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A critical review of methods for the assessment of patient-level interactions in individual participant data meta-analysis of randomized trials, and guidance for practitioners

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Abstract

Objective: Treatments may be more effective in some patients than others, and individual participant data (IPD) meta-analysis of randomized trials provides perhaps the best method of investigating treatment-covariate interactions. Various methods are used; we provide a comprehensive critique and develop guidance on method selection.

Study Design and Setting: We searched MEDLINE to identify all frequentist methods and appraised them for simplicity, risk of bias, and power. IPD data sets were reanalyzed.

Results: Four methodological categories were identified: PWT: pooling of within-trial covariate interactions; OSM: ''one-stage'' model with a treatment-covariate interaction term; TDCS: testing for difference between covariate subgroups in their pooled treatment effects; and CWA: combining PWT with meta-regression. Distinguishing across- and within-trial information is important, as the former may be subject to ecological bias. A strategy is proposed for method selection in different circumstances; PWT or CWA are natural first steps. The OSM method allows for more complex analyses; TDCS should be avoided. Our reanalysis shows that different methods can lead to substantively different findings.

Conclusion: The choice of method for investigating interactions in IPD meta-analysis is driven mainly by whether across-trial information is considered for inclusion, a decision, which depends on balancing possible improvement in power with an increased risk of bias.

Keywords: Meta-analysis; IPD; RCT; Interaction; Subgroup; Methodology

1. Introduction

The main aim of meta-analysis is to combine estimates of a particular effect across independent studies—frequently the effect of a treatment assessed in randomized controlled trials (RCTs)—to obtain a summary estimate of effect and standard error. Because of the inevitable differences in trial design and population, some variation in effect is to be expected. The widely used random-effect model of DerSimonian and Laird [1] was proposed to account for this. There are, however, statistical and clinical benefits to be had from investigating *how* factors influence the treatment effect—in other words, the nature of interactions between such factors and treatment. In meta-analysis of aggregate data (from publications or supplied by investigators), trial-level heterogeneity is often explored using subgroup analyses or meta-regression [2]. However, to assess *patient*-level heterogeneity in this framework, individual patients must be assigned trial-level average values, which is inefficient and risks bias because of the ''ecological fallacy'' [3].

We may overcome some of these problems by obtaining individual participant data (IPD) for each trial. Treatment, outcome, and covariate measurements are then known for each patient within each trial, representing the best opportunity to explore treatment-covariate interactions. More powerful and flexible analyses can be done and, in particular, patient-level heterogeneity in the treatment effect can be separated from trial-level heterogeneity and investigated directly. Various methods of accomplishing this are used in practice and, as previously observed [4], most IPD literature concentrates either on documenting these methods or on proposing

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What is new?

Key findings

- Methodology for analyzing treatment by patient-level covariate interactions in individual participant data (IPD) meta-analysis is not yet fully established, and practical guidance is limited.
- A common approach, that estimates treatment effects within covariate subgroups and tests the differences between these subgroup estimates, is shown to be at risk of bias and should be discouraged.
- An approach that estimates a ''within-trial'' patient-level interaction only is recommended. ''Across-trial'' information is at risk of bias, and if it is to be used to supplement the ''within-trial'' information it should be done with caution.

What this adds to what was known?

- Although methodology in this area is discussed elsewhere, this is generally of a technical nature without a clear presentation of each distinct methodological approach.
- Clear guidance is given to help systematic reviewers assess whether a treatment effect varies across patient-level covariates using appropriate methodology.

What is the implication, what should change now?

- Estimating treatment effects within covariate subgroups and testing the differences between these subgroup estimates should not be used further. Instead, the guidance given in this article should be followed to select an appropriate method.
- If the data are unsuitable for assessing patient-level covariate interactions (e.g., sparse categories or large heterogeneity across trials), reviewers should state this rather than attempt to draw conclusions, which would likely be unreliable.

new statistically advanced techniques (e.g., [5]). A recent article by Thompson et al. [6] discusses most of these methods for IPD meta-analysis of time-to-event data, but we focus specifically on treatment-covariate interaction estimation in trials, describing the relevant issues in greater detail and including in our critique one further commonly used method.

