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Meta-analysis and Cumulative Meta-analysis for Correlations: Methodology and Applications

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Abstract

Meta-analysis and cumulative meta-analysis of pairwise correlations are carried out among the three cholesterol variables: low-density lipoprotein (LDL), non-high density lipoprotein (NHDL) and Apolipoprotein B (APOB), in a study to assess efficacy of Ezetimibe coadministered with statins in patients with hypercholesterolemia. Cochran's Q statistic is used to test the homogeneity of correlations, and the test is carried out based on the correlations themselves, and based on the transformed quantities obtained by applying Fisher's transformation. Type I errors of the tests are evaluated by simulation. Meta-analysis of the correlations is carried out under a random effects model, and appropriate forest plots are obtained. A cumulative meta-analysis is also carried out. Homogeneity test using Cochran's Q statistic resulted in inflated type I errors when the correlations are directly used, unless the sample sizes are large within each study. However, homogeneity test carried out after Fisher's variance-stabilizing transformation controls the type I error probability. In all cases, the homogeneity test resulted in a rejection of the homogeneity hypothesis concerning the correlations. Nevertheless, meta-analysis and cumulative meta-analysis were carried out, noting that the pairwise correlations among LDL, NHDL and APOB are all quite high.

Keywords and Phrases: Cochran's $Q-$statistic, Cumulative Meta-analysis, Fisher's Transformation, Forest Plot, Type I Error Probability.

AMS Classification: Primary 62F99; Secondary 62F03, 62F25.

1 Introduction

Pearson's correlation coefficient is the primary effect size for assessing the linear relationship between two variables. The effect size can be taken to be the value of the population correlation ρ itself, or ζ, based on Fisher's variance-stabilizing transformation, given by

$$\zeta = \frac{1}{2}\Big[\ln\frac{1+\rho}{1-\rho}\Big].$$

These measures are readily estimated using the sample correlation r:

$$\hat{\rho} = r,$$
$$\hat{\zeta} = z = \frac{1}{2}\Big[\ln\frac{1+r}{1-r}\Big],$$

with respective approximate variances as (see Rao [1])

$$\sigma^2(\hat{\rho}) \approx \frac{(1-\rho^2)^2}{n-1},$$
$$\sigma^2(\hat{\zeta}) \approx \frac{1}{n-3}.$$

The estimated variances are then obtained by replacing ρ in the above expressions by its estimate, namely, r:

$$\hat{\sigma}^2(r) = \frac{(1-r^2)^2}{n-1},$$
$$\hat{\sigma}^2(z) = \frac{1}{n-3}.$$

A standard test for checking homogeneity of effect sizes is a test due to Cochran [2], which is carried out using an approximate chisquare distribution. If the effect size of interest is a correlation, homogeneity can be tested based on the correlation itself, or based on the Fisher's transformed variable. A natural question is whether the choice between these two alternatives makes any difference. It turns out that for Cochran's homogeneity test statistic, the chisquare distribution can be a poor approximation if we deal directly with the correlations, but is quite satisfactory if we make the Fisher's transformation. This has already been noted in the literature; see Field [3], Sanchez-Meca and Marin-Martinez [4], and Viechtbauer [5]. Numerical results in this direction are also reported in the next section. The message appears to be that a transformation of the estimated effect size may provide a more accurate chisquare approximation for the Cochran's homogeneity test statistic. The above cited articles, as well as Hedges and Vevea [6] also address methodology for combining correlations.

The motivation for our investigation came from a meta-analysis of the results from 29 different studies primarily dealing with the cholesterol lowering efficacy of

Ezetimibe co-administered with statins, in comparison with statins alone. Some of these studies also had Ezetimibe alone and Placebo arms. Data were available on the three variables low-density lipoprotein (LDL), non-high density lipoprotein (NHDL) and Apolipoprotein B (APOB), and the problem of interest is inference concerning the three pairwise correlations among these variables. The correlations turned out to be quite high; in fact, very often, above 0.90. Meta-analysis of the pairwise correlations among these three variables is reported in Section 3 of this article. It turns out that the homogeneity hypothesis is rejected in each case, indicating heterogeneity among the correlations across the studies. Nevertheless, we have performed a meta-analysis for combining the evidence on the correlations from the different studies. We have done this under a random effects model, and have reported the results along with appropriate forest plots.

