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

The Emerging Risk Factors Collaboration*

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ABSTRACT

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 paper describes statistical approaches adopted in the Emerging Risk Factors Collaboration, in which primary data from over 1 million participants in over 100 prospective studies have been collated to enable detailed analyses of a variety of 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.

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KEY MESSAGES

Summarising exposure-risk relationships based on individual time-to-event data from multiple studies enhances the detail and power of epidemiological analyses

A 2-step meta-analysis method is proposed to combine study-specific associations estimated 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 which are not measured in all studies

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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 to meta-analysis of aggregated published data, including: harmonisation of definitions for risk markers as well as disease outcomes; ability to update follow-up information; consistent approaches to adjustment for confounding; characterisation 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 paper describes and illustrates statistical methods that are being used in the Emerging Risk Factors Collaboration (ERFC), an analysis of individual records from over 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 randomised 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 harmonised 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 follow-up from 4 to 33 years; the crude mean fibrinogen was 3.02g/L (pooled within-study SD 0.65g/L).

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METHODS AND ILLUSTRATIVE ANALYSES

Principal meta-analysis methods

This exposition initially assumes that all data derive from prospective cohorts; other designs are addressed towards the end of the paper. 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, randomised group. So separately for each study s=1…S, with strata k=1…K_s (for most studies K_s=2 just for the two sexes) and individuals i=1…n_s with exposure of interest E_{si} and other covariates $\boldsymbol{X}_{si}$, the hazard at time t after baseline is modelled as:

$$\log(h_{ski}(t \mid E_{si}, \boldsymbol{X}_{si})) = \log h_{0sk}(t) + \beta_s E_{si} + \boldsymbol{\gamma}_s \boldsymbol{X}_{si} \qquad (1)$$

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 $\boldsymbol{X}_{si}$.

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:

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

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 heterogeneity[17] reflects the strength of evidence for heterogeneity. The impact of heterogeneity on the imprecision of the overall log hazard ratio 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 is

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

$$\begin{aligned} &\log(h_{ski}(t \mid E_{si}, X_{si})) = \log h_{0sk}(t) + \beta_s E_{si} + \boldsymbol{\gamma}_s \boldsymbol{X}_{si} \\ &\beta_s = \beta + \eta_s;\ \text{where } \eta_s \sim N(0, \tau^2) \end{aligned} \qquad (3)$$

Computational problems are, however, formidable in a dataset the size of the ERFC.[20] A 2-step analysis has only the slight disadvantage that the first-step variances v_s in a 2-step analysis are not in general exactly those implied in a 1-step method, although 1-step and 2-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 summarised in the upper part of **Table 1**. The study-specific HRs are shown in **Figure 1**. The random-effects combined HR exp(β) is estimated as 1.57 (95% CI 1.47 to 1.67) per 1g/L higher baseline fibrinogen concentration, and an I^2 of 64% (95% CI 48% to 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 to 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 estimated from the random-effects meta-analysis by $\exp(\hat{\beta} \pm t_{S-2}\sqrt{Var(\hat{\beta}) + \hat{\tau}^2})$ where t is the 2.5-percentile of a t-distribution and S the number of studies.[12] In the case of the fibrinogen data, this 95% prediction interval is 1.18 to 2.08. Because of the presence of heterogeneity, this

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interval is much wider than the 95% CI for exp(β), 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 hazard 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 standard deviation (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 SDs varied considerably between studies.[23] It is also important to assess the possibility of non-linear risk relationships which 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 to the bottom group, are estimated 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 confidence intervals 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 confidence intervals will be wide and non-linearity cannot be ruled out. Sensitivity analyses, employing different scales for the exposure (eg, 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.

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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 (0.65g/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. Secondly, while it might be preferable to use fractional polynomials[28] or splines[29] to investigate curvature, this is not straightforward in a 2-step random-effects meta-analysis because different functional forms might be appropriate for different studies. These problems would be reduced if a 1-step meta-analysis method were computationally feasible. Thirdly, in **Figure 2**, the choice of fifths is rather arbitrary, and it is not entirely clear what 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, and 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, and inclusion of polynomial terms and interactions with other

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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 in the Discussion.