In this article, we identify the principal published methods to assess treatment-covariate interactions, and critically appraise them to summarize their advantages and disadvantages. We then develop guidance on which approach might be used in different circumstances. We apply the methods to IPD data sets comparing interventions for cancer to illustrate their use in practice, before making some concluding remarks. Because these data sets all relate to time-to-event outcome measures, this article will focus on such outcome measures while also providing broader guidance.

2. Methods in the literature to analyze treatment-covariate interactions

A literature search of Medline (1966–2009) was performed to identify the main approaches for analyzing patient-level treatment-covariate interactions, both proposed in theory and used in practice, and also previous methodological reviews (see Appendix A). However, our search was not planned to quantify the number of reviews using these approaches in practice. We limited ourselves to frequentist approaches as these are most commonly used by systematic reviewers. Four categories of methods were identified, all of which may be fitted using standard statistical software unless otherwise stated. For simplicity, in this section we consider two competing treatments and a patient covariate that is binary, continuous, or ordered categorical. We assume that if the covariate is not binary then the interaction can be adequately represented by a linear interaction term. A mathematical presentation of the four methods is provided in Appendix B.

2.1. Pooling of within-trial covariate interactions (PWT)

This approach is based on the familiar weighted-average meta-analysis of aggregate data, but here we pool treatment-covariate interaction effects instead of main study effects [7]. Interactions are estimated independently within each trial using regression models or contingency tables, and are pooled using inverse-variance meta-analysis. Like the equivalent technique for main effects, this method can be described as ''*two-stage*'' [8] in that two separate sets of calculations must be carried out, the second using the output of the first.

2.2. "One-stage" model with a covariate interaction term (OSM)

An alternative approach is to estimate the treatment-covariate interaction using all available data in a single model containing terms representing trial membership, treatment, covariate, and treatment-covariate interaction [9], as detailed in Appendix B. Alternatively, the interaction term may be replaced by two independent terms, representing across- and within-trial interaction effects [5]. The treatment effect may be fixed or random, but the latter is computationally difficult for time-to-event data (see next section).

2.3. Testing for treatment effect differences across covariate subgroups (TDCS)

This next method, commonly applied (e.g., [10–14]), arose as a simple way of analyzing the effect of *categorical* covariates on the treatment effect, and indeed cannot be used with continuous covariates. This is a two-stage approach in which inverse-variance pooled treatment effects are first estimated within each patient subgroup, and secondly tested for differences using a trend line or ANOVA. Both the within-subgroup treatment estimates and the resulting interaction effect are estimated almost exclusively using fixed effects in practice, although this is not imperative. Interaction and trend in treatment effect across levels of a patient-level categorical covariate are tested in a similar manner to the partitioned Q test for subgroups used in aggregate-data meta-analyses [15].

2.4. "Manually" combining separately calculated within- and across-trial effects (CWA)

The PWT method estimates a "within-trial" effect. In contrast, a meta-regression fits a trend line through trial-level treatment effects and covariate means, and estimates an independent "across-trial" effect. The possibility suggests itself, therefore, to apply both methods and combine the two interaction effect estimates "manually" so as to use the maximum amount of information in the data [16]. To do this, an inverse-variance meta-analysis with either fixed or random effects might be used. Alternatively, the analyst may weight the two estimates according to the perceived quality of each (see next section).

3. Critique of the methods

We next critique these methods with respect to simplicity, efficiency, and potential for bias, with particular emphasis on whether across-trial evidence of covariate interaction should be included. The evidence for an interaction from within trials, for example using PWT, may be considered to be of higher quality because within each trial the patients with different values of covariate are recruited and managed within the confines of a single trial protocol. By contrast, the apparent evidence for a patient-level treatment-covariate interaction obtained across trials, as in a meta-regression, is highly susceptible to ecological bias, because trials may differ in many respects other than simply the distribution of that covariate [17]. Whether or not to include such "across-trial" evidence will be discussed later. Although we have limited ourselves to frequentist approaches, any of the methods can also be used in a Bayesian framework—in fact, doing so offers some advantages such as a more straightforward estimation of random effects. Our critique, summarized in Table 1, concentrates on methods as currently available from mainstream statistical packages, rather than their theoretical potential.