In Section 3, we have also reported the results from a cumulative meta-analysis of the correlations. We recall that cumulative meta-analysis is defined as the repeated performance of meta-analysis whenever a new trial becomes available for inclusion, and the procedure is often used to track evidence of the event under study over time; see Lau, Schmid and Chalmers [7] and Leimu and Koricheva [8]. In cumulative meta-analysis studies are added one at a time, typically according to the date of the study, and the results are summarized as each new study is added. Results of a cumulative meta-analysis of the correlations are reported in Section 3 along with plots. The paper is concluded with a brief discussion in Section 4.

2 The Meta-analysis of Correlations

In this section we briefly describe the standard statistical meta-analysis procedure in general terms; see Hedges and Olkin [9] and Hartung, Knapp and Sinha [10].

If $\hat{\theta}_i$'s are the estimated effect sizes from k different studies with true effect sizes $\theta_1, \theta_2, \ldots, \theta_k$ and with corresponding estimated variances $\hat{\sigma}_i^2(\hat{\theta}_i)$ ($i = 1, 2, \ldots, k$), the test statistic due to Cochran ([2]) for testing homogeneity of effect sizes

$$H_0 : \theta_1 = \theta_2 = \ldots = \theta_k$$

is given by

$$Q = \sum_{i=1}^{k} w_i \left(\hat{\theta}_i - \hat{\theta}_{fix}\right)^2 \quad \text{where,} \quad w_i = \frac{1}{\hat{\sigma}_i^2(\hat{\theta}_i)}, \quad \hat{\theta}_{fix} = \frac{\sum w_i \, \hat{\theta}_i}{\sum w_i},$$

Under H_0, the distribution of Q is approximated by a χ^2 with $k-1$ df. The test rejects H_0 at level α if $Q > \chi^2_{k-1;1-\alpha}$, where $\chi^2_{k-1;1-\alpha}$ is the $100(1-\alpha)$th percentile of the chi-square distribution with $k-1$ df.

Assume we do not reject H_0, then a combined estimate of the common effect size θ is given by a weighted combination of the $\hat{\theta}_i$'s, namely, $\hat{\theta}_{fix}$ defined above, with

confidence interval for θ as follows,

CI_1 : Large-sample confidence interval
$\hat{\theta}_{fix} \pm \sqrt{1/\sum_i w_i}\ z_{1-\alpha/2}$,
CI_2 : Follmann and Proschan [11]
$\hat{\theta}_{fix} \pm \sqrt{1/\sum_i w_i}\ t_{k-1;1-\alpha/2}$,
CI_3 : Hartung and Knapp [12], Sidik and Jonkman [13]
$\hat{\theta}_{fix} \pm \sqrt{q}\ t_{k-1;1-\alpha/2},\ q = \frac{1}{k-1}\sum_{i=1}^{k} w_i(\hat{\theta}_i - \hat{\theta}_{fix})^2 / \sum_{i=1}^{k} w_i = Q/[(k-1)\sum_{i=1}^{k} w_i]$,

where $z_{1-\alpha/2}$ denotes the $100(1-\alpha/2)$th percentile of the standard normal distribution, and $t_{k-1;1-\alpha/2}$ denotes the $100(1-\alpha/2)$th percentile of the t-distribution with $k-1$ df.

If H_0 is rejected, it is not proper to do meta-analysis unless we find reasons for heterogeneity and make an attempt to explain them. Suppose the lack of homogeneity is because the mean themselves might arise from a so called super population, thus leading to their variability and apparent differences. We can then conduct the meta-analysis using one-way random effects model.