The ERFC's 2-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 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 towards unity on adjusting for four additional covariates (last row of **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 1g/L higher baseline fibrinogen falls from 1.57 to 1.38 on adjusting for these covariates, so that 29% (calculated as [log1.57–log1.38]/log1.57) of the effect is 'explained' by the observed values of these confounders. The change in the respective Wald χ_1^2 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 2-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:

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

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The estimates of the interaction terms δ_s are combined using random-effects meta-analysis, as in (2). The overall interaction, δ_W say, 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:

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

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, while studies which 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 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

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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 confidence intervals of the subgroup-specific estimates are necessarily compatible with the estimate and confidence interval 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 (for example 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 affects 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, while 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, while 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 proportional hazards (PH), meaning that the regression coefficients in model (1) do not change with time since baseline measurement.

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While the effect of any covariate measured at baseline may plausibly decrease over time, the prime interest is whether the proportional hazards 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 based on Schoenfeld residuals.[35] These independent χ_1^2 statistics can be summed across the S studies, yielding a χ_S^2 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:

$$\begin{aligned} &\log(h_{ski}(t \mid E_{si}, X_{si})) = \log h_{0sk}(t) + \beta_s E_{si} + \xi_s t E_{si} \\ &\xi_s = \xi + \eta_s;\ \text{where}\ \eta_s \sim N(0, \tau^2) \end{aligned} \qquad (6)$$

where β_s are separate fixed effects, and the focus is on the estimate of ξ which can be tested using a χ_1^2 statistic.

The results of these analyses for fibrinogen are shown in **Table 4**. The summed χ_{31}^2 statistics are less than expectation, as is the more powerful χ_1^2 statistic. So, in this case (and perhaps surprisingly given the extent of data), there is no evidence of departures from proportional hazards 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.

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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**. Since the within-person correlation of fibrinogen measurements on different occasions is about 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 1g/L higher "usual" (ie, long-term average) fibrinogen level. As methods that correct for regression dilution cannot correct for 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 fewer than 10% of the study's 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

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log HRs with robust standard errors,[44] although this modification generally has only a small effect.

Although some participants may have multiple events (eg, 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 report to facilitate their adoption by others; example programs in Stata[45] are available from 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 to 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

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interactions for characteristics that vary both within and between studies, and to assessment of the proportional hazards assumption.

A common practical problem in IPD meta-analyses is how to adjust for confounders which 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 (HDL-C, LDL-C 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 where 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. Characterising 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 characterising the shape, magnitude and independence of associations between risk factors and disease (which may be relevant to judgements 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 characterising the cross-sectional correlates (and, hence, potential determinants) of risk markers.[23] Although

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this paper has not addressed issues related to risk prediction (ie, 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 which involves discussion of how the "area under an ROC curve" can be adapted for time-to-event data[51] 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 a variety of 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 Cancer[47] 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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Table 1

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

NA not applicable

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Table 2

Combined hazard ratios for CHD per 1g/L increase in baseline fibrinogen: random-effects meta-analysis adjusting for baseline confounding variables.

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

[†] smoking coded as current vs. other; tchol = total cholesterol; sbp = systolic blood pressure; bmi = body mass index

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Table 3

Interactions between baseline fibrinogen (g/L) and potential effect modifiers for risk of CHD: differences in log hazard ratios 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	154211	-0.095 (0.029)	0.001	0% (0, 40)
Systolic blood pressure (10 mmHg)	31	154211	-0.021 (0.010)	0.032	21% (0, 50)
Body mass index (5 kg/m^2)	31	154211	-0.079 (0.023)	<0.0001	3% (0, 31)
Total cholesterol (1 mmol/L)	31	154211	-0.025 (0.014)	0.081	1% (0, 41)
Sex: women vs. men					
Between-study interaction	31	154211	0.120 (0.092)	0.21	NA
Within-study interaction	16	90529	0.089 (0.061)	0.15	0% (0, 52)
Overall pooled interaction[†]	31	154211	0.098 (0.051)	0.054	NA

NA not applicable

[†] Meta-analysis of between-study and within-study interactions

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Table 4

Non-proportional hazards (PH) for CHD risk assessed by the interaction of baseline fibrinogen (g/L) and time (years). The models include adjustment for age at baseline as a linear term.

