.797	3.070	0.002
Fram Offspring (10)	men	1.370	1.198	1.567	4.592	0.000
Fram Offspring (10)	women	1.380	1.145	1.663	3.384	0.001
AMORIS(21)	pooled	1.510	1.471	1.551	30.484	0.000
INTERHEART(22)	pooled	1.320	1.281	1.361	17.951	0.000
Women's Health(12)	women	1.400	1.276	1.536	7.132	0.000
ISIS(23)	pooled	1.630	1.538	1.728	16.462	0.000
Overall		1.428	1.347	1.514	11.981	0.000

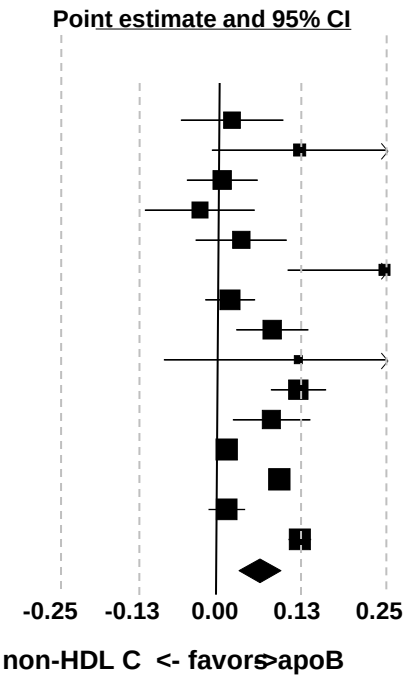


Meta Analysis

Figure A3. Forest plot of apoB relative risk ratios among 12 independent published reports with both apoB and non-HDL-C relative risk ratios. The relative risk ratio is significantly greater ($p<0.05$) than 1.0 within each study and highly significant ($p<0.001$) overall. Heterogeneity was also highly significant ($p <0.001$).

Log apoB relative risk ratio (RRR) - non-HDL C RRR

Study name	Subgroup within study	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Health Professionals (16)	men	0.015	0.041	0.002	-0.064	0.094	0.370	0.711
Nurses' Health(11)	women	0.118	0.069	0.005	-0.017	0.253	1.716	0.086
MONICA/KORA(10)	men	0.000	0.028	0.001	-0.055	0.055	0.000	1.000
MONICA/KORA(10)	women	-0.034	0.043	0.002	-0.119	0.051	-0.783	0.434
Health Professionals(18)	men	0.029	0.036	0.001	-0.042	0.100	0.805	0.421
Casale Monferrato(19)	pooled	0.247	0.076	0.006	0.098	0.396	3.253	0.001
Copenhagen Heart(13)	men	0.012	0.020	0.000	-0.027	0.051	0.599	0.549
Copenhagen Heart(13)	women	0.076	0.029	0.001	0.020	0.132	2.649	0.008
Chin-Shan Cohort(20)	pooled	0.116	0.105	0.011	-0.090	0.322	1.103	0.270
Fram Offspring (10)	men	0.116	0.022	0.000	0.073	0.159	5.228	0.000
Fram Offspring (10)	women	0.075	0.031	0.001	0.015	0.135	2.434	0.015
AMORIS(21)	pooled	0.007	0.004	0.000	-0.001	0.015	1.622	0.105
INTERHEART(22)	pooled	0.087	0.005	0.000	0.078	0.096	18.009	0.000
Women's Health(12)	women	0.007	0.015	0.000	-0.022	0.036	0.471	0.638
ISIS(23)	pooled	0.118	0.009	0.000	0.100	0.136	12.593	0.000
		0.056	0.016	0.000	0.024	0.087	3.425	0.001

