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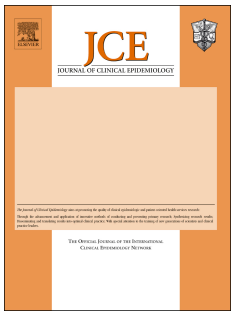

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T. Pérez, J. McLellan, R. Perera

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EXTRACTION OF UNADJUSTED ESTIMATES OF PROGNOSTIC ASSOCIATION FOR META-ANALYSIS: SIMULATION METHODS AS GOOD ALTERNATIVES TO TREND AND DIRECT METHOD ESTIMATION

T Pérez[a], J McLellan[b], R Perera[b]*

[a]Department of Statistics and Operational Research III. Faculty of Statistical Studies, Complutense University of Madrid, Madrid, Spain.
[b]National Institute for Health Research School for Primary Care Research, Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

* Corresponding author
e-mail: rafael.perera@phc.ox.ac.uk
Postal address: Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG. UK

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Abstract:

Objective: Systematic reviews and meta-analysis are the standard methods to assess the association between prognostic markers and major events/conditions. However, the summary measures reported are not always explicitly presented and therefore different indirect methods of extracting estimates have been proposed. The aim of this study is to present two new alternative methods for obtaining summary statistics to be included in a meta-analysis of prognostic studies based on simulating individual patient data and to compare them with the already known generalized least squares for trend estimation method and direct method.

Study Design and settings: We have checked the performance of these methods using a between study comparison, including 122 studies, and a within study comparison, based on data from one of the studies.

Results: The results obtained in this study show that generalized least squares for trend estimation method appears to overestimate the effect size when reported information is incomplete. For the within study comparison, the closest approximation to the direct estimates was obtained using the approach based on simulating individual participant data.

Conclusion: The proposed simulation methods are a good alternative when other well-known indirect methods cannot be used.

Word count: 189

Key words: Meta-analysis; Prognostic marker; Generalized Least Squares for Trend Estimation; Simulated data.

Running tittle: Indirect methods in meta-analysis

What is new?

Key findings

Methods based on simulating individual participant data may be consider as an alternative for extracting estimates in meta-analysis of prognostic marker studies.

What this adds to what was known?

When reported information is incomplete the well-known indirect methods may not be appropriate.

What is the implication and what should change now?

The use of these methods increase the number of studies that may be included in meta-analyses.

1. Motivation

Evidence of the association between prognostic markers and major events/conditions should be compiled using a systematic process similar to that used for therapeutic interventions [1]. Single studies that assess the clinical value of prognostic markers tend to have a relatively small number of patients, which would impact on their statistical power for detecting any real associations [2]. Systematic reviews and in particular meta-analysis methodology have therefore been proposed as an alternative to allow a useful assessment of these associations [3] [4].

Systematic reviews and meta-analysis of aggregated data from published studies are well established for the comparisons of treatment interventions. However the methods are not as well developed for prognostic research, which generally uses observational epidemiological studies with slight differences in the summary measures used to capture the association (e.g. log hazard ratio and its variance when the studies involve time to event data or relative risk and odds ratio for dichotomous data).

The main issues that make systematic reviews of prognostic studies challenging are: a) poor indexing, b) poor reporting of Summary measures, c) Heterogeneity of Studies, and d) Selective reporting/publication bias [2] [5] [6]. Given these, the use of individual patient data has been suggested as the best strategy to obtain valid estimates from systematic reviews of prognostic studies [5] [7] [8] [9] [10] [11]. However, there are major resource implications and only a handful of reviews have attempted to obtain individual patient data [5] [7] [8] [12] [13].

Reporting of summary measures of the association are not always explicitly presented for each study [2]. Nevertheless, in many studies relevant information is presented so that the association between the prognostic factor and the event/condition can be identified. Bekkering et al [14] describe four types of reported associations that can be identified when performing a systematic review, >> insert Table **1**.

>> insert Table 1. Types of reported associations.<<

Indirect methods of extracting estimates are frequently considered when reported information is of type 1 but incomplete or heterogeneous. For the particular case of time to event outcome, the Cochrane handbook advises that the effect measure should be expressed as a hazard ratio. Parmar et al [15] presented some methods for performing analysis of the published literature for survival data. They provided a clear hierarchy in the approaches presented. If a hazard ratio and its variance are available directly for an individual trial, then these values should be used. If either statistic is not available directly then as many of the indirect methods as possible should be used. Riley et al [2] performed a systematic review of tumour marker for neuroblastoma using different direct and indirect methods based on the approach of Parmar et al [15] to increase the number of occasions an estimate of the log(hazard ratio) and its variance could be obtained. Guyot et al [16] proposed a method which derives from the published Kaplan Meier survival curves a close approximation to the original individual patient time-to-event data from which they were generated. Therefore time to event outcome will not be considered in this paper.

Cheˆne and Thompson [17] derived methods to estimate the log odds ratio when data is reported as means, type 2. An important assumption of the methods is that the prognostic marker has an approximately normal distribution with equal standard deviations in cases and controls. Though a normal distribution could be appropriate for many prognostic markers, differences in standard deviations between the comparison groups are likely [18] [19] [20] [21] [22].

Greenland et al [23] and Berlin et al [24] discussed methods for trend estimation for quantile-based or category data, type 3 and type 4. However a limitation of this method arises when reported results, such as the absence of sufficient information on exposure levels in the different groups, do not allow the estimation of log odds, risk, or hazard ratio per unit increase in prognostic marker and its standard error [14].

