

THEORY AND METHODS

Statistical methods for the time-to-event analysis of individual participant data from multiple epidemiological studies

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Background Meta-analysis of individual participant time-to-event data from multiple prospective epidemiological studies enables detailed investigation of exposure–risk relationships, but involves a number of analytical challenges.

Methods This article describes statistical approaches adopted in the Emerging Risk Factors Collaboration, in which primary data from more than 1 million participants in more than 100 prospective studies have been collated to enable detailed analyses of various risk markers in relation to incident cardiovascular disease outcomes.

Results Analyses have been principally based on Cox proportional hazards regression models stratified by sex, undertaken in each study separately. Estimates of exposure–risk relationships, initially unadjusted and then adjusted for several confounders, have been combined over studies using meta-analysis. Methods for assessing the shape of exposure–risk associations and the proportional hazards assumption have been developed. Estimates of interactions have also been combined using meta-analysis, keeping separate within- and between-study information. Regression dilution bias caused by measurement error and within-person variation in exposures and confounders has been addressed through the analysis of repeat measurements to estimate corrected regression coefficients. These methods are exemplified by analysis of plasma fibrinogen and risk of coronary heart disease, and Stata code is made available.

Conclusion Increasing numbers of meta-analyses of individual participant data from observational data are being conducted to enhance the statistical power and detail of epidemiological studies. The statistical methods developed here can be used to address the needs of such analyses.

Keywords Meta-analysis, epidemiological studies, individual participant data, statistical methods, survival analysis

Introduction

Combining information across several studies using meta-analysis can enhance precision for quantitative summaries of evidence.¹ Re-analysis of individual participant data (IPD) from multiple epidemiological studies has several advantages compared with meta-analysis of aggregated published data, including harmonization of definitions for risk markers as well as disease outcomes; ability to update follow-up information; consistent approaches to adjustment for confounding; characterization of the shape of exposure–risk relationships; greater ability to correct for regression dilution bias; and determination of how exposure–risk relationships depend on age, sex and other potential effect modifiers.^{2–4} This article describes and illustrates statistical methods that are being used in the Emerging Risk Factors Collaboration (ERFC), an analysis of individual records from more than 1.2 million participants in 116 prospective studies in predominantly Western populations of major cardiovascular disease outcomes.^{5–8} The ERFC includes mostly prospective cohort studies (a few based in randomized trials), as well as some nested case–control and case–cohort studies. For each participant in the ERFC, the coordinating centre has collated, verified and harmonized individual records on baseline risk markers, confounders, other characteristics, major cardiovascular morbidity and cause-specific mortality.⁵ Available repeat survey data, which provide serial measurements, have also been collected to help address measurement error and within-person variability.^{3,9}

As the ERFC subsumes the Fibrinogen Studies Collaboration,¹⁰ we have illustrated the statistical methods used in the ERFC by analysis of plasma fibrinogen concentration and the risk of coronary heart disease (CHD) in the Fibrinogen Studies Collaboration dataset involving individual data on 154 211 participants from 31 prospective studies. CHD is defined as first non-fatal myocardial infarction or coronary death in those without known cardiovascular disease at the initial examination.¹⁰ A total of 7118 CHD events occurred during an average of 9 years of follow-up. Across the 31 studies, the number of CHD events ranged from 17 to 1474 and the follow-up ranged from 4 to 33 years; the crude mean fibrinogen was 3.02 g/l [pooled within-study standard deviation (SD) 0.65 g/l].

Methods and illustrative analyses

Principal meta-analysis methods

This exposition initially assumes all data are derived from prospective cohorts; other designs are addressed towards the end of the article. The main analyses are based on Cox proportional hazards (PH) models,¹¹ estimated for each study separately. The PH models are stratified by sex and, if applicable, randomized

group. So separately for each study $s=1\dots S$, with strata $k=1\dots K_s$ (for most studies, $K_s=2$ just for the two sexes) and individuals $i=1\dots n_{si}$, with exposure of interest E_{si} and other covariates \mathbf{X}_{si} , the hazard at time t after baseline is modelled as

$$\log(h_{ski}(t | E_{si}, \mathbf{X}_{si})) = \log h_{0sk}(t) + \beta_s E_{si} + \gamma_s \mathbf{X}_{si} \quad (1)$$

The evolution of risk over time is thus modelled independently for each stratum in each study, as represented by the non-parametric baseline hazards $h_{0sk}(t)$. The β_s are the parameters of interest, being the log hazard ratios (HRs) per unit increase in the exposure in study s , adjusted for the confounding effects of the covariates \mathbf{X}_{si} .

These estimated log HRs can be combined over studies using random-effects meta-analysis,¹² which incorporates heterogeneity between studies as described below. Fixed-effects meta-analysis can also be used^{3,13,14} and has been employed in parallel analyses in the ERFC. Writing the variance of the estimated β_s as v_s , the random-effects meta-analysis model is given by

$$\begin{aligned} \hat{\beta}_s &= \beta_s + \varepsilon_s, & \text{where } \varepsilon_s &\sim N(0, v_s) \\ \beta_s &= \beta + \eta_s, & \text{where } \eta_s &\sim N(0, \tau^2) \end{aligned} \quad (2)$$

Here β is the average log HR, the estimate of which combines within-study information on the relationship between exposure and risk, while allowing for heterogeneity in the true log HRs between studies as represented by the variance τ^2 . A standard moment estimator of τ^2 is used,¹⁵ although other estimation methods are available.¹⁶ The statistical significance of the standard test for heterogeneity¹⁷ reflects the strength of evidence for heterogeneity. The impact of heterogeneity on the imprecision of the overall log HR is expressed in terms of I^2 , the percentage of variance in the point estimates of the study-specific log HRs that is attributable to between-study variation as opposed to sampling variation,¹⁸ for which a confidence interval (CI) is also available.¹⁹ Values of I^2 close to 0% correspond to lack of heterogeneity. In addition, specific sources of heterogeneity are explored by investigating the impact of various factors (e.g., age, sex and other potential effect modifiers) on the strength of the association between exposure and risk, as described in later sections.