3.1. Estimating interaction effects using within-trial information only

Arguably the simplest method conceptually and practically is PWT. As this method uses within-trial information only, trials with little variation in the covariate contribute only modest information to the estimate. Further, where the covariate is categorical, trials with data in only one subgroup must be discarded.

By contrast, the most computationally intensive and potentially complex approach reviewed here is the use of OSM. These models are sometimes used in epidemiological studies where the data have a multilevel structure, but are currently not routinely used for meta-analysis. They allow much greater flexibility and maximize the power available in the data, and could be considered as a "gold standard" because two-stage models can be obtained from them as special cases [5]. OSM permits multiple parameters to be estimated simultaneously, allowing the possibility of performing complex analyses and testing a wider range of hypotheses. We can parameterize the model to estimate the within-trial interaction effect specifically (in its more basic form, the model instead estimates a single interaction coefficient equivalent to a weighted average of within- and across-trial effects). However, there are significant computational challenges in the fitting of random treatment effects to time-to-event outcome data [5], and furthermore, with very large data sets the computational time is likely to be greater than for PWT [6].

Estimating trial heterogeneity can cause problems with convergence, and where such heterogeneity exists, the failure of fixed-effect OSM to represent it can lead to inappropriate standard errors. Generally speaking, such models require greater care to be taken to avoid misrepresentation of the data, and are more likely to require extensive statistical expertize. Some reviewers have stated a preference for OSM on the basis that use of two-stage methodology negates some of the advantages that IPD provides [18], although theoretically there is no reason for the power of OSM to significantly exceed that of PWT if across-trial information is not used [5].

3.2. Including across-trial information

The use of across-trial information is controversial and, given that within-trial interaction effects are easily estimated in isolation (such as with PWT), many analysts may never use it. However, in circumstances in which more power is desired and the increased risk of bias is considered acceptable, for example if the analysis is hypothesis generating, the addition of across-trial information is a possible solution. It can be shown that, in circumstances where PWT has low power, a meta-regression (across-trial information only) can provide greater power [19]. This is the motivation behind the CWA method, in which the PWT estimate and meta-regression slope are examined and

Table 1
Summary table of methods discussed in this article

Method	PWT	OSM	TDCS	CWA
Description	Pooling of within-trial patient-level interactions	One-stage model with covariate interaction term, and either fixed or random treatment effect.	Calculating pooled treatment effects within covariate subgroups and testing for differences between these.	PWT combined with a meta-regression.
Within-trial, across-trial information or both?	Within-trial information only	Within- and across-trial effects estimated separately; can be combined.	Implicit combination of within- and across-trial information, which cannot be separated.	Within- and across-trial effects estimated separately; can be combined.
Difficulty of use	Low. Straightforward to apply	High for time-to-event outcomes with heterogeneity between trials, as random-effect models not well developed. Moderate for other outcome types or if random effects not required. Requires statistical modeling expertize and statistical software such as Stata.	Low, unless random effects are used, in which case moderate.	Low. Although there are three steps (PWT; trial-level meta-regression; calculation of weighted average) they are each straightforward.
Key subjective decisions to be made	None	There are relatively more distributional assumptions to be made, which may be partly subjective. Need to decide if across-trial information will be considered and if so the criteria for inclusion.	None, as the combination of across- and within-trial information is implicit.	Need to decide if across-trial information will be considered and if so the criteria for inclusion. Also, need to decide the relative weighting of the two if estimates combined.
Bias and power	Bias is minimized but power may be low, particularly if variation is largely between rather than within trials.	Increased complexity has potential for bias from model misspecification; but assuming model is a good fit, power should be maximized. If across-trial information is included then power may increase further but with a corresponding increased risk of bias.	Power is moderate, because all information is used, but may not be maximized because not all correlation is accounted for. The risk of bias is high because of lack of knowledge of individual across- and within-trial estimates, and standard errors for the interaction effect may be inappropriate.	If across-trial information is discarded, power and risk of bias are identical to PWT. Otherwise, inclusion of across-trial information may increase power but at an increased risk of bias.