In this paper we describe two additional approaches to achieve summary data when reported associations are of type 2, 3, or 4, based on simulating individual participant data, as an alternative when previous methods cannot be applied. These approaches assume normality of the prognostic marker but unlike Cheˆne and Thompson´s methods [17], allow different standard deviations to be considered. We describe these methods and then present an example of these applied to a recent systematic review of the association of lipid markers and cardiovascular events [25].

We performed two comparisons of these methods: *indirectly* by carrying out the equivalent of a sensitivity analysis in a systematic review comparing pooled estimates; and *directly* by comparing for a single study the estimates obtained by the two new methods to the summary estimates directly provided for one of the studies in the systematic review [26].

For the indirect comparison the pooled estimates of results obtained by either one of the simulated methods (studies providing data from Types 2 to 4) are presented alongside that obtained when summary estimates are directly provided (Type 1). For the direct comparison we use the CARDS trial to evaluate differences between the simulated methods and the direct estimates [26].

Aims

To present two alternative methods for obtaining unadjusted summary statistics to be included in a meta-analysis of prognostic studies based on simulating individual patient data and to compare them with the generalized least squares for trend estimation method and direct method.

2. Methods for generating prognostic estimates

2.1 Generalized least squares for trend estimation method

Methods for trend estimation are particularly useful when the marker is not consider as a quantitative variable in the original study but as categorical variable with one category serving as the common referent group [24] and the relationship between increasing (or decreasing) levels of the prognostic marker and the risk of the outcome is assumed to follow a linear pattern. Adequate reporting of these summarized data is needed to consider generalized least squares method as an indirect method for obtaining summary statistics:

(1) a detailed description of each category, including lower and upper limits,

(2) mean or median exposure in each group,

(3) number of cases, number of controls,

4) relative risks (or ORs) and their corresponding confidence interval.

Based on this information, the generalized least squares for trend (glst) approach estimates the expected change on the log relative risks for a unit change of the prognostic marker incorporating correlations among log relative risks since they were obtained using a common referent group.

The model considered is:

$$y = \begin{pmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{pmatrix}; X = \begin{pmatrix} x_{11} & x_{12} & \cdots & x_{1p} \\ \vdots & \vdots & & \vdots \\ x_{i1} & x_{i2} & & x_{ip} \\ \vdots & \vdots & & \vdots \\ x_{n1} & x_{n2} & & x_{np} \end{pmatrix}; \beta = \begin{pmatrix} \beta_1 \\ \vdots \\ \beta_p \end{pmatrix}; \varepsilon = \begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \\ \vdots \\ \varepsilon_n \end{pmatrix}$$

$$y = X\beta + \varepsilon$$

Where y is an n×1 vector of reported estimated log relative risks for the nonreference prognostic marker levels, X is an n×p matrix of covariates where the first column identifies the nonreference prognostic marker levels and the remaining p-1 columns may represent transformation of the first column, β is a p×1 vector of unknown regression coefficients and ε is an n×1 vector of random errors. The mean and variance-covariance matrix are given by:

$$E(\varepsilon)=0,\ \mathrm{Cov}=(\varepsilon)=\Sigma=\begin{pmatrix}\sigma_{11} & & & & \\ \vdots & \ddots & & & \\ \sigma_{i1} & & \sigma_{ii} & & \\ \vdots & & & \ddots & \\ \sigma_{n1} & \cdots & \sigma_{ni} & \cdots & \sigma_{nn}\end{pmatrix}$$

Estimator ***b*** of the regression coefficients β is obtained using generalized least squares method:

$$b=(X^t\Sigma^{-1}X)^{-1}X^t\Sigma^{-1}y$$

However as we have already mentioned, it is quite common that results reported are incomplete, e.g. any of the following is missing: the numbers of cases or controls (or the denominator in cohort studies), the odds ratio, the confidence interval, the group median or mean; or only unbounded upper or lower categories are shown. Bekkering et al [14] present solutions in the case of results based on dose-response meta-analyses.

We have used the glst approach under two different settings as described in >> insert Table **2**.

Method 1: optimal conditions where all the required information was reported or some simple solutions could be applied as proposed in Bekkering et al [14] *glst level 1*.
Method 2: in cases where the group mean was missing and data were reported as categorical with three or less levels and undefined lower or upper categories were presented; *glst level 2*. In this case, information was estimated by using the method of Cheˆne and Thompson [17].

>> insert Table 2. Type of estimation based on reported information<<

2.2 **Simulating individual patient data method**

In this section we describe how to obtain summary statistics (OR) from prognostic studies with quantitative markers by simulating individual patient data (IPD), assuming a normal distribution of the marker. In particular we present two simulation methods (see >> insert Table **2**).

Method 3 – First Algorithm: If baseline parameters for those with and without the outcome of interest e.g. mean and SD of the marker for case and control groups, are provided these parameters can be used to simulate IPD for each group.

>>insert Table **3** presents our proposed algorithm for computing the odds ratio (OR) if the marker is increased by one unit.

>>insert Table 3. An algorithm for computing the OR for a one-unit increase knowing baseline parameters for cases and controls<<

*This method allows simulating values for a great number of biological and medical variables because most of them have approximately normal distributions, e.g. TC, SBP or weight. Different distribution is assumed for each subgroup (cases/controls).

Method 4 – Second Algorithm: In some studies, baseline parameters for each marker are available for the whole sample and not by groups (cases/controls). In this situation, simulation methods can be applied when the number of events and no events by levels of the marker are provided, i.e. the marker measurement is divided in two or three categories and the numbers of cases/controls, of each category, are reported. The algorithm considered in this situation is given in >>insert Table **4**.