- Observational model:
$$\hat{\theta}_i \sim N\left(\theta_i, \hat{\sigma}_i^2(\hat{\theta}_i)\right)$$
- Structural model:
$$\theta_i \sim N\left(\theta, \tau^2\right)$$
- Marginally,
$$\hat{\theta}_i \sim N\left(\theta, \tau^2 + \hat{\sigma}_i^2(\hat{\theta}_i)\right)$$

A common choice to estimate τ^2 is the DerSimonian-Laird estimator [14], defined as

$$\hat{\tau}^2_{DSL} = \frac{Q-(k-1)}{\sum w_i - \sum w_i^2 / \sum w_i}.$$

Then a combined estimate of θ is given by

$$\hat{\theta}_{ran} = \frac{\sum_{i=1}^{k} v_i\ \hat{\theta}_i}{\sum_{i=1}^{k} v_i}, \quad v_i = [\hat{\tau}^2 + \hat{\sigma}_i^2(\hat{\theta}_i)]^{-1}$$

with its confidence interval as follows,

CI_1 : Large-sample confidence interval
$\hat{\theta}_{ran} \pm \sqrt{1/\sum_i v_i}\ z_{1-\alpha/2}$,
CI_2 : Follmann and Proschan [11]
$\hat{\theta}_{ran} \pm \sqrt{1/\sum_i v_i}\ t_{k-1;1-\alpha/2}$,
CI_3 : Hartung and Knapp [12], Sidik and Jonkman [13]
$\hat{\theta}_{ran} \pm \sqrt{q}\ t_{k-1;1-\alpha/2}, \quad q = \frac{1}{k-1}\sum_{i=1}^{k} v_i(\hat{\theta}_i - \hat{\theta}_{ran})^2 / \sum_{i=1}^{k} v_i$.

Now suppose we have population correlations ρ_1, ρ_2, ..., ρ_k from k independent studies, and consider the problem of testing homogeneity of the correlations,

$$H_0 : \rho_1 = \rho_2 = \ldots = \rho_k. \tag{1}$$

Suppose r_1, r_2, ..., r_k are the corresponding sample correlations based on samples of sizes n_1, n_2, ..., n_k, respectively, and z_1, z_2, ..., z_k are the corresponding $z-$transformed quantities. Cochran's homogeneity statistics, say $Q(r)$ and $Q(z)$, based on the r_i's and the z_i's, respectively, are given by

$$\begin{aligned} Q(r) &= \sum_{i=1}^{k} \frac{(n_i-1)(r_i-\bar{r})^2}{(1-r_i^2)^2} \quad \text{where, } \bar{r} = \frac{\sum_{i=1}^{k} r_i\ (n_i-1)/(1-r_i^2)^2}{\sum_{i=1}^{k} (n_i-1)/(1-r_i^2)^2}, \\ Q(z) &= \sum_{i=1}^{k} (n_i-3)(z_i-\bar{z})^2 \quad \text{where, } \bar{z} = \frac{\sum_{i=1}^{k} z_i\ (n_i-3)}{\sum_{i=1}^{k} (n_i-3)} \end{aligned} . \tag{2}$$

Since the chisquare distribution for $Q(r)$ and $Q(z)$ are only approximations, we simulated the type I error rates of the corresponding homogeneity tests. The simulation study was carried out using the R software (2009) (Version 2.10.1). We first considered $k = 29$ studies and chose the sample sizes n_i's corresponding to the application discussed in the next section. For various values of the population correlations ρ_i's, assumed to be all equal to ρ, the type I error rates of the homogeneity tests based on $Q(r)$ and $Q(z)$ are given in Table 1 below. Each estimated Type I error rate is based on 10,000 simulation runs, by generating a random sample directly from the distribution of the sample correlation coefficient.

Table 1: Type I error rates for the sample sizes in the application, for a 5% significance level.

ρ	$Q(r)$	$Q(z)$
0.1	0.0557	0.0491
0.2	0.0589	0.0489
0.3	0.0589	0.0494
0.4	0.0588	0.0495
0.5	0.0605	0.0509
0.6	0.0605	0.0493
0.7	0.0637	0.0521
0.8	0.0615	0.0515
0.9	0.0647	0.0542

The numerical results in Table 1 show that the homogeneity test based on $Q(r)$, that directly uses the correlations, has a slightly inflated type I error. Nevertheless, the test is somewhat accurate. However, the homogeneity test based on $Q(z)$, i.e.,

based on the Fisher's z-transformed variable, maintains the type I error satisfactorily. We note that the sample sizes used in Table 1 are fairly large.

From a practical point of view, it maybe of some interest to see how the tests will perform when the sample sizes are small. For sample sizes all equal to 20, and all equal to 100, and the number of studies $k = 4$, 8 and 32, Table 2 and Table 3 give the type I error rates of the two tests.