The above procedure is a two-step method: first, each study is analysed separately in (1) and then the log HRs are combined in (2). A one-step method would be preferable in principle, writing a combined model as

$$\begin{aligned} \log(h_{ski}(t | E_{si}, \mathbf{X}_{si})) &= \log h_{0sk}(t) + \beta_s E_{si} + \gamma_s \mathbf{X}_{si} \\ \beta_s &= \beta + \eta_s, & \text{where } \eta_s &\sim N(0, \tau^2) \end{aligned} \quad (3)$$

Computational problems are, however, formidable in a dataset the size of the ERFC.²⁰ A two-step analysis has only the slight disadvantage that the first-step

Table 1 Combined HRs for the relationship between baseline fibrinogen (g/l) and CHD risk, adjusted for a linear effect of age at baseline in each study separately

Method	HR (95% CI)	Log HR, $\hat{\beta}$ (SE)	Heterogeneity		
			Between-study variance $\hat{\tau}^2$	P-value	I^2 (95% CI)
Untransformed fibrinogen: log HRs per 1 g/l increase					
Random-effects meta-analysis	1.57 (1.47–1.67)	0.450 (0.033)	0.018	<0.0001	64% (48, 76)
Fixed-effects meta-analysis	1.52 (1.47–1.57)	0.419 (0.018)	NA	<0.0001	NA
Transformed fibrinogen: log HRs per SD increase—random-effects meta-analysis					
Untransformed fibrinogen	1.34 (1.29–1.40)	0.294 (0.022)	0.008	<0.0001	64% (48, 76)
Log fibrinogen	1.38 (1.32–1.45)	0.325 (0.025)	0.010	<0.0001	65% (48, 76)
Study-specific SD score fibrinogen	1.34 (1.29–1.40)	0.292 (0.021)	0.007	<0.0001	63% (45, 75)
Study-specific SD score log fibrinogen	1.37 (1.31–1.44)	0.316 (0.024)	0.009	<0.0001	64% (47, 76)
Untransformed fibrinogen					
Quadratic term for fibrinogen	0.96 (0.91–1.01)	−0.045 (0.027)	0.007	0.013	40% (7, 61)

NA: not applicable; SE: standard error.

variances v_s in a two-step analysis are not in general exactly those implied in a one-step method, although one-step and two-step methods usually produce very similar results.^{21,22}

For the case of fibrinogen and the risk of CHD, adjusting only for the linear effect of age at baseline in each study, these analyses are summarized in the upper part of Table 1. The study-specific HRs are shown in Figure 1. The random-effects combined HR $\exp(\beta)$ is estimated as 1.57 (95% CI 1.47–1.67) per 1 g/l higher baseline fibrinogen concentration, and an I^2 of 64% (95% CI 48–76) indicates substantial heterogeneity across studies (test for heterogeneity, $P < 0.0001$). By comparison, a fixed-effects meta-analysis estimate gives a lower point estimate of 1.52 with a narrower 95% CI of 1.47–1.57.

The above estimates and CIs relate to the overall mean HR across all studies. Also of interest is the range of true HRs across studies, representing those in different contexts or populations. It can be expressed by the 95% prediction interval for the true HR in a new study and is estimated from the random-effects meta-analysis by $\exp(\hat{\beta} \pm t_{S-2} \sqrt{\text{var}(\hat{\beta}) + \hat{\tau}^2})$, where t is the 2.5-percentile of a t-distribution and S is the number of studies.¹² In the case of the fibrinogen data, this 95% prediction interval is 1.18–2.08. Because of the presence of heterogeneity, this interval is much wider than the 95% CI for $\exp(\beta)$, as shown at the bottom of Figure 1, but remains above 1, indicating that the relationships in different studies are consistently positive.

Choice of exposure scale

An assumption of the above model is that the log HR increases linearly with the exposure. It might be more appropriate, however, to choose a log scale for some exposures to improve linearity. Alternatively, the use

of a study-specific SD score might reduce heterogeneity of the risk association between studies. In the case of fibrinogen, for example, the distributions were slightly positively skewed and the SD varied considerably between studies.²³ It is also important to assess the possibility of non-linear risk relationships that could indicate a threshold or a plateau for risk.