>>insert Table 4. An algorithm for computing the OR for a one-unit increase when baseline parameters are not provided<<

*Biological or medical variable may be the same e.g. TC, SBP or weight. However, in this case, the global distribution is considered instead of subgroups, cases/controls.

>>insert Table 5. Examples of data presented in four trials and their link to the proposed method.<<

3 Comparing results of different estimators obtained by different methods

Examples of data presented in different articles and their suitability to the different methods proposed are presented in >>insert Table **5**.

We illustrate the performance of these methods using a between study comparison and a within study comparison. The between study comparison is based on studies identified in a systematic review of the relation between lipid levels and cardiovascular disease [25]. The within study comparison is based on data from one of the studies identified in the above review. For this direct comparison we use as a reference the estimate obtained from the individual patient data.

3.1 **INDIRECT COMPARISON – pooled data as reference**

Based on data from a systematic review evaluating the association of lipid markers and cardiovascular events we were able to perform an indirect comparison of the different methods, >>insert Table **6**. We have used three options as reference in our comparisons:

a) the pooled estimate obtained from the direct method (R1)
b) the pooled estimate obtained from all methods (R2)
c) the pooled estimate obtained from all methods except the one being compared (R3)

A total of 122 studies were included. In 54 of them (46.7%), summary statistics (OR) were extracted directly from the papers, “direct method”. In others studies instead of the odds, risk, or hazard ratio and confidence interval (or standard error), the information provided was the risk of event across different levels of the lipid measurement, with one category serving as the referent group. Method 1 was considered in 10.6% of the studies and Method 2 in 6.5% of the studies. In these cases a generalized least squares for trend estimation was performed using the **glst** command in Stata [30] and package **dosremeta** in R [31], both methods are described in section 2.1 and in >> insert Table **2**. Finally, in others studies, data were obtained by simulating individual participant data (IPD), Method 3 in 17.2% of the studies and

Method 4 in 18.8% of the studies. These two methods are described in Section 2.2 and in >> insert Table **2**. Two R-based codes have been developed to accommodate these methods. Two examples of these codes are presented in Appendix A.

>>insert Figure **1**->>insert fig 2Figure **2** show forest plots for serum cholesterol (TC), (all for CVD events, both adjusted and unadjusted results) broken down by extraction method. The corresponding figures for HDL-cholesterol (HDL) and LDL-cholesterol (LDL) can be found in the Appendix B, Figures **Error! Reference source not found.**-B4.

>>insert Figure 1. Prognostic markers & methods of extraction. TC (unadjusted)/CVD events))<<

>>insert fig 2Figure 2. TC (adjusted)/CVD events)<<

>>insert Table 6. Hazard ratios and 95% CI<<

3.2 DIRECT COMPARISON – individual participant data (IPD) to define reference

We carried out a direct comparison of the results obtained based on the different methods by focusing on the data from a single study in the Review, the CARDS study [26].

The Collaborative AtoRvastatin Diabetes Study (CARDS) is a multicentre, randomized, placebo-controlled, double-blind clinical trial of primary prevention of cardiovascular disease in patients with Type 2 diabetes. 2838 patients aged 40–75 years in 132 centres in the UK and Ireland were randomised to placebo (n=1410) or atorvastatin 10 mg daily (n=1428), however only patients in the placebo group have been considered in this analysis, because modelling of this group is easier as no allowance for treatment effects are required [32].

As a reference we consider the direct estimator of the OR and 95%CI achieved from a logistic regression model using IPD, considering cardiovascular event (yes/no) as the dependent variable and lipid measurement as the independent variable.

>>insert Table **7** shows examples of information considered for each method for the CARDS study. In Method 1 the independent variable (e.g. TC) was included as categorical, with five levels (quintiles) or three levels (tertiles). Then the ORs of cardiovascular event across different levels of the lipid measurement with last group as the reference were provided. With this information a generalized least squares for trend estimation was performed. Method 2 uses the same ORs as Method 1, but in order to determine the impact of unbounded upper and lower categories on this estimation, the independent variable was included as categorical with three levels and first and last limits were omitted. Simulation process described in Table 3 was used in Method 3, where the mean and the SD for cases and controls were directly estimated from the IDP of the CARDS study. A logistic regression model was fitted for each simulated sample. The average of the corresponding ORs is the estimate of the OR. Finally, all steps presented in Table 4 were followed in Method 4. In this case, the mean and the SD of the whole sample, the predetermined categories, and the rate of

event within each category were obtained from the paper [26]. The drawback of this case is that the distributions by subgroups (events/no events) are unknown. The use of the rates of events by categories allows overcoming this problem.

>>insert Table **8** shows results obtained using each method of extracting estimates of the ORs for cardiovascular disease, for three lipid measures: serum cholesterol (TC), HDL-cholesterol (HDL), LDL-cholesterol (LDL).

>>insert Table 7. Examples of information considered for each method, from the CARDS study<<

>>insert Table 8. OR and 95% CI for a one-unit increase and mean square error (MSE) for simulation methods.<<

*Point estimate outside the original 95%CI for Reference. Green colour highlights the estimates closest to the Reference. Red colour highlights those estimates with largest difference to the Reference.

- The behaviour of the Methods across the different outcomes is relatively consistent but different to what was observed in the indirect comparisons.
- Method 1 underestimates the association for TC and LDL although it is very similar to that observed for HDL
- Method 2 appears to overestimate for all the outcomes
- Method 3 appears to provide the most consistent result compared to the reference
- Method 4 underestimates the association for TC and LDL although it is similar to that observed for HDL
- HDL has the most consistent estimates except for Method 2.