Table 2: Type I error rates, for a 5% significance level, when $n_i = 20$, for $i = 1, 2, ..., k$

	$k = 4$		$k = 8$		$k = 32$	
ρ	$Q(r)$	$Q(z)$	$Q(r)$	$Q(z)$	$Q(r)$	$Q(z)$
0.1	0.1146	0.0475	0.1857	0.0551	0.4125	0.0542
0.2	0.1176	0.0540	0.1749	0.0579	0.3897	0.0539
0.3	0.1067	0.0500	0.1655	0.0544	0.3592	0.0519
0.4	0.0970	0.0497	0.1314	0.0475	0.3137	0.0495
0.5	0.0871	0.0517	0.1227	0.0521	0.2640	0.0477
0.6	0.0668	0.0508	0.0989	0.0495	0.2104	0.0539
0.7	0.0516	0.0515	0.0756	0.0471	0.1580	0.0480
0.8	0.0305	0.0472	0.0526	0.0466	0.1200	0.0496
0.9	0.0207	0.0503	0.0352	0.0467	0.0784	0.0430

Table 3: Type I error rates, for a 5% significance level, when $n_i = 100$, for $i = 1, 2, ..., k$

	$k = 4$		$k = 8$		$k = 32$	
ρ	$Q(r)$	$Q(z)$	$Q(r)$	$Q(z)$	$Q(r)$	$Q(z)$
0.1	0.0573	0.0466	0.0707	0.0498	0.0884	0.0491
0.2	0.0625	0.0510	0.0700	0.0530	0.0943	0.0530
0.3	0.0625	0.0506	0.0698	0.0536	0.0897	0.0512
0.4	0.0563	0.0480	0.0644	0.0511	0.0861	0.0487
0.5	0.0527	0.0474	0.0604	0.0469	0.0822	0.0474
0.6	0.0523	0.0491	0.0571	0.0469	0.0733	0.0500
0.7	0.0520	0.0544	0.0535	0.0493	0.0679	0.0483
0.8	0.0459	0.0491	0.0481	0.0464	0.0658	0.0503
0.9	0.0430	0.0502	0.0451	0.0478	0.0601	0.0495

The overall conclusion emerging from the above tables is that the homogeneity test based on $Q(r)$ should not be used, unless the sample sizes are large within studies. The performance of $Q(r)$ becomes worse when the sample sizes within studies are small, the number of studies is large, and the common correlation ρ is small. In fact, for $k = 32$ and the sample sizes within each study equal to 20, the type I error probability can

be as high as 0.41! The type I error probabilities of $Q(r)$ given in Table 2 and Table 3 also show a decreasing trend as ρ becomes large. On the other hand, in all scenarios considered for simulation, the test based on $Q(z)$ continues to perform satisfactorily.

3 Application

The application that we shall discuss in this section is on the meta-analysis of the results from 29 different studies primarily dealing with the cholesterol lowering efficacy of Ezetimibe co-administered with statins (Treatment 1), in comparison with statins alone (Treatment 0); see [15]-[41] (two studies each are reported in Cruz-Fernandez et al. [24] and in Gagne′ et al. [30]). We refer to Figure 1 and Figure 2, where the sample sizes in the different studies are explicitly given. Furthermore, 15 studies had subjects not on statin at baseline (referred to as subjects belonging to the "first line"), and 14 studies had subjects on statin at baseline (referred to as subjects belonging to the "second line"). Data were available on the three variables LDL, NHDL and APOB, at baseline, and at the termination of the studies. The problem of interest in this investigation is inference concerning the three pairwise correlations among these variables, at baseline and at study-end. Furthermore, it is of interest to separately analyze the correlations for subjects in the first line and for those in the second line, and also for those under Treatment 0 and Treatment 1. We first tested the homogeneity of the pairwise correlations for the correlations in all the different categories mentioned above. Based on the statistic $Q(z)$, the homogeneity hypothesis is rejected in all cases; in fact, the p-value is less than 0.0001 in all the cases.

In spite of the above, we did perform a meta-analysis of the pairwise correlations among the variables under a random effects model, and obtained forest plots. For example, a forest plot based on the baseline correlations between the variables LDL and NHDL is given in Figure 1. The figure gives the confidence intervals computed from the different studies, along with the results of the meta-analysis based on a random effects model. The plot in Figure 1 is obtained using the correlation data at baseline between the pair LDL and NHDL based on all available data on the pair. Here w(random) stands for the weights v defined in Section 2. From the meta-analysis reported in Figure 1, we conclude that the baseline correlation between LDL and NHDL is quite high.