Abbreviations: PWT, pooling of within-trial covariate interaction; OSM, ''one-stage'' model with a covariate interaction term; TDCS, testing for treatment effect differences across covariate subgroups; CWA, ''manually'' combining separately calculated within- and across-trial effects.

potentially combined by means of a further weighted average. This approach has been discussed elsewhere for meta-analysis of randomized trials [16] or epidemiological data [6], and simulation has shown that CWA can indeed increase power relative to PWT, especially where data is scarce [20]. However, PWT and CWA often give markedly differing estimates of effect [21] because of ecological bias. Consequently, most analysts prefer to use within-trial information alone [7,16], although some consider that combining evidence is not unreasonable [20] because the allocation to the patient covariate is not randomized (excepting factorial designs where another treatment is considered as the covariate), and so even within-trial information may be somewhat biased. A similar practice is sometimes used in meta-analysis of main effects, where cohort or case-control studies can provide evidence in circumstances where there are few, if any, randomized trials. The CWA approach gives the analyst the freedom to study the two effects separately and, further, the potential to choose the weightings in the final combination step, allowing the potential ''down weighting'' of across-trial evidence to reflect its susceptibility to bias. This is analogous with the

approach sometimes used in meta-analyses of observational studies to deal with lower quality studies, although it is of course open to bias from the analyst if the weighting is not specified in advance. In any case, the selection of the weights is inevitably subjective. Because the use of across-trial information is controversial, it should be decided a priori whether to consider it for inclusion in the analysis, and the reasons behind the decision should be critically discussed as part of the analysis.

In addition to the CWA approach, there are further options available to the reviewer. Firstly, OSM can be parameterized such that within-trial and across-trial effects are estimated simultaneously by a single combined interaction term (see Appendix B). This is a simpler model to fit than the separate within- and across-trial parameterization, and may also have greater power. However, the challenges with OSM described above still remain [6].