Conclusions

Meta-analysis using individual participant data (IPD), where the raw data are synthesised from multiple studies, has been considered as the gold-standard for synthesising prognostic factor studies [8] [9] [10] [11]. A major obstacle for this kind of meta-analysis is the fact that it is more expensive, time-consuming, requires close cooperation between study coordinators and several years to complete [11]. Even if a meta-analysis of individual participant data is well planned, it may be useful to perform a meta-analysis of the published literature as a precursor to the larger project [15].

The main aim of this paper was to present two alternative methods for obtaining summary statistics to be included in a meta-analysis of prognostic studies based on simulating individual patient data (Method 3 and Method 4). A comparison with the generalized least squares for trend estimation method (Method 1 and Method 2) and direct method have been made.

Several authors [23] [24] [30] [33], considered that Method 1 is particularly useful when the full original data are not accessible, however results obtained in this study with this method appears to “underestimate” the effect size based on the comparisons we have made.

In those studies where means and SD for cases and controls are reported, Method 3 appears as an alternative approach to estimate the risk for a one-unit increase, assuming that the prognostic marker has an approximately normal distribution. Indeed Method 3 provided the best estimates in the direct comparison, with values of MSE close to 0. However, the closer the marker distribution is from the normal distribution the better the estimation and this might limit its use at least for untransformed data.

However, for some parameters (e.g. triglycerides where logarithmic transformation is generally considered due to skewed distributions) to assume that the distribution of the marker is well approximated by the normal distribution is not valid. Inaccurate simulated values of the marker can be detected based on the histogram or estimating a kernel density for a single simulated sample and comparing it to further summary statistics reported for the marker (e.g. median, IQR, etc.). If severe discrepancies are observed, the validity of the assumption should be questioned and then these methods should not be considered.

When comparing Method 2 with Reference, it can be observed that the lack of information about the limits has a great impact on the estimation, as expected, so it might provide biased estimates. Method 4 appears as a good option, although it needs mean and SD of the marker but this information is usually reported.

A weakness of Method 3 and Method 4 is that relative risk or OR can be estimated, but unfortunately we do not have enough information to estimate HR. Despite some researchers regard all these effect sizes as similar and therefore they assume that it is correct to combine them [34] others [15] considered that replacing HR by OR or RR is inefficient and that could lead to inappropriate conclusions. Tierney et al. [35] explain that ORs and RRs are applicable for measuring dichotomous outcomes, but less appropriate for analysing time-to-event outcomes.

An important limitation of the indirect comparison done in this study is the issue of heterogeneity across the studies. We cannot determinate whether the differences on estimators are due to the differences between methods or between studies.

It should be pointed out that these methods are proposed to increase the number of studies included in the meta-analysis and in this sense we do not expect an improvement compare to the well-known indirect methods but a good alternative in case those cannot be used.

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[36]

Table 1. Types of reported associations.

Type 1	Quantitative variable based: data reported as odds, risk, or hazard ratio per unit increase in prognostic marker, or as regression coefficients.
Type 2	Means: data reported as means or mean differences in exposure, comparing those with and without disease.
Type 3	Quantile based: data reported as ratios comparing groups as defined by quantiles of either total numbers or numbers of controls.
Type 4	Categories: data reported as ratios comparing unequal-sized groups.

Table 2. Type of estimation based on reported information

Type of data and Available information	Method of Estimation
Quantile-based or Categorical data Detailed categories description, lower and upper limits of each category, mean or median exposure in each group, number of cases, number of controls, relative risks (or ORs) and their Cis, or simple to be estimated if missing, Bekkering et al (2008).	Method 1: glst level 1
Categorical data (3 or less levels) Poor description of the categories, the group mean was missing and unbounded upper or lower categories are shown, but number of cases, number of controls, relative risks (or ORs) and their Cis are reported.	Method 2: glst level 2
Mean data Mean and SD for cases (patients with event) and controls (patients without event)	Method 3: Simulate data, first Algorithm
Quantile-based or Categorical data Global Mean and SD. Number of cases and controls by levels of the marker. But relative risks (or ORs) and their Cis are not reported.	Method 4: Simulate data, second Algorithm

Table 3. An algorithm for computing the OR for a one-unit increase knowing baseline parameters for cases and controls

Step	Procedure
1	Simulate two random samples* of sizes n_1=number of patients with event and n_0=number of patients without event, from normal distributions, using baseline parameters
2	Join both samples in a new variable
3	Create an indicator variable that takes on the value "1" for data from the first sample and the value "0" other case
4	Fit a logistic regression model considering variables obtained on step 2 and step 3, keeping the corresponding OR
5	Repeat steps (1) - (4), 10^3 times
6	Calculate the average of the ORs, this value is the estimate of the OR and the 2.5^{th} and 97.5^{th} percentiles are the estimates of the lower and upper confidence limits respectively.

*This method allows simulating values for a great number of biological and medical variables because most of them have approximately normal distributions, e.g. TC, SBP or weight. Different distribution is assumed for each subgroup (cases/controls).

Table 4. An algorithm for computing the OR for a one-unit increase when baseline parameters are not provided

Step	Procedure
1	Simulate a random sample* of size n=number total of patients, from a normal distribution, considering the overall baseline mean and SD as the parameters of the global distribution
2	Sort this sample according to predetermined categories
3	Determinate the observed frequency in the sample that belongs to each category
4	Calculate the expected number of events of each category so that the probability of event matches with information reported in the article
5	Define a dummy variable ("1" means event, "0" means no event) that accurately represents the information obtained in step 4
6	Fit a logistic regression model considering variables obtained on step 2 and step 5 keeping the corresponding OR
7	Repeat steps (1) - (6), 10^3 times
8	Calculate the average of the ORs, this value is the estimate of the OR and the 2.5th and 97.5th percentiles are the estimates of the lower and upper confidence limits respectively.