To assess linearity, as in previous studies,³ the distributions of the exposure are divided into quantile groups such as fifths; such quantile groups can be defined within each study or across all studies. HRs in each quantile group, compared with the bottom group, are estimated by using Cox PH regression in each study separately. These log HRs within each study are not independent (their correlations are available from standard regression software), because they are all relative to the same reference group. So the set of log HRs are pooled across studies using a multivariate version of random-effects meta-analysis^{24,25} to allow for their inter-correlations both within and between studies. These pooled log HRs are plotted against the mean exposure level in each quantile group. Assessing linearity is easier using CIs derived by floating absolute risk methods^{26,27} so that each estimate (including that for the reference category) has a measure of uncertainty and is less correlated with the others. Judging linearity visually from strongly correlated estimates can be misleading: for example, if the reference group is small, then all the standard CIs will be wide and non-linearity cannot be ruled out. Sensitivity analyses, employing different scales for the exposure (e.g. log, SD score) or assessing curvature using polynomial terms, are also used to investigate whether heterogeneity between studies is reduced or the substantive conclusions affected.

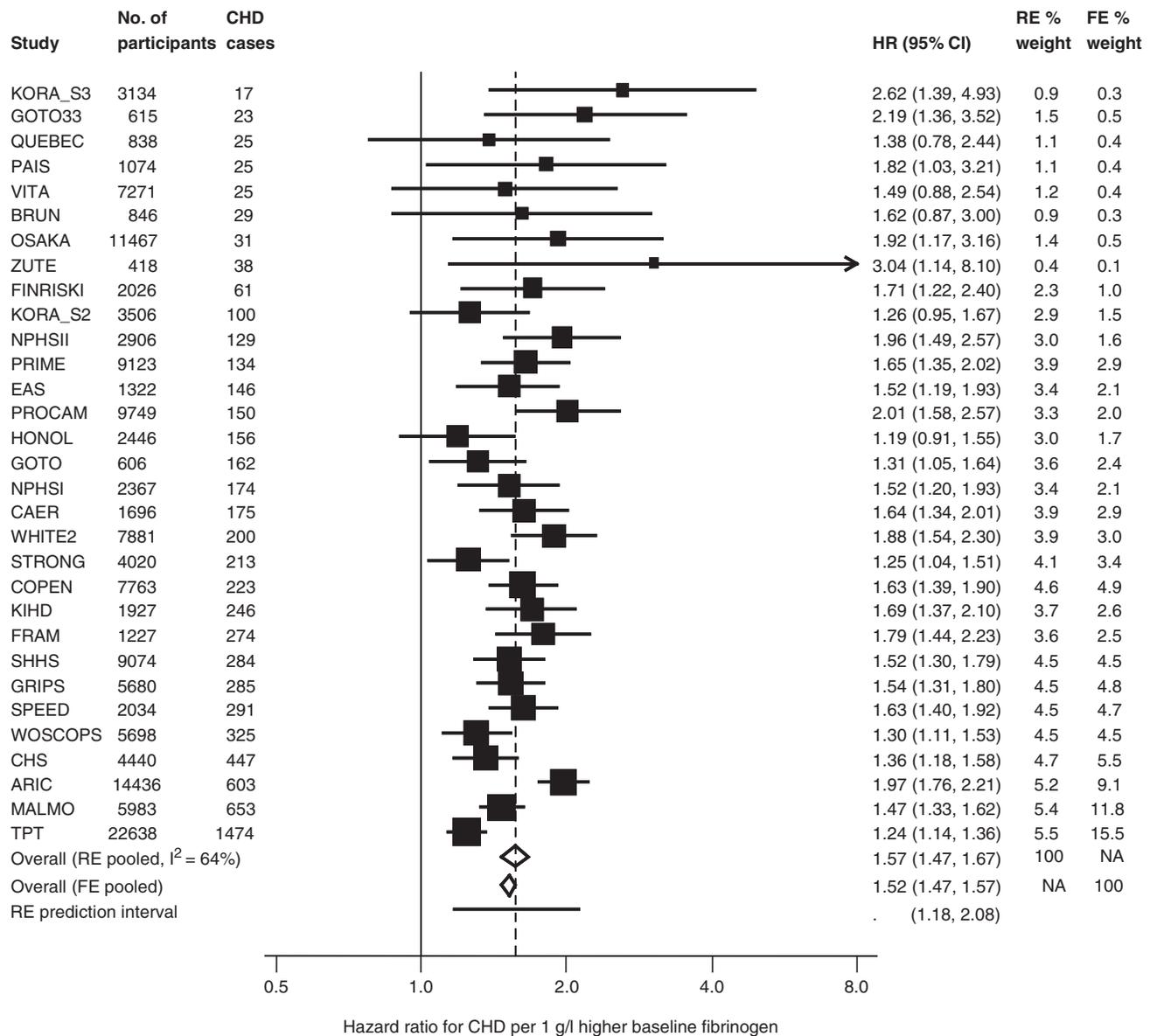


Figure 1 Study-specific HRs and 95% CIs (log scale) for the relationship of baseline fibrinogen with CHD in 31 studies, and meta-analysis. A 95% prediction interval for the true HR in a new study is also shown. Results are adjusted for age at baseline as a linear term. For acronyms to the studies, see Ref. 10. RE, random effects; FE, fixed effects; NA, not applicable.

Figure 2 shows the results of an analysis by study-specific fifths of fibrinogen in relation to CHD risk, which suggests that a log-linear model for risk is satisfactory.¹⁰ Examples of sensitivity analyses are shown in the lower part of Table 1. These compare untransformed fibrinogen, log fibrinogen, study-specific SD fibrinogen score, and study-specific SD log fibrinogen score. For comparability, results are expressed as the HR per 1-SD higher baseline fibrinogen; in the first two analyses, this refers to the pooled within-study SD (0.65 g/l for untransformed

fibrinogen). The results from all analyses are quantitatively similar, including the extent of heterogeneity. Including a quadratic term for untransformed fibrinogen in the first analysis provides little evidence of curvature in the risk relationship ($P=0.09$). In the case of fibrinogen, therefore, the heterogeneity between studies is not due to the choice of exposure scale.