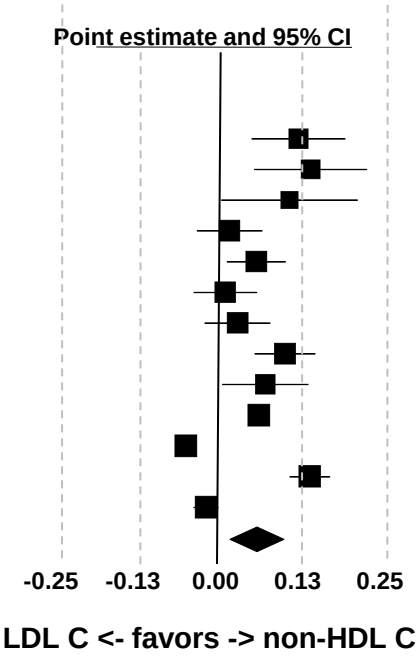


Meta Analysis

Figure A4. Log apoB RRR – log non-HDL-C RRR forest plot of 12 independent published studies with both apoB and non-HDL-C vascular risk associations. This analysis counts the three reports stratified by sex as six separate studies and excludes a Women's Health Study report(12) based on a subset of the later Women's Health Study report (19). The overall mean difference in log relative risk ratios (95% confidence interval) of 0.056 (0.024, 0.087) equates to a 5.7% (2.4%, 9.1%), $p<0.001$, advantage favoring apoB over non-HDL-C as a marker of atherogenic risk.

Log non-HDL C relative risk ratio (RRR) - log LDL C RRR

Study name	Subgroup within study	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Health Professionals(16)	men	0.115	0.037	0.001	0.042	0.188	3.104	0.002
Nurses' Health(11)	women	0.134	0.044	0.002	0.047	0.221	3.009	0.003
Health Professionals(18)	men	0.101	0.054	0.003	-0.004	0.207	1.888	0.059
Casale Monferrato(19)	pooled	0.010	0.026	0.001	-0.041	0.061	0.386	0.700
Copenhagen Heart(13)	men	0.051	0.024	0.001	0.005	0.097	2.158	0.031
Copenhagen Heart(13)	women	0.004	0.025	0.001	-0.046	0.053	0.142	0.887
Chin-Shan Cohort(20)	pooled	0.022	0.026	0.001	-0.029	0.074	0.849	0.396
Fram Offspring (10)	men	0.094	0.024	0.001	0.047	0.142	3.889	0.000
Fram Offspring (10)	women	0.065	0.034	0.001	-0.003	0.132	1.885	0.059
AMORIS(21)	pooled	0.055	0.007	0.000	0.042	0.068	8.378	0.000
INTERHEART(22)	pooled	-0.056	0.005	0.000	-0.066	-0.046	-11.120	0.000
Women's Health(12)	women	0.132	0.016	0.000	0.100	0.164	8.049	0.000
ISIS(23)	pooled	-0.026	0.010	0.000	-0.046	-0.005	-2.466	0.014
Overall		0.050	0.021	0.000	0.009	0.091	2.380	0.017

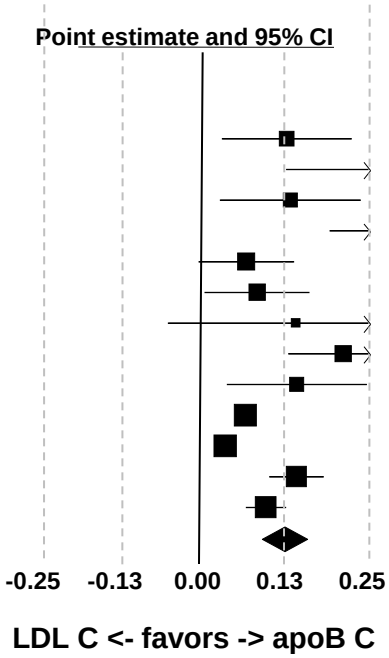


Meta Analysis

Figure A5. Log non-HDL-C RRR – log LDL-C RRR forest plot of the 11 independent published reports with both non-HDL-C and LDL-C relative risk ratios among the 13 published reports with both apoB and non-HDL-C relative risk ratios. This analysis counts the two reports stratified by sex as four separate studies and excludes a Women's Health Study report(12) based on a subset of the later Women's Health Study report (19). The overall mean difference in log relative risk ratios (95% confidence interval) of 0.050 (0.009, 0.091) equates to a 5.1% (0.9%, 9.5%), p=0.017, advantage favoring non-HDL-C over LDL-C as a marker of atherogenic risk.