*Biological or medical variable may be the same e.g. TC, SBP or weight. However, in this case, the global distribution is considered instead of subgroups, cases/controls.

Table 5. Examples of data presented in four trials and their link to the proposed method.

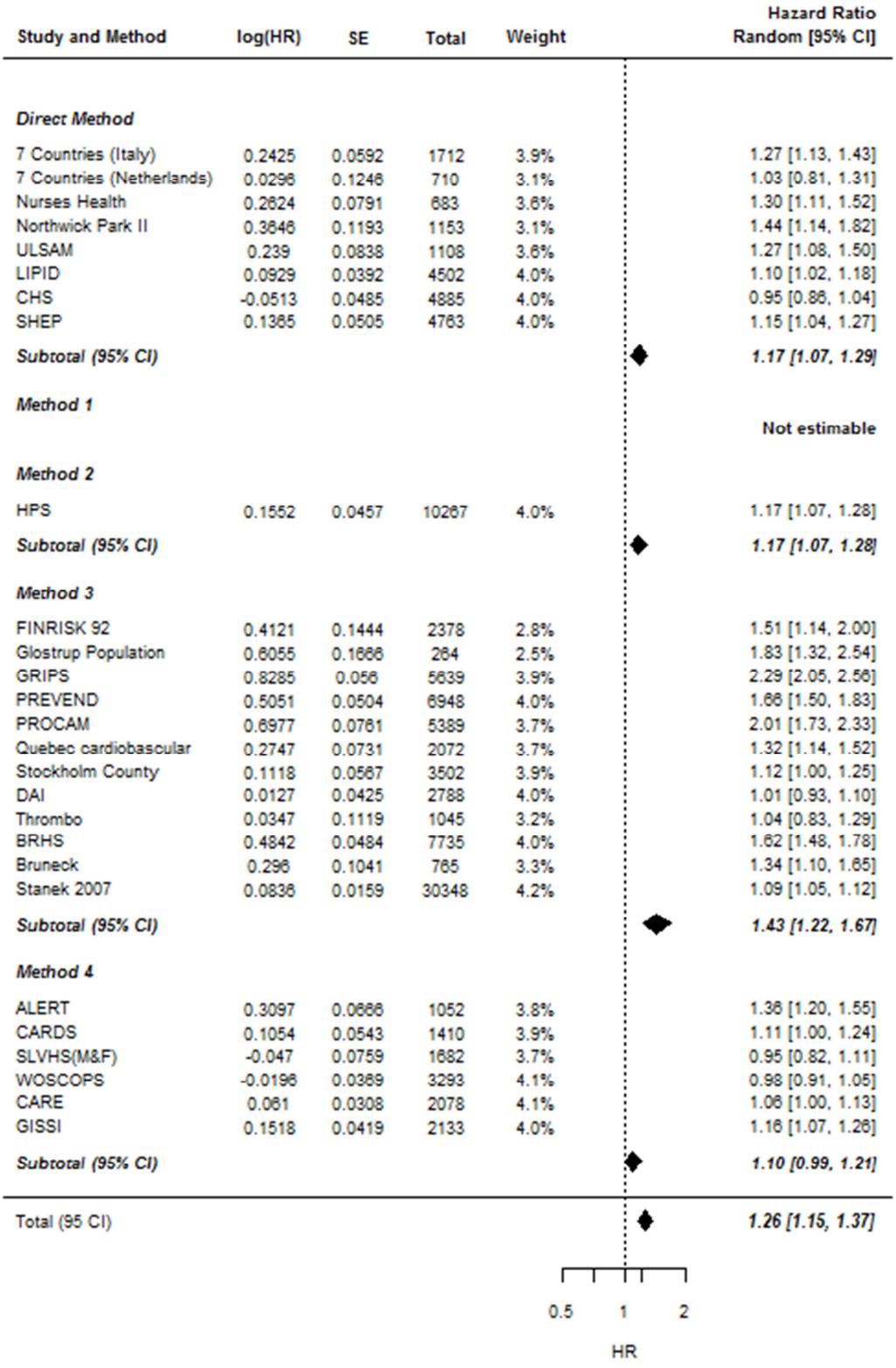
Type of data	Marker and outcome	Data presented in the paper				
Method 1: Quantile-based from Women´s health Study [27]	TC and CVD event	TC Quintile (mmol/l)	Mean	Nº Subject	Mortality Per 10.000 p/y	RR (95% CI)
		(2.1-2.6)	4.18	4908	4.85	1
		(4.7-5.1)	4.92	4112	5.57	0.93 (0.55-1.58)
		(5.2-5.7)	5.48	5409	6.91	1.05 (0.65-1.68)
		(5.8-6.3)	6.06	4063	12.35	1.76 (1.13-2.76)
		(6.4-17.8)	7.14	4875	22.77	2.77 (1.84-4.18)
Method 2: Categorical data from AFCAPS/*TexCAPS Study* [28]	LDL and CVD event	LDL Tercile (mg/dl)	N	Nº Cases	RR (95% CI)	
		≤142	2210	37	1	
		143-156	2196	33	0.897 (0.563-1.429)	
		≥157	2199	46	1.249 (0.813-1.918)	
Method 3: Mean data from CLIP Study [20]	TC and CVD event	Baseline TC level was 264.3 +/- 32.9 mg/dl (mean +/- standard deviation) in controls (n=2106) and 270.2 +/-25.8 mg/dl in cases (n=25)				
Method 4: Categorical data [29]	LDL and CVD event	Baseline LDL level was 111 +/- 29.85 mg/dl in the whole sample (n=2232)		Category	Rate %	
				<100	17.9	
				100-130	16.0	
				>130	15.8	