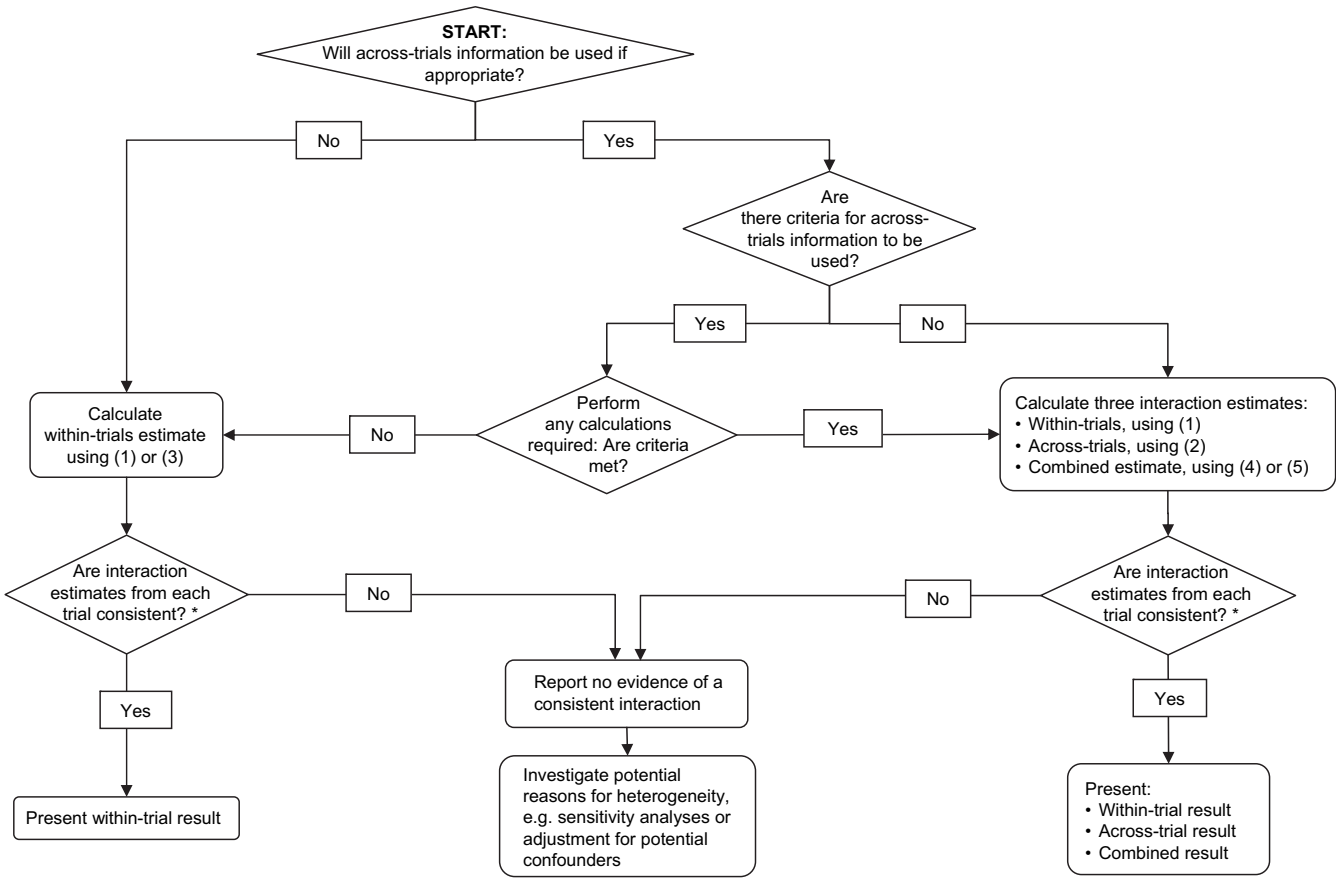
The TDCS method might appear to be an attractive way to analyze interactions, particularly with categorical covariates. It is simple to implement in its most common form, which makes use of the Peto odds ratio method [22] or the ''log-rank'' modification to this for time-to-event data [8], neither of which rely on iterative procedures and require no specialist software. These approximate the maximum likelihood estimates of the odds ratio and Cox hazard ratio (HR), respectively [22–24]. There are, however, serious drawbacks. Measuring within-subgroup effects implicitly involves combining patient data across trials; therefore, some across-trial information concerning the interaction must be used. But trials can contribute patients to more than one subgroup, so some within-trial information must also be used. Hence, an indeterminate mixture of within- and across-trial information will be present, with no way to recover estimates of the separate effects or therefore assess the risk of bias from the inclusion of across-trial information [16,19], in contrast to the other methods in this section. Further, within-trial correlations arising from trials supplying data to more than one covariate subgroup will not be accounted for, leading to a loss of efficiency and inappropriate standard errors. Lastly, heterogeneity in treatment effects across trials is usually ignored. These problems could partly be addressed by adding complexity, for instance by adding random effects to the within-subgroup meta-analyses, the across-subgroup trend, or both, as appropriate. However, these suggestions have not been formally tested, and such added complexity negates the original simplicity of the approach. We therefore do not recommend the TDCS method for formal testing of patient-level treatment-covariate interactions.

In conclusion, then, the choice of approach is governed chiefly by whether the use of across-trial information is considered and secondly by the resources available to the analyst together with the complexity of the modeling required. This latter may vary from estimation of a simple scalar interaction term, representing a solely relative effect, through to that of an absolute, nonlinear interaction effect adjusted for other covariates. We therefore propose a strategy for method selection.

4. A proposed strategy for method selection

Our proposed strategy is illustrated in Fig. 1. Firstly, an a priori decision should be made as to whether to consider including across-trial information. If within-trial information only is to be used, for example if a prior hypothesis is being tested and minimizing bias is of primary importance, we suggest the PWT method as it is straightforward to implement and interpret while having a low risk of bias. The choice of whether to fit fixed or random effects to the interaction is subject to the same arguments as discussed elsewhere for main (treatment) effects [25]. In particular, we caution against the automatic use of random effects where there is evidence of heterogeneity across interaction effects (e.g., a large I^2 or an obvious outlier). In such situations further investigation may be required, such as a check for model misspecification by inspecting the form of the interaction within each trial separately. Another possible source of heterogeneity in the interaction is confounding: if a second known covariate also interacts with treatment, and if the association between these two covariates differs across trials, then the original interaction may be altered. This may be solved through adjustment for the second covariate, if known and available. This is simply performed both for PWT (where additional terms are added to the model for each trial) and for OSM. If heterogeneity remains, it is probably best to conclude that the interaction is inconsistent across trials.