Similar plots can obviously be obtained for all the different types of correlations. Similar to Figure 1, Figure 2 provides a forest plot obtained after using Fisher's transformation. We note that the results are somewhat similar to those in Figure 1. Here we would like to emphasize that when the homogeneity hypothesis is rejected, which is the scenario in our case, it is more appropriate to use a random effects model for performing the meta-analysis, as already noted in Section 2. Consequently, we have not included the analysis under a fixed effects model.

For the baseline correlation data between the variables LDL and NHDL, we shall now report the results of a cumulative meta-analysis based on a random effects model.

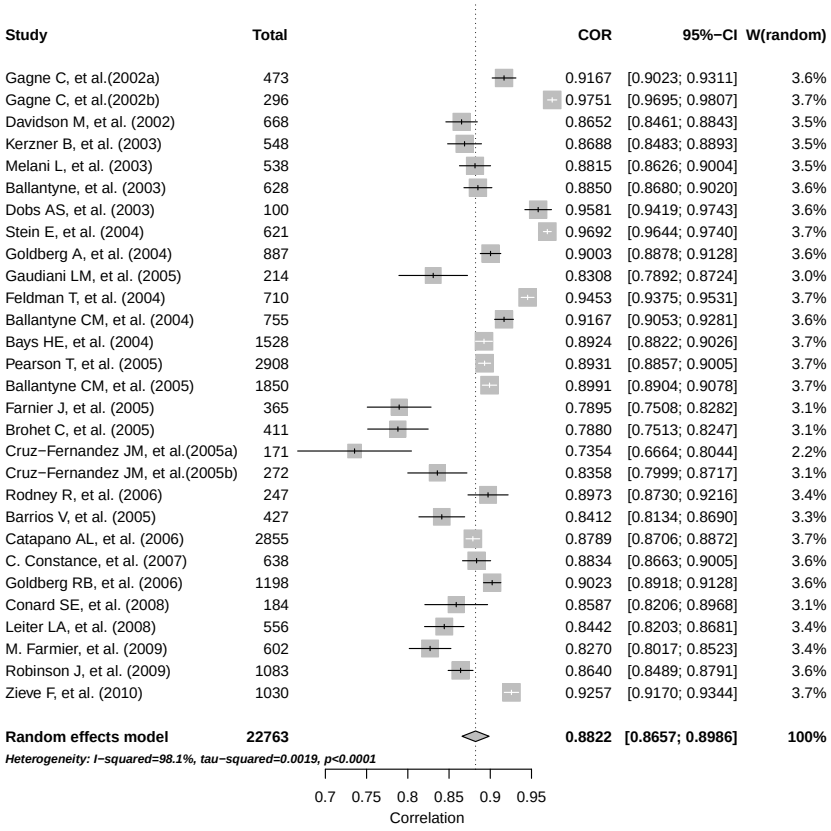

Figure 1: Meta-analysis of the Baseline Correlation Between LDL and NHDL.

We note that in a graph of a cumulative meta-analysis, the results from individual studies are not reported; rather, the cumulative results are reported as each study is added, chronologically. The plot of the cumulative meta-analysis is given in Figure 3 (based directly on the correlations) and Figure 4 (based on Fisher's transformation). Each horizontal line in the plot represents the summary of the results as each study is added. We note that the confidence interval for the correlation stabilized at study 15. Further inclusion of the studies, until study 21, did not produce any appreciable difference in the confidence interval. The interval did change marginally with the inclusion of study 22, and remained more or less stable in the rest of the analysis. The same pattern shows up in both Figure 3 and Figure 4.