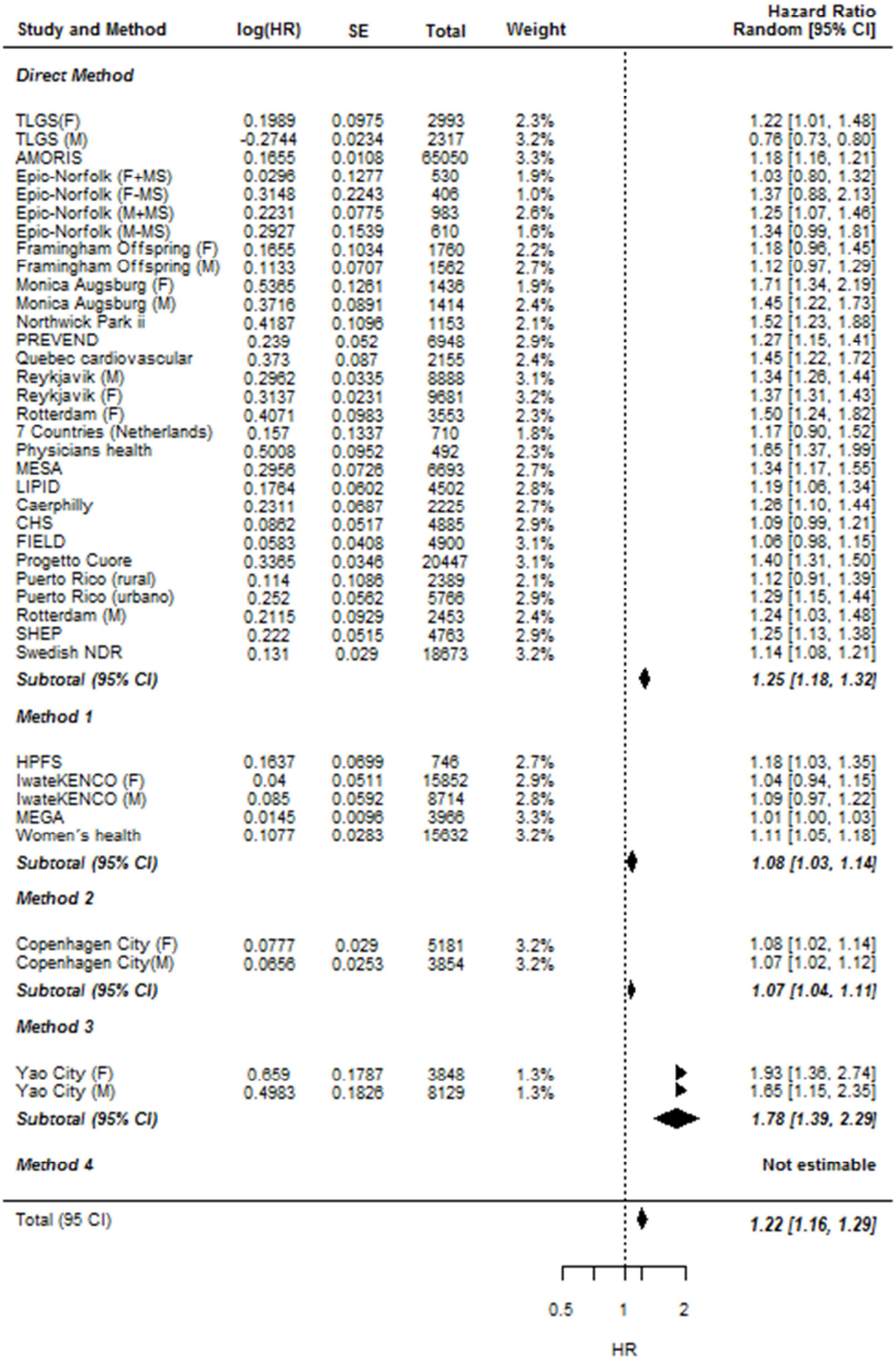
Table 6. Hazard ratios and 95% CI

	Reference						Indirect methods of estimation			
Marker	**Direct**	**Total**	**Total(-M1)**	**Total(-M2)**	**Total(-M3)**	**Total(-M4)**	**Method 1**	**Method 2**	**Method 3**	**Method 4**
	R1	R2	R3							
TC unadjusted	1.17(1.07-1.29)	1.26(1.15-1.37)	-	1.26(1.15-1.37)	1.14(1.06, 1.21)	1.31(1.18, 1.45)	-	1.17(1.07-1.28)	1.43(1.22-1.67)	1.10(0.99-1.21)
Nº studies (%)	8 (29%)	27 (100%)	0 (0%)	26 (96%)	15 (55%)	21 (77%)	0 (0%)	1 (3%)	12 (44%)	6 (22%)
TC adjusted	1.25(1.18-1.32)	1.22(1.16-1.29)	1.24 (1.17,1.32)	1.23(1.16,1.30)	1.21(1.15,1.27)	-	1.08(1.03-1.14)	1.07(1.04-1.11)	1.78(1.39-2.29)	-
Nº studies (%)	30 (76%)	39 (100%)	34 (87%)	37 (94%)	37 (94%)	0 (0%)	5 (13%)	2 (5%)	2 (5%)	0 (0%)
LDL unadjusted	1.05(0.81-1.37)	1.20(1.07-1.34)	-	1.18 (1.05,1.33)	1.08 (0.98,1.20)	1.29 (1.09,1.53)	-	1.43(1.22-1.58)	1.48(1.18-1.84)	1.07(1.00-1.14)
Nº studies (%)	7 (25%)	28 (100%)	0 (0%)	26 (89%)	19 (67%)	18 (64%)	0 (0%)	2 (7%)	9 (32%)	10 (35%)
LDL adjusted	1.18(1.09-1.28)	1.15(1.08-1.21)	1.17 (1.09,1.25)	1.15 (1.08,1.23)	-	-	1.07(1.00-1.15)	1.12(1.08-1.17)	-	-
Nº studies (%)	14 (63%)	22 (100%)	17 (77%)	19 (86%)	0 (0%)	0 (0%)	5 (22%)	3 (13%)	0 (0%)	0 (0%)
HDL unadjusted	0.73(0.65-0.82)	0.80(0.75-0.86	-	0.81 (0.75,0.88)	0.81 (0.74,0.89)	0.74 (0.67,0.81)	-	0.57(0.49-0.66)	0.78(0.69-0.88)	0.93(0.85-1.01)
Nº studies (%)	10 (30%)	33 (100%)	0 (0%)	31 (93%)	22 (63%)	23 (69%)	0 (0%)	2 (6%)	11 (33%)	10 (30%)
HDL adjusted	0.84(0.79-0.89)	0.85(0.81-0.90)	0.85 (0.80,0.89)	0.85 (0.80,0.89)	0.86 (0.82,0.90)	-	0.92(0.79-1.08)	0.93(0.85-1.01)	0.64(0.48-0.85)	-
Nº studies (%)	29 (74%)	39 (100%)	34 (87%)	36 (92%)	37 (94%)	0 (0%)	5 (12%)	3 (7%)	2 (5)	0 (0%)

Table 7. Examples of information considered for each method, from the CARDS study

Type of data	Marker and outcome	Data considered				
Direct Method:	TC and CVD event	IPD				
Method 1: Quantile-based with known limits	TC and CVD event	TC Tertile (mmol/l) (2.4-5.0) (5.0-5.7) (5.7-8.3)	Mean 3.7 5.4 7.5	Cases 36 41 50	Controls 420 429 434	OR (95% CI) 0.69 (0.44-1.01) 0.80 (0.52-1.24) 1