Method	*Estimated non-PH parameter*	*χ^2 test*		*Heterogeneity*
	ξ (SE)	*χ^2 (df)*	*p-value*	*I^2 (95% CI)*
Summed χ_1^2 statistics of non-PH parameter from each study	NA	24 (31)	0.80	NA
Summed χ_1^2 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)

NA not applicable

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Table 5

Combined hazard ratios for CHD per 1g/L increase in fibrinogen, corrected for measurement error. All analyses are adjusted for age at baseline, sex, smoking, total cholesterol, systolic blood pressure and body mass index.

Measurement error correction	*Hazard ratio (95% CI)*	*Log hazard ratio (SE)*
No measurement error correction	1.38 (1.31 to 1.45)	0.320 (0.026)
Measurement error in fibrinogen	1.96 (1.76 to 2.17)	0.672 (0.053)
Measurement error in fibrinogen, smoking, total cholesterol, systolic BP, and body mass index	1.85 (1.66 to 2.06)	0.617 (0.055)

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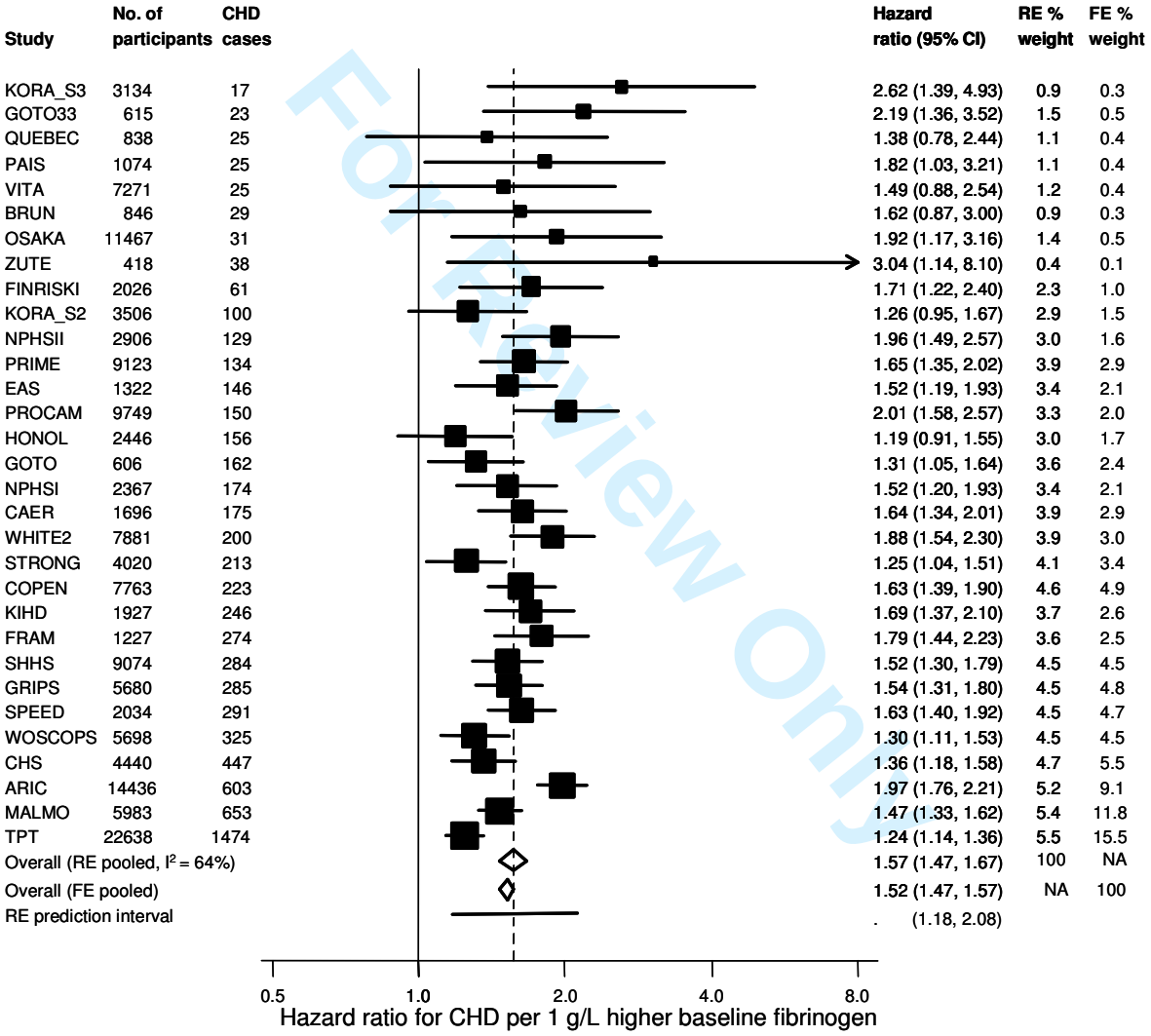
Figure 1