A few technical issues in such analyses merit consideration. First, the visual assessment of linearity and the comparison between different exposure

scales are informal. Second, although it might be preferable to use fractional polynomials²⁸ or splines²⁹ to investigate curvature, this is not straightforward in a two-step random-effects meta-analysis, because different functional forms might be appropriate for different studies. These problems would be reduced if one-step meta-analysis methods were computationally feasible. Thirdly, in Figure 2, the choice of fifths is rather arbitrary, and it is not entirely clear what

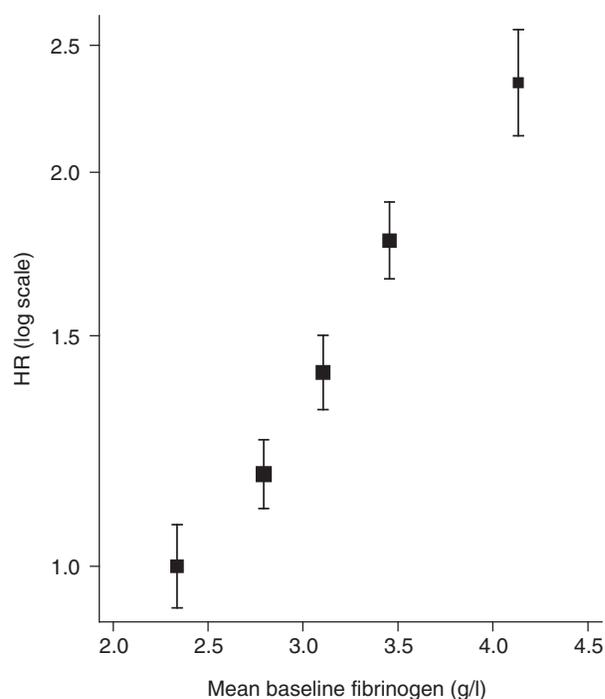


Figure 2 Combined log HRs with 95% CIs based on floating absolute risks for the relationship between baseline fibrinogen (g/l) and CHD risk, plotted against mean baseline fibrinogen in fifths. From multivariate random-effects meta-analysis, adjusted for a linear effect of age at baseline in each study separately.

levels of fibrinogen the log HRs should be plotted against; for example, this could be the mean fibrinogen in each fifth weighted by the number of events rather than by the number of participants. Finally, the effect of measurement error and within-person variation in fibrinogen may distort the shape of the exposure–disease relationship, as discussed later.

Covariate adjustment

Age is the most important confounder in many epidemiological applications, so adjustment for age demands particular attention. For linear terms, age-at-baseline in a PH model is equivalent to including current age as a time-dependent variable, but the latter is computationally more difficult to fit. Assuming a simple linear term for age at baseline may, however, be inadequate, resulting in residual confounding. Alternatives include adjustment or stratification by age categories at baseline, as well as inclusion of polynomial terms and interactions with other covariates (especially sex). Empirical comparison of alternatives as sensitivity analyses is useful to check for adequate age adjustment. In principle, similar considerations apply to other covariates, but in practice, the use of linear terms is usually sufficient unless the covariates are both highly prognostic and substantially correlated with the exposure of interest. One important practical problem often encountered is that not all studies measure all the desired confounders; an approach to this situation is described under section ‘Discussion’.

The ERFC’s two-step approach allows the confounding effects (γ_s in model 1) to be different in each study. Examples of age and other confounder adjustments for the fibrinogen dataset are given in Table 2. In this case, linear adjustment for age at baseline appears to be adequate, because more complex forms of adjustment hardly change the results. No precision is lost by stratification using narrow age bands. The overall HR for fibrinogen is reduced

Table 2 Combined HRs for CHD per 1 g/l increase in baseline fibrinogen: random-effects meta-analysis adjusting for baseline confounding variables

With adjustment for	HR (95% CI)	Log HR $\hat{\beta}$ (SE)	χ^2_1	Heterogeneity		
				Between-study variance $\hat{\tau}^2$	P-value	I^2 (95% CI)
Age	1.57 (1.47–1.67)	0.450 (0.033)	181	0.018	<0.0001	64% (48, 76)
Age as 5-year age bands	1.57 (1.47–1.68)	0.451 (0.033)	183	0.018	<0.0001	64% (48, 76)
Stratification by 5-year age bands	1.57 (1.47–1.68)	0.451 (0.033)	182	0.018	<0.0001	64% (48, 76)
Age sex \times age	1.57 (1.47–1.68)	0.450 (0.034)	180	0.018	<0.0001	65% (48, 76)
Age age ²	1.56 (1.46–1.67)	0.447 (0.033)	179	0.018	<0.0001	64% (48, 76)
Age age ² sex \times age sex \times age ²	1.57 (1.47–1.67)	0.448 (0.034)	177	0.019	<0.0001	65% (49, 76)
Age smoking tchol sbp bmi ^a	1.38 (1.31–1.45)	0.320 (0.026)	156	0.006	0.028	35% (0, 58)

SE: standard error.