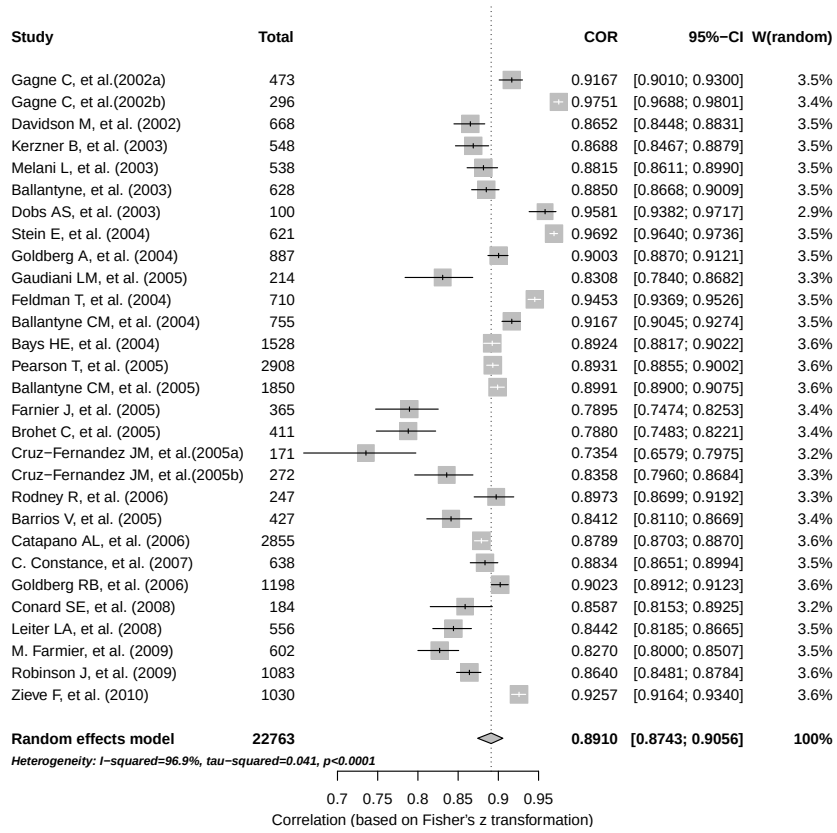

Figure 2: Meta-analysis of the Baseline Correlation Between LDL and NHDL, after Fisher's Transformation.

We would also like to add the following comments regarding Figure 3 and Figure 4. The sequential entry of the studies, as they appear in Figure 3 and Figure 4, is not according to the date of publication. However, they have indeed been entered chronologically based on the date of completion of each study, since such information was made available to us. The date of publication of the different studies did not follow their chronological order of completion. All of the plots have been obtained using the R computing package.

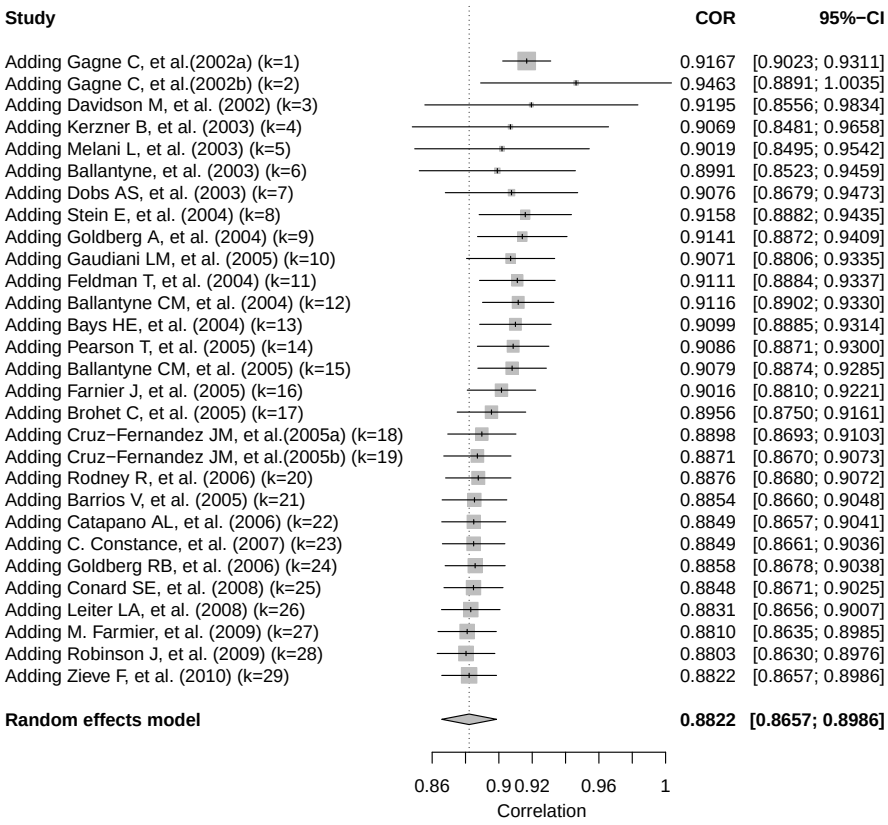

Figure 3: Cumulative Meta-analysis of the Baseline Correlation Between LDL and NHDL.