Study-specific hazard ratios and 95% confidence intervals (log scale) for the relationship of baseline fibrinogen with CHD in 31 studies, and meta-analysis. A 95% prediction interval for the true hazard ratio in a new study is also shown. Results are adjusted for age at baseline as a linear term. For acronyms to studies, see reference 10.



RE Random effects; FE fixed effects; NA not applicable

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Figure 2

Combined log hazard ratios 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.

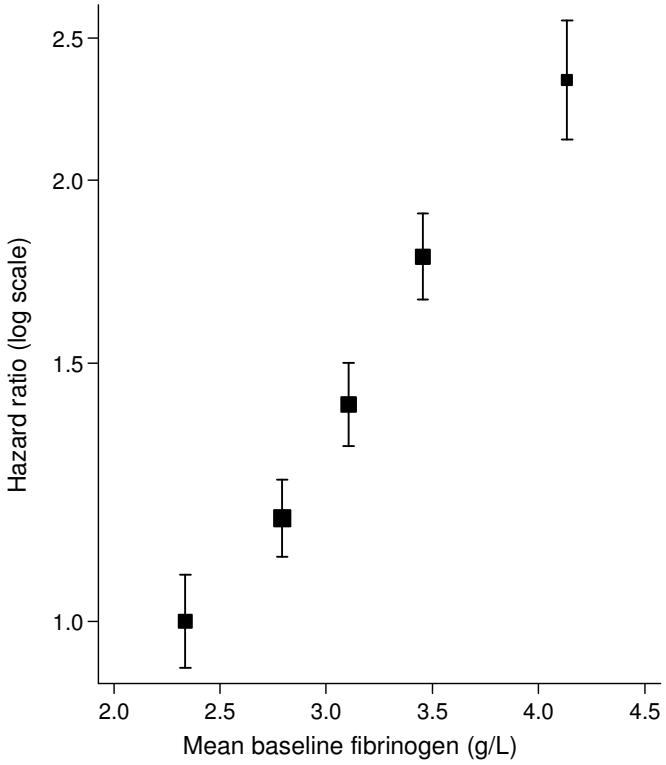
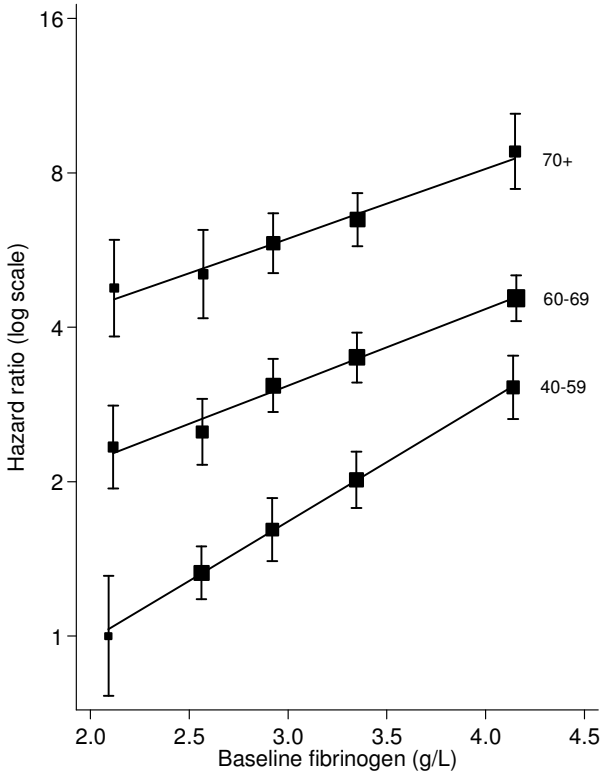


Figure 3

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 hazard ratios with 95%CIs based on floating absolute risks, plotted against mean baseline fibrinogen in fifths.