If the inclusion of across-trial information is being considered, we recommend two possible approaches. Firstly, estimates of the within trials, across trials, and combined effects could be presented, for which the CWA method is a convenient choice. Graphical presentation is greatly beneficial here (see next section), and Riley et al. [16] demonstrate the use of plots to informally judge the possible degree of ecological bias. Secondly, formal criteria could be specified for the inclusion of across-trial information, whereby the combined and within-trial estimates would be presented if the criteria are met, and the within-trial estimate alone if not. We do not propose any specific criteria of our own, although we note that clearly the risk of appreciable bias is lower when the within- and across-trial effect estimates are similar. Formal tests of difference between estimates (i.e., of ecological bias) may be used to quantify this, although statistical significance is unlikely to be reached, because of imprecision, even if the underlying bias is substantial. Simmonds and Higgins [19] have developed statistics to quantify the relative power of within- vs. across-trial interaction information, but not specifically to reflect ecological bias. Whichever approach is taken the within-trial effect estimate should be presented, and if the combined estimate is also presented then a suitable note



Key: (1) PWT; (2) meta-regression; (3) OSM within-only; (4) OSM combined; (5) CWA

* e.g. non-significant heterogeneity; fixed- and random-effect results consistent

Fig. 1. Flow diagram of recommended approaches.

of caution regarding ecological bias should be included. If criteria are used for the inclusion of the across-trial information, these need to be clearly stated and pursued objectively.

The advice given so far is aimed at reviewers who wish to avoid complex statistical modeling, especially those analyzing time-to-event data where extra methodological difficulties exist. However for those with suitable expertize and resources, OSM provides a powerful and versatile alternative in many situations. Finally, although the TDCS method is not recommended, the objection is not to the production of meta-analytic results by subgroup per se (which has potential graphical use—see next section), but to the statistical comparison of such results across subgroups.

5. Suggestions for graphical presentation

If the covariate is categorical (either ordered or not), a forest plot of within-subgroup estimates remains probably the clearest means of displaying the treatment effect by subgroup. Underneath the subgroup effects graphic, we suggest adding one or more interaction effects (within, across, or combined), each represented by a symbol such as a clear circle that cannot be confused with the subgroup estimates nor with a standard meta-analysis pooled estimate (generally represented with black squares and a clear diamond, respectively). These interactions should be derived from an appropriate model such as PWT, CWA, or OSM. If across-trial information concerning the interaction is considered then displaying interaction estimates simultaneously for within- and across-trial effects gives clear and immediate representations of their size, direction, and precision, thus providing great benefit in assessing the risk of ecological bias. Because of the issues affecting the TDCS method described earlier, the subgroup-specific estimates will not necessarily be compatible with the interaction estimate, although this fact is unlikely to be problematic in practice [6].

Figs. 2, 3a, and 4 demonstrate this approach, although they include output from many methods for illustration. This is a new approach to graphical presentation, rarely if ever seen at present, and we suggest it here as the default presentational style for future treatment-covariate interaction analyses using IPD. Assuming the treatment effect is