^aSmoking coded as current vs other; tchol: total cholesterol; sbp: systolic blood pressure; bmi: body mass index.

towards unity on adjusting for four additional covariates (last row in Table 2), and the extent of heterogeneity decreases. Thus, some of the original heterogeneity between studies seems to be due to differing impacts of these confounders in different studies. The age-adjusted HR per 1 g/l higher baseline fibrinogen falls from 1.57 to 1.38 on adjusting for these covariates, so 29% [calculated as $(\log 1.57 - \log 1.38) / \log 1.57$] of the effect is 'explained' by the observed values of these confounders. The change in the respective Wald χ^2 statistics reflects a slight decrease in the strength of evidence for an association.³

Joint effects

An important advantage of IPD is that it provides the opportunity for systematic investigation of the exposure–risk relationship at different levels of other variables. This evaluation of factors that modify the overall log HRs estimated above involves assessing their interactions on this scale with the exposure of interest. When effect modifiers are variables measured in individuals, such as age or other risk markers, these interactions are most effectively assessed using within-study information.^{4,30} Here a two-step procedure has again been adopted, first estimating the interaction in each study separately. For example, for a single potential effect modifier X_{si} , the model in study s is

$$\log(h_{ski}(t|E_{si}, X_{si})) = \log h_{0sk}(t) + \beta_s E_{si} + \gamma_s X_{si} + \delta_s E_{si} X_{si} \quad (4)$$

The estimates of the interaction terms δ_s are combined using random-effects meta-analysis, as in (2). The overall interaction, δ_w , is then based on only within-study information. Model (4) can be extended by including adjustments for other confounders, and indeed their interactions with the exposure of interest; this enables investigation of whether, as is possible, a particular interaction is confounded by other main effects or interactions.

Some potential effect modifiers are assessed only at the study level; for example, the type of population recruited or the laboratory methods used for measuring the exposure. For such variables, any information on interactions relies entirely on between-study comparisons, which are assessed using random-effects meta-regression.³¹ Using the estimates of β_s from (1), model (2) is extended to include a study level covariate X_s by writing

$$\begin{aligned} \hat{\beta}_s &= \beta_s + \varepsilon_s, \quad \text{where } \varepsilon_s \sim N(0, s_s^2) \\ \beta_s &= \beta + \delta_B X_s + \eta_s, \quad \text{where } \eta_s \sim N(0, \tau^2) \end{aligned} \quad (5)$$

δ_B is the between-study interaction term, with statistical significance assessed allowing for the residual between-study heterogeneity τ^2 .

A few variables, notably sex and ethnic group, have potential interactions for which both within-study

and between-study information may be important. For example, studies involving both men and women provide within-study information on sex interactions, whereas studies that comprise members of one sex alone can only be used to assess interactions across studies. In this case, the within-study interaction δ_w is estimated as in model (4) based on studies of both sexes, and the between-study interaction δ_B is estimated using model (5) in which X_s is the proportion of women in each study. Provided they are similar, these two asymptotically independent estimates of interaction can themselves be combined. As between-study information on interactions is prone to numerous potential sources of between-study confounding,³² there is a trade-off between increased precision and possible bias in choosing whether to use between-study information in addition to within-study information.^{22,33,34}

Presenting interactions in a way that is intelligible to readers is not easy. For a binary variable identifying two subgroups, the exponent of the interaction term is a ratio of HRs, but it is simpler to present two separate meta-analyses, one in each subgroup. However, because the between-study heterogeneity, τ^2 in (2), now affects each of these estimates, the (multivariate) meta-analytic weighting of study-specific subgroup estimates is different from the weighting of study-specific interactions. So neither the estimates nor the CIs of the subgroup-specific estimates are necessarily compatible with the estimate and CI of the interaction term. In practice, this problem is not usually severe. For continuous variables, the exponent of the interaction term is a ratio of HRs per unit increase in the effect modifier. Similarly, for presentation, it is easier to present the HR estimates according to study-specific quantile groups (e.g. thirds or fifths) of the effect modifier distribution.

Examples of interaction analyses for fibrinogen are shown in Table 3. The interactions with body mass index and age at baseline are clear, but the interactions with other variables are less marked. Including the body mass index and age interactions simultaneously hardly affect their respective estimates. There is more consistency in the interaction terms across studies than for the main effect of fibrinogen, as indicated by the lower values of I^2 . For investigating a possible sex interaction, δ_B is estimated from a meta-regression of the study-specific log HRs on the proportion of women in each study. The SE of the interaction term is smaller for δ_w than δ_B , so the majority (73%) of the information comes from within-study information. It is sensible to rely on the within-study pooled interaction estimate, especially when it contributes the majority of the information, because of the potential for bias in the between-study estimate.²² The sex-specific combined log HRs (not shown) and the combined sex interaction term are similar but not identical. The sex interaction term represents the correct analysis,

Table 3 Interactions between baseline fibrinogen (g/l) and potential effect modifiers for risk of CHD: differences in log HRs adjusted for the main effects of baseline age, smoking, total cholesterol, systolic blood pressure and body mass index

Potential effect modifier	Estimated interaction between the potential effect modifier and fibrinogen				
	Number of cohorts	Number of subjects	Estimate δ (SE)	P-value	Heterogeneity I^2 (95% CI)
Age (10 years)	31	154 211	-0.095 (0.029)	0.001	0% (0, 40)
Systolic blood pressure (10 mmHg)	31	154 211	-0.021 (0.010)	0.032	21% (0, 50)
Body mass index (5 kg/m ²)	31	154 211	-0.079 (0.023)	<0.0001	3% (0, 31)
Total cholesterol (1 mmol/l)	31	154 211	-0.025 (0.014)	0.081	1% (0, 41)
Sex: women vs men					
Between-study interaction	31	154 211	0.120 (0.092)	0.21	NA
Within-study interaction	16	90 529	0.089 (0.061)	0.15	0% (0, 52)
Overall pooled interaction ^a	31	154 211	0.098 (0.051)	0.054	NA

NA: not applicable; SE: standard error.