Log apoB relative risk ratio (RRR) - log LDL C RRR

Study name	Subgroup within study	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Health Professionals (16)	men	0.125	0.051	0.003	0.025	0.225	2.440	0.015
Nurses' Health(11)	women	0.251	0.066	0.004	0.122	0.380	3.824	0.000
Health Professionals(18)	men	0.130	0.055	0.003	0.022	0.239	2.353	0.019
Casale Monferrato(19)	pooled	0.257	0.035	0.001	0.188	0.326	7.332	0.000
Copenhagen Heart(13)	men	0.063	0.038	0.001	-0.011	0.137	1.663	0.096
Copenhagen Heart(13)	women	0.079	0.041	0.002	-0.002	0.161	1.918	0.055
Chin-Shan Cohort(20)	pooled	0.138	0.100	0.010	-0.058	0.334	1.384	0.166
Fram Offspring (10)	men	0.210	0.043	0.002	0.125	0.296	4.847	0.000
Fram Offspring (10)	women	0.140	0.055	0.003	0.032	0.248	2.538	0.011
AMORIS(21)	pooled	0.061	0.008	0.000	0.047	0.076	8.167	0.000
INTERHEART(22)	pooled	0.031	0.007	0.000	0.017	0.045	4.363	0.000
Women's Health(12)	women	0.139	0.022	0.000	0.097	0.182	6.402	0.000
ISIS(23)	pooled	0.093	0.016	0.000	0.061	0.125	5.671	0.000
Overall		0.120	0.018	0.000	0.085	0.154	6.823	0.000



Meta Analysis

Figure A6. Log apoB RRR – log LDL-C RRR forest plot of the 11 independent published reports with both apoB and LDL-C relative risk ratios among the 13 reports with both apoB and non-HDL-C relative risk ratios. This analysis counts the two reports stratified by sex as four separate studies and excludes a Women's Health Study report(12) based on a subset of the later Women's health Study report (19). The overall mean difference in log relative risk ratios (95% confidence interval) of = 0.120 (0.085, 0.154) = equates to a 12.7% (8.9%, 16.6%), $p<0.001$, advantage apoB over LDL-C as a marker of atherogenic risk.