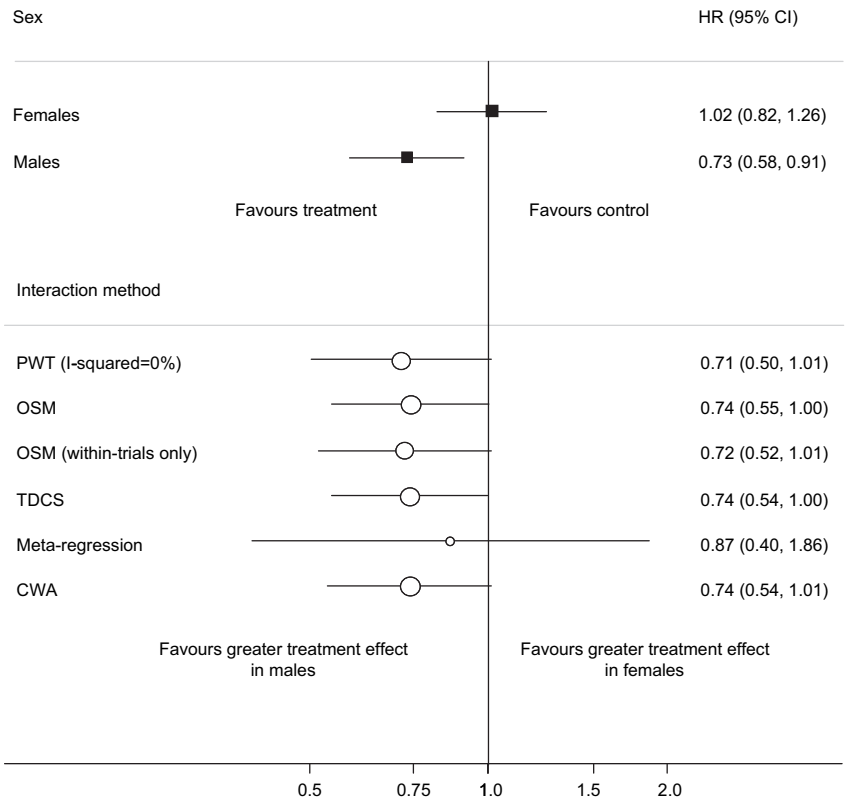


Fig. 2. Treatment effect by sex: sarcoma data set. Independently pooled results for male and female subgroups, and covariate interaction estimates from each of the methods under discussion.

estimated as a hazard or odds ratio, then the interaction estimate is a ratio of ratios, on the same scale and with a similar interpretation. An interaction with a binary covariate is the ratio of the hazard or odds ratios within the two categories. For multiple ordered categories or continuous factors, the interaction effect represents the proportional increase in hazard or odds ratio per category or unit of the covariate.

We have two suggestions for continuous covariates. If PWT is used, a forest plot of within-trial interaction coefficients could be presented along with the pooled interaction estimate. Alternatively, a continuous plot of covariate against treatment effect with confidence limits could be generated using OSM (for linear interactions; see Fig. 3b) or fractional polynomials [26].

6. Case studies

We examined a total of 19 covariates within 5 IPD meta-analyses looking at the effects of treatments on survival (time to death) in the field of cancer [10–14]. Overall, few significant treatment-covariate interactions were found (data not shown). Three case studies were selected to illustrate some of the issues described above [10–12] and to demonstrate a variety of covariate data types (binary, categorical, continuous). Each analysis was originally performed using the TDCS method, by means of the ''log-rank'' modification for time-to-event data [8] to the Peto odds ratio method [22]. Treatment-covariate interactions were reanalyzed and our results compared with those published. For illustrative purposes, we present estimates of the interaction from all four methods we have presented and also from a meta-regression, but highlight the methods that could be selected if either across-trial information is excluded or included without a set of criteria (Fig. 1). The combining of within- and across-trial estimates with CWA is done using fixed-effects inverse-variance weighting only.

6.1. Binary covariate (sarcoma data set [10]; treatment interaction with sex)

Fig. 2 shows that the results from all the methods considered here give broadly consistent results: some evidence of a qualitative interaction effect, suggesting that the treatment is more effective in men than in women. The across-trial effect has a relatively wide confidence interval (CI), indicating low power, and the combined estimate (using OSM or CWA) is almost identical to the within-trial estimate alone. Because heterogeneity in the interaction estimates is low (PWT $I^2 = 0\%$), we suggest PWT should be applied using fixed effects giving an HR = 0.71, 95% CI: 0.50, 1.01, $P = 0.058$. The conclusion is little changed from