^aMeta-analysis of between-study and within-study interactions.

whereas the sex-specific HRs are probably the preferable method of presentation in applied publications, especially when given in a diagram. As noted above, effect modification is being assessed on the HR scale. Thus, although the HRs per unit higher fibrinogen decrease with increasing age, the absolute risk gradients increase (Figure 3).

Proportional hazards

An assumption of all the models considered so far is of PH, meaning that the regression coefficients in model (1) do not change with time since baseline measurement. Although the effect of any covariate measured at baseline may plausibly decrease over time, the prime interest is whether the PH assumption is appropriate for the exposure of interest. This can be evaluated in each study separately by including an interaction between the exposure and time, or by the commonly used diagnostic tool based on Schoenfeld residuals.³⁵ These independent χ^2_1 statistics can be summed across the S studies, yielding a χ^2_S statistic testing the hypothesis that PH holds in each study.

This approach is, however, not a powerful test against the plausible alternative hypothesis that HRs tend to decline over time in all studies. A better method is to combine the interaction terms between the exposure and time over studies. Using random-effects meta-analysis, and assuming linear time-dependence, the model is given by

$$\log(h_{ski}(t|E_{si}, X_{si})) = \log h_{0sk}(t) + \beta_s E_{si} + \xi_s t E_{si} \quad (6)$$

$$\xi_s = \xi + \eta_s, \quad \text{where } \eta_s \sim N(0, \tau^2)$$

where β_s are separate fixed effects, and the focus is on the estimate of ξ , which can be tested using a χ^2_1 statistic.

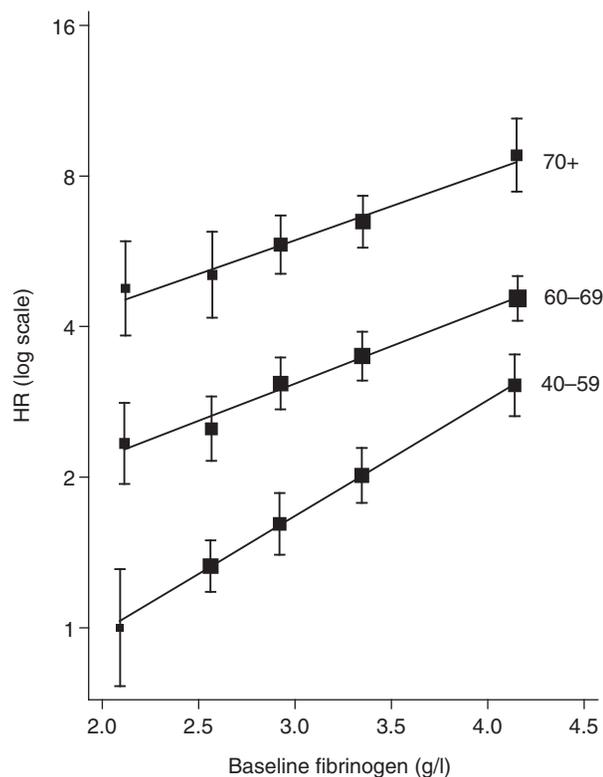


Figure 3 Interaction of baseline fibrinogen and age, derived from a proportional hazards model with time-dependent effect of age in each study and combined using multivariate random-effects meta-analysis. Log HRs with 95% CIs based on floating absolute risks, plotted against mean baseline fibrinogen in fifths.

The results of these analyses for fibrinogen are shown in Table 4. The summed χ^2_{31} statistics are less than expectation, as is the more powerful χ^2_1 statistic. So, in this case (and perhaps surprisingly given the

Table 4 Non-PHs for CHD risk assessed by the interaction of baseline fibrinogen (g/l) and time (years)

Method	Estimated non-PH parameter, ξ (SE)	χ^2 test		Heterogeneity I^2 (95% CI)
		χ^2 (df)	P-value	
Summed χ^2_1 statistics of non-PH parameter from each study	NA	24 (31)	0.80	NA
Summed χ^2_1 statistics from tests of Schoenfeld residuals in each study	NA	21 (31)	0.90	NA
Random-effects meta-analysis of study-specific non-PH parameters	0.0016 (0.0045)	0.12 (1)	0.73	0% (0, 40)

The models include adjustment for age at baseline as a linear term. NA: not applicable; SE: standard error; df: degrees of freedom.

extent of data), there is no evidence of departures from PH for fibrinogen and no evidence of heterogeneity between studies in this regard. The final method provides an estimate of the non-PH parameter ξ , which indicates that over a 20-year period the estimated change in the exposure log HR is small. In ERFC, this random-effects pooling of the interaction terms between exposure and time is used to assess the PH assumption. It provides extra power against a plausible alternative hypothesis and is consistent with the approach described above for quantifying other interactions. If there was substantial evidence against the PH assumption, it would be necessary to summarise the exposure–risk relationship either in discrete intervals of time or as a trend over time.