Even though we carried out the analysis for all the pairwise correlations among the three variables LDL, NHDL and APOB, in the paper we have only reported results for the correlation between LDL and NHDL. The pattern and the conclusions turned out to be very similar for the other two correlations as well; i.e., for the correlation between LDL and APOB and that between NHDL and APOB. Thus we have not reported these results.

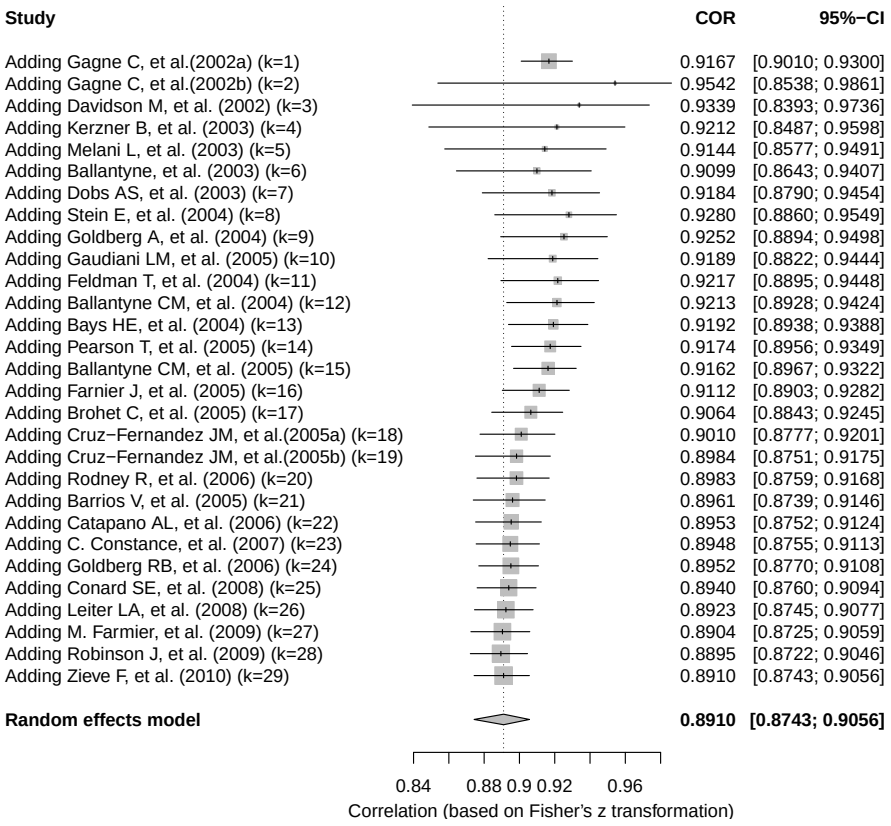

Figure 4: Cumulative Meta-analysis of the Baseline Correlation Between LDL and NHDL, after Fisher's Transformation.

4 Discussion

In this report, we first made an investigation of the performance of Cochran's Q test for testing the homogeneity of correlations. Based on numerical results, we have concluded that the test should not be used based on the correlations themselves; rather, the test should be carried out after making Fisher's variance stabilizing transformation. Otherwise, the test could result in highly inflated type I error probabilities, especially when the number of studies is large, and the sample sizes within studies are small. This conclusion is not new, and has already been noted in the literature; see [3], [4] and [5]. We then performed a meta-analysis of the pairwise correlations among the three cholesterol variables LDL, NHDL and APOB. A cumulative meta-analysis was also carried out. It should be noted that in this application, the homogeneity hypothesis was rejected. However, the meta-analysis was performed after noting that several of the pairwise correlations was high; in fact above 0.90.

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