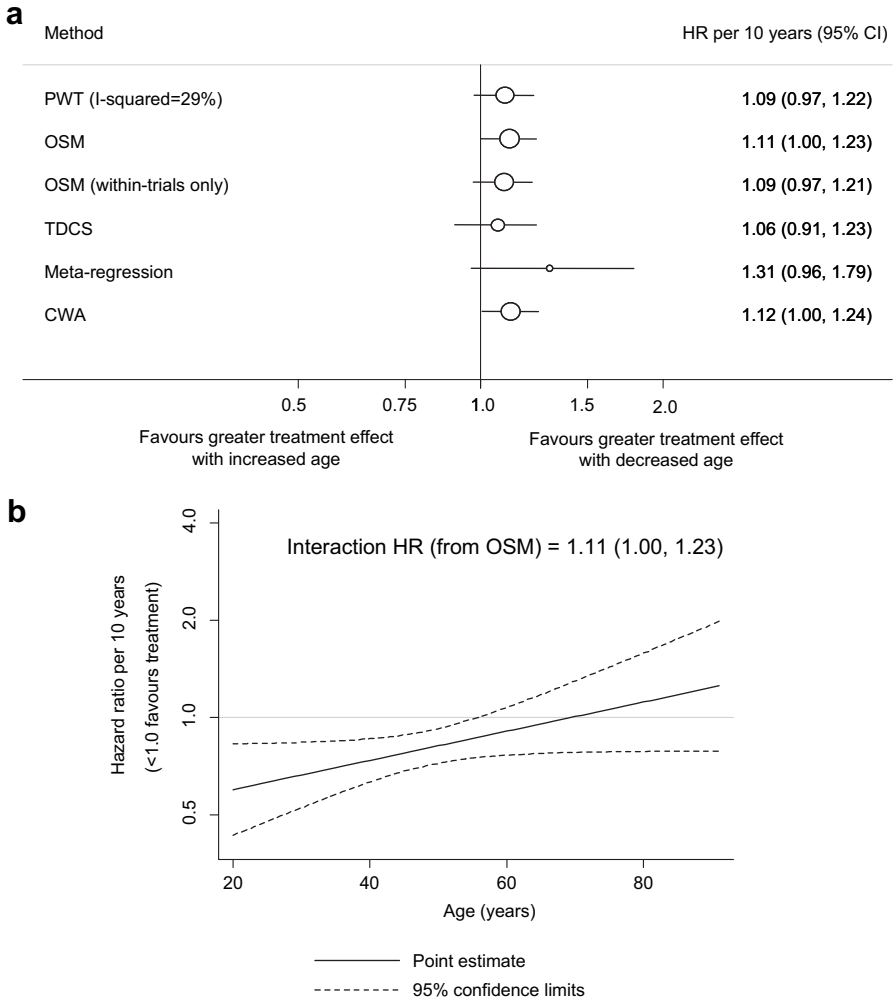


Fig. 3. a. Treatment effect by age: cervix data set. Covariate interaction estimates from each of the methods under discussion. b. Absolute treatment effect by age: cervix data set. Estimated hazard ratio and 95% confidence interval for absolute treatment effect by age at randomization (in units of 10 years).

the original analysis using TDCS, where the interaction HR was 0.74 (95% CI: 0.54, 1.00; $P = 0.049$).

6.2. Continuous covariate (cervical cancer data set [11]; treatment interaction with age)

When originally analyzed, the TDCS method was used which required that age be categorized. No linear trend was seen across age categories ($P = 0.48$). If instead age is used as a continuous linear factor, Fig. 3a shows that the magnitude of the (fixed-effect) within-trial estimate is small, whereas that of the across-trial effect is noticeably larger. The within-trial effect has noticeably greater precision. The combined estimate by CWA is a modest effect significant at the 5% level (HR = 1.12; 95% CI: 1.00, 1.24; $P = 0.044$). However, there is possible trial heterogeneity in the within-trial interaction (using PWA: $I^2 = 29\%$; $P = 0.12$), which arguably merits further investigation.

Assuming that the risk of ecological bias is acceptable, fixed-effect OSM using within- and across-trial information may be used to estimate the absolute effect of treatment by age which may then be shown in a continuous plot with confidence limits (Fig. 3b). Where feasible plots of this type have great value, showing in this case that treatment effect declines with age and may only be beneficial to patients aged under 55.

6.3. Ordered categorical covariate (PORT data set [12]; treatment interaction with nodal status)

The original analysis using TDCS showed reasonable evidence of a linear trend in treatment effect across nodal status categories ($P = 0.016$), suggesting that the treatment may be harmful for those with zero or one affected with lymph nodes. Several trials have few patients in one or more nodal status categories, and others do not obviously show a linear trend in isolation, so further investigation might be warranted. However, trial heterogeneity in the interactions is low (PWT $I^2 = 16\%$; $P = 0.31$), and the within-trial interaction HR (using fixed-effect PWT) shows no effect (HR = 0.91; 95% CI: 0.74, 1.11; $P = 0.34$). The across-trial HR is of noticeably greater magnitude, with