Other topics

When the focus is on estimating underlying aetiological associations, it is necessary to adjust for the effect of measurement error and within-person variation. For the exposure of interest, this addresses the often serious underestimation caused by regression dilution bias,^{9,36,37} and for covariates it reduces residual confounding.³⁸ Methods exist to correct for regression dilution bias in exposure variables in IPD meta-analysis.^{3,13,14} Novel methods that enable concurrent adjustment for measurement error both in the exposure of interest and in covariates have been developed for use in the multiple study context of the ERFC, but they are technically demanding and have been described in full elsewhere.^{39,40} Examples of these analyses for fibrinogen are shown in Table 5. Because the within-person correlation of fibrinogen measurements on different occasions is ~ 0.5 ,³⁹ the overall log HR corrected for measurement error in fibrinogen alone is about twice the uncorrected estimate (leading to a corrected HR of 1.96 vs 1.38 uncorrected). Multivariate correction for measurement error in four confounders makes the log HR for fibrinogen slightly less extreme, as expected because residual confounding is reduced, with an estimated HR of 1.85 per 1 g/l higher ‘usual’ (i.e. long-term average) fibrinogen level. As methods that correct for regression dilution cannot correct for

Table 5 Combined HRs for CHD per 1 g/l increase in fibrinogen, corrected for measurement error

Measurement error correction	HR (95% CI)	Log HR (SE)
No measurement error correction	1.38 (1.31–1.45)	0.320 (0.026)
Measurement error in fibrinogen	1.96 (1.76–2.17)	0.672 (0.053)
Measurement error in fibrinogen, smoking, total cholesterol, systolic blood pressure and body mass index	1.85 (1.66–2.06)	0.617 (0.055)

SE: standard error. All analyses are adjusted for age at baseline, sex, smoking, total cholesterol, systolic blood pressure and body mass index.

unmeasured covariates, residual confounding may persist after their use.

Some cohorts in the ERFC have analysed particular risk markers in a nested case–control or case–cohort design. Nested case–control studies are analysed with similar methods to those described for cohort studies, but they involve logistic regression.⁴¹ For individually matched studies, conditional logistic regression is appropriate. For frequency-matched studies, ordinary logistic regression is used with the matching factors as covariates. Such analyses either provide estimates of HRs (if matched controls were selected to be disease-free at the time the case had an event) or odds ratios (if the selected controls were disease-free at the end of the study).⁴² Provided the disease is relatively rare (say <10% of the study participants), odds ratios approximate HRs and it is reasonable to combine them in a meta-analysis. For nested case–cohort studies, the analysis should allow for the fact that some members of the randomly selected cohort also become cases.⁴³ A modified PH regression model then provides estimates of log HRs with robust standard errors,⁴⁴ although this modification generally has only a small effect.

Although some participants may have multiple events (e.g. two CHD events at separate time points,

or a CHD event followed by another type of event, such as a stroke or death from cancer), analyses in the ERFC focus on first events by censoring participants after their first CHD event, after another non-fatal event such as stroke (when cohorts have recorded them), and after death from any cause. The rationale for this approach is that major cardiovascular disease events may disrupt the association between baseline risk factors and subsequent disease risk. The ERFC does not, however, censor individuals at the time of cardiovascular investigations or interventions (such as angiography or coronary bypass operations) or at the diagnosis of angina because the incidence of such occurrences is not recorded reliably enough in sufficient studies. Sensitivity analyses that implement alternative censoring criteria can assess potential biases that might arise through these decisions on censoring.

The constraints on comprehensiveness in IPD meta-analyses mainly relate to the identification of relevant studies and provision of data. In the ERFC, studies have been identified from publications, extensive literature searches, and correspondence with authors of relevant reports. The ERFC has included the large majority of Western prospective studies with any relevant exposure markers and >20 000 person-years of follow-up. Hence, although publication and reporting biases are potential concerns in all meta-analyses, they may be less so in the ERFC.

Discussion

The statistical methods used in the ERFC have been explicitly described and illustrated in this article to facilitate their adoption by others; example programs in Stata⁴⁵ are available from <http://www.phpc.cam.ac.uk/MEU/ERFC/Software.html>. The ERFC methods extend previous approaches in several respects.^{46–48} Strategies being used in the ERFC to adjust for measurement error concurrently in levels of both confounders and exposures should help improve estimates of the underlying aetiological association between exposures and disease outcomes by reducing residual confounding. Methods used in the ERFC give specific consideration to the analysis of interactions for characteristics that vary both within and between studies and to assessment of the PH assumption.

A common practical problem in IPD meta-analyses is how to adjust for confounders that are measured only in a subset of the studies. For the fibrinogen example, age and four other confounders (Table 2) were measured in all participants in all studies. However, additional confounders, such as lipid fractions (high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides), were available in only about half of the studies.¹⁰ More comprehensive adjustment for confounding can only be easily achieved by restricting the dataset

to the latter studies, but such restriction omits information on partial adjustment from the other studies. We have previously described an approach that uses the partially adjusted HRs, which can be estimated in all studies, and the more comprehensively adjusted log HRs, which can be estimated only in a subset of studies, in a bivariate meta-analysis.⁴⁹ This approach acknowledges the correlations between the partially and the more comprehensively adjusted log HRs within studies in which both can be estimated but uses the full dataset to contribute to the estimation of a combined more comprehensively adjusted log HR.