Method 2: Quantile-based with unknown limits	TC and CVD event	TC (mmol/l) <5.0 (5.0-5.7) >5.7		Cases 36 41 50	Controls 420 429 434	OR (95% CI) 0.69 (0.44-1.01) 0.80 (0.52-1.24) 1
Method 3: Mean and SD data	TC and CVD event	TC level was 5.33 +/- 0.82 mmol/l (mean +/- standard deviation) in controls (n=1283) and 5.49 +/-0.74 mmol/l in cases (n=127)				
Method 4: Categorical data	TC and CVD event	TC level was 5.35 +/- 0.82 mmol/l (mean +/- standard deviation) of the whole sample (n=1409)			Category <5.4 >5.4	Rate % 7.9 10.1


Study and Method
log(HR)
SE
Total
Weight
Hazard Ratio
Random [95% CI]
Direct Method
7 Countries (Italy) 0.2425 0.0592 1712 3.9% 1.27 [1.13, 1.43]
7 Countries (Netherlands) 0.0296 0.1246 710 3.1% 1.03 [0.81, 1.31]
Nurses Health 0.2624 0.0791 683 3.6% 1.30 [1.11, 1.52]
Northwick Park II 0.3646 0.1193 1153 3.1% 1.44 [1.14, 1.82]
ULSAM 0.239 0.0838 1108 3.6% 1.27 [1.08, 1.50]
LIPID 0.0929 0.0392 4502 4.0% 1.10 [1.02, 1.18]
CHS -0.0513 0.0485 4885 4.0% 0.95 [0.86, 1.04]
SHEP 0.1365 0.0505 4763 4.0% 1.15 [1.04, 1.27]
Subtotal (95% CI) 1.17 [1.07, 1.29]
Method 1
Not estimable
Method 2
HPS 0.1552 0.0457 10267 4.0% 1.17 [1.07, 1.28]
Subtotal (95% CI) 1.17 [1.07, 1.28]
Method 3
FINRISK 92 0.4121 0.1444 2378 2.8% 1.51 [1.14, 2.00]
Glostrup Population 0.6055 0.1666 264 2.5% 1.83 [1.32, 2.54]
GRIPS 0.8285 0.056 5639 3.9% 2.29 [2.05, 2.56]
PREVEND 0.5051 0.0504 6948 4.0% 1.66 [1.50, 1.83]
PROCAM 0.6977 0.0761 5389 3.7% 2.01 [1.73, 2.33]
Quebec cardiobascular 0.2747 0.0731 2072 3.7% 1.32 [1.14, 1.52]
Stockholm County 0.1118 0.0567 3502 3.9% 1.12 [1.00, 1.25]
DAI 0.0127 0.0425 2788 4.0% 1.01 [0.93, 1.10]
Thrombo 0.0347 0.1119 1045 3.2% 1.04 [0.83, 1.29]
BRHS 0.4842 0.0484 7735 4.0% 1.62 [1.48, 1.78]
Bruneck 0.296 0.1041 765 3.3% 1.34 [1.10, 1.65]
Stanek 2007 0.0836 0.0159 30348 4.2% 1.09 [1.05, 1.12]
Subtotal (95% CI) 1.43 [1.22, 1.67]
Method 4
ALERT 0.3097 0.0666 1052 3.8% 1.36 [1.20, 1.55]
CARDS 0.1054 0.0543 1410 3.9% 1.11 [1.00, 1.24]
SLVHS(M&F) -0.047 0.0759 1682 3.7% 0.95 [0.82, 1.11]
WOSCOPS -0.0196 0.0369 3293 4.1% 0.98 [0.91, 1.05]
CARE 0.061 0.0308 2078 4.1% 1.06 [1.00, 1.13]
GISSI 0.1518 0.0419 2133 4.0% 1.16 [1.07, 1.26]
Subtotal (95% CI) 1.10 [0.99, 1.21]
Total (95 CI) 1.26 [1.15, 1.37]
0.5
1
2
HR