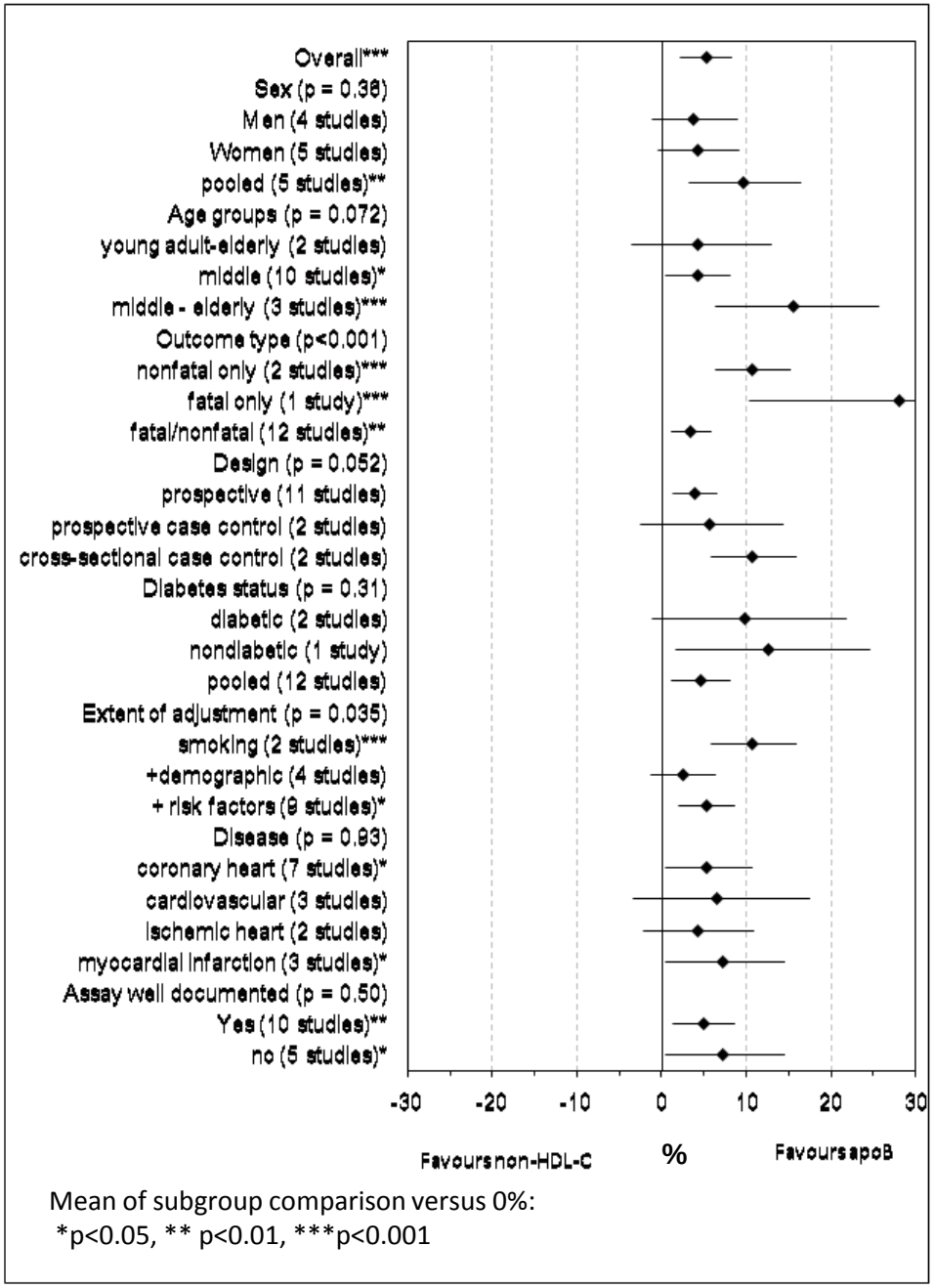


Figure A7. Subgroup analyses by study attributes. The p-values for each section indicate result from testing equality of the difference between the apoB and non-HDL-C log relative risk ratios across the section's subgroups. "Assay well documented" reflects the authors' judgment regarding reported assurances re: assay/specimen quality.