An unresolved issue concerns the estimation of a possibly non-linear exposure–risk relationship when the exposure is measured with error. Homogeneous measurement error, with a variance that does not depend on level of the exposure, will tend to make a non-linear association appear more linear. Conversely, measurement error that, for example, increases with level of the exposure will make a linear association appear non-linear. Characterizing the shape of the underlying exposure–disease relationship, while taking into account possibly heterogeneous measurement error, is not well studied, especially in the context of IPD meta-analysis.⁵⁰ One approach may be to model the underlying association using fractional polynomials or splines, while carefully estimating measurement error variance as a function of exposure level.

As distinct from characterizing the shape, magnitude and independence of associations between risk factors and disease (which may be relevant to judgments about an exposure's potential aetiological relevance), IPD meta-analyses of multiple studies can provide additional useful information. For example, we have previously described the ERFC's approach to characterizing the cross-sectional correlates (and, hence, potential determinants) of risk markers.²³ Although this article has not addressed issues related to risk prediction (i.e. the extent to which measuring an additional exposure could better identify the risk of disease outcomes for individuals), there is considerable interest in the use of information from multiple prospective studies to help inform risk stratification and/or screening strategies. A separate literature exists that involves discussion of how the 'area under an Receiver operating characteristic (ROC) curve' can be adapted for time-to-event data⁵¹ and the extent to which individuals are re-classified into risk groups that would affect the subsequent intervention offered.^{52,53} We have adapted and illustrated some of these predictive metrics for use in the multiple study situation,⁵⁴ and further such work comprises a future methodological research agenda.

Increasing numbers of IPD meta-analyses of observational data are being conducted in order to enhance the statistical power and detail of epidemiological studies. The scientific value of such approaches has now been demonstrated in relation to various exposures

and disease outcomes in many different consortia, exemplified by the Prospective Studies Collaboration,³ the Asia Pacific Cohort Studies Collaboration,⁵⁵ the Breast Cancer Genetics Linkage Consortium,⁵⁶ the Collaborative Group on Hormonal Factors in Breast Cancer,⁵⁷ the US Pooling Project of Prospective Studies of Diet and Cancer⁴⁷ and the GENOMOS Genetic Markers for Osteoporosis Consortium.⁵⁸ The statistical methods developed here can be used to address the needs of such analyses. Appropriate meta-analytical methods may also have applications to analyses of large purpose-designed multi-centre prospective observational studies, such as the pan-European EPIC study,⁵⁹ UK Biobank^{60,61} and the subsequent planned meta-analysis of such studies.⁶²

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KEY MESSAGES

- Summarizing exposure–risk relationships on the basis of individual time-to-event data from multiple studies enhances the detail and power of epidemiological analyses.
- A two-step meta-analysis method is proposed to combine study-specific associations estimated by using Cox regression.
- These methods allow investigation of the appropriate exposure scale, adjustment for confounders, and checking the proportional hazards assumption.
- Within-study and between-study information for interactions need to be distinguished.
- More technically demanding issues include adjustment for measurement error and within-person variation, and handling confounders that are not measured in all studies.

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Commentary: Like it *and* lump it? Meta-analysis using individual participant data

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Meta-analysis—the synthesis of quantitative information from related studies—is one of the most popular research methods of the past 20 years. Though the large majority of meta-analyses synthesise aggregate data (e.g. hazard ratio estimates) obtained from publications or investigators, there have been repeated calls to facilitate meta-analysis of individual participant data (IPD),¹ where the raw participant-level data are obtained from each study and synthesized. IPD is the original source material, which brings many opportunities over the aggregate data approach,² like standardizing statistical analyses in each study; deriving desired summary results directly, independent of study reporting; checking modelling assumptions; and assessing participant-level effects, interactions and non-linear trends. The approach is increasingly applied,² despite the extra cost, time and complexity required to obtain and manage raw data.³ Commendable examples of IPD meta-analysis are those conducted by the Emerging Risk Factors Collaboration (ERFC),⁴ who have remarkably gathered IPD from 116 prospective studies and over 1.2 million participants.

While meta-analysis methods using aggregate data are well established and fairly routine, methods for IPD meta-analysis are more complex and not well known. They require statistical models specific to the type of data under investigation and must account for the clustering of patients within studies, while

appropriately synthesizing effects of interest across studies. The article in this issue of the *IJE* by Thompson *et al.*⁵ is thus both pertinent and timely. The authors consider IPD meta-analysis to identify risk factors for a time-to-event outcome, as in the ERFC. I will now expand on a few issues in the article and emphasize some methodological challenges that remain.

The authors describe two-step IPD meta-analysis methods, where Cox models are fitted within each study separately and then relevant parameter estimates pooled across studies. This methodology is sound, but I agree with their comment that in principle a one-step approach is preferred, where the IPD are analysed simultaneously in a single model that accounts for clustering of participants within studies. One-step hierarchical Cox models with random-effects are achievable,⁶ and a single modelling framework is more convenient. The biggest advantage of the one-step approach arises when modelling non-linear trends and dealing with non-proportional hazards, as it more easily allows established procedures like fractional polynomials⁷ and cubic splines⁸ to be implemented. However, the one-step approach is computationally intensive,⁶ especially in situations with large numbers of participants, but this problem will ease as software and computational speed improves. The one-step approach may also be more feasible when using flexible parametric survival models,⁹ rather than the Cox model. These allow the baseline