Study and Method
log(HR)
SE
Total
Weight
Hazard Ratio
Random [95% CI]
Direct Method
TLGS(F) 0.1989 0.0975 2993 2.3% 1.22 [1.01, 1.48]
TLGS (M) -0.2744 0.0234 2317 3.2% 0.76 [0.73, 0.80]
AMORIS 0.1655 0.0108 65050 3.3% 1.18 [1.16, 1.21]
Epic-Norfolk (F+MS) 0.0296 0.1277 530 1.9% 1.03 [0.80, 1.32]
Epic-Norfolk (F-MS) 0.3148 0.2243 406 1.0% 1.37 [0.88, 2.13]
Epic-Norfolk (M+MS) 0.2231 0.0775 983 2.6% 1.25 [1.07, 1.46]
Epic-Norfolk (M-MS) 0.2927 0.1539 610 1.6% 1.34 [0.99, 1.81]
Framingham Offspring (F) 0.1655 0.1034 1760 2.2% 1.18 [0.96, 1.45]
Framingham Offspring (M) 0.1133 0.0707 1562 2.7% 1.12 [0.97, 1.29]
Monica Augsburg (F) 0.5365 0.1261 1436 1.9% 1.71 [1.34, 2.19]
Monica Augsburg (M) 0.3716 0.0891 1414 2.4% 1.45 [1.22, 1.73]
Northwick Park ii 0.4187 0.1096 1153 2.1% 1.52 [1.23, 1.88]
PREVEND 0.239 0.052 6948 2.9% 1.27 [1.15, 1.41]
Quebec cardiovascular 0.373 0.087 2155 2.4% 1.45 [1.22, 1.72]
Reykjavik (M) 0.2962 0.0335 8888 3.1% 1.34 [1.26, 1.44]
Reykjavik (F) 0.3137 0.0231 9681 3.2% 1.37 [1.31, 1.43]
Rotterdam (F) 0.4071 0.0983 3553 2.3% 1.50 [1.24, 1.82]
7 Countries (Netherlands) 0.157 0.1337 710 1.8% 1.17 [0.90, 1.52]
Physicians health 0.5008 0.0952 492 2.3% 1.65 [1.37, 1.99]
MESA 0.2956 0.0726 6693 2.7% 1.34 [1.17, 1.55]
LIPID 0.1764 0.0602 4502 2.8% 1.19 [1.06, 1.34]
Caerphilly 0.2311 0.0687 2225 2.7% 1.26 [1.10, 1.44]
CHS 0.0862 0.0517 4885 2.9% 1.09 [0.99, 1.21]
FIELD 0.0583 0.0408 4900 3.1% 1.06 [0.98, 1.15]
Progetto Cuore 0.3365 0.0346 20447 3.1% 1.40 [1.31, 1.50]
Puerto Rico (rural) 0.114 0.1086 2389 2.1% 1.12 [0.91, 1.39]
Puerto Rico (urbano) 0.252 0.0562 5766 2.9% 1.29 [1.15, 1.44]
Rotterdam (M) 0.2115 0.0929 2453 2.4% 1.24 [1.03, 1.48]
SHEP 0.222 0.0515 4763 2.9% 1.25 [1.13, 1.38]
Swedish NDR 0.131 0.029 18673 3.2% 1.14 [1.08, 1.21]
Subtotal (95% CI) 1.25 [1.18, 1.32]
Method 1
HPFS 0.1637 0.0699 746 2.7% 1.18 [1.03, 1.35]
IwateKENCO (F) 0.04 0.0511 15852 2.9% 1.04 [0.94, 1.15]
IwateKENCO (M) 0.085 0.0592 8714 2.8% 1.09 [0.97, 1.22]
MEGA 0.0145 0.0096 3966 3.3% 1.01 [1.00, 1.03]
Women´s health 0.1077 0.0283 15632 3.2% 1.11 [1.05, 1.18]
Subtotal (95% CI) 1.08 [1.03, 1.14]
Method 2
Copenhagen City (F) 0.0777 0.029 5181 3.2% 1.08 [1.02, 1.14]
Copenhagen City(M) 0.0656 0.0253 3854 3.2% 1.07 [1.02, 1.12]
Subtotal (95% CI) 1.07 [1.04, 1.11]
Method 3
Yao City (F) 0.659 0.1787 3848 1.3% 1.93 [1.36, 2.74]
Yao City (M) 0.4983 0.1826 8129 1.3% 1.65 [1.15, 2.35]
Subtotal (95% CI) 1.78 [1.39, 2.29]
Method 4
Not estimable
Total (95 CI) 1.22 [1.16, 1.29]
0.5
1
2
HR