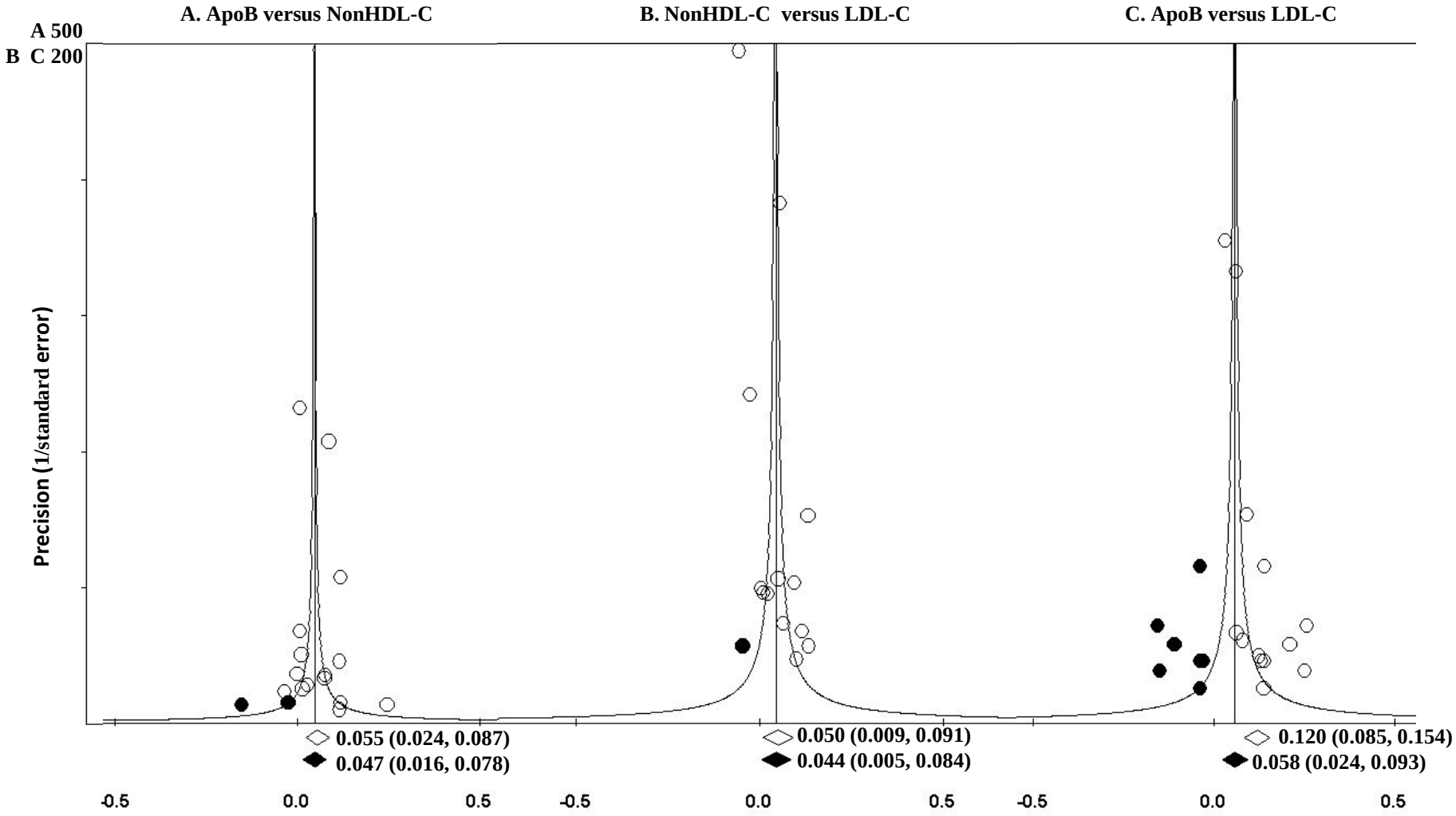


Figure A8. Selection bias assessments: funnel plots of precision by difference in log relative risk ratios. The empty circles represent the observed studies while the empty diamonds represents the overall random effects means and 95% confidence intervals of the observed studies. If smaller studies were not published owning to non-significant findings, one would expect the distribution of empty circles to be skewed to the right. The black filled circles represent studies imputed to balance the distribution around the overall estimate and the black diamonds represent overall average adjusted by including the imputed studies. After adjustment each overall difference remains statistically significant.

A Meta-Analysis of Low-Density Lipoprotein Cholesterol, Non-High-Density Lipoprotein Cholesterol, and Apolipoprotein B as Markers of Cardiovascular Risk

Allan D. Sniderman, Ken Williams, John H. Contois, Howard M. Monroe, Matthew J. McQueen, Jacqueline de Graaf and Curt D. Furberg

Circ Cardiovasc Qual Outcomes. 2011;4:337-345; originally published online April 12, 2011;
doi: 10.1161/CIRCOUTCOMES.110.959247
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-7705. Online ISSN: 1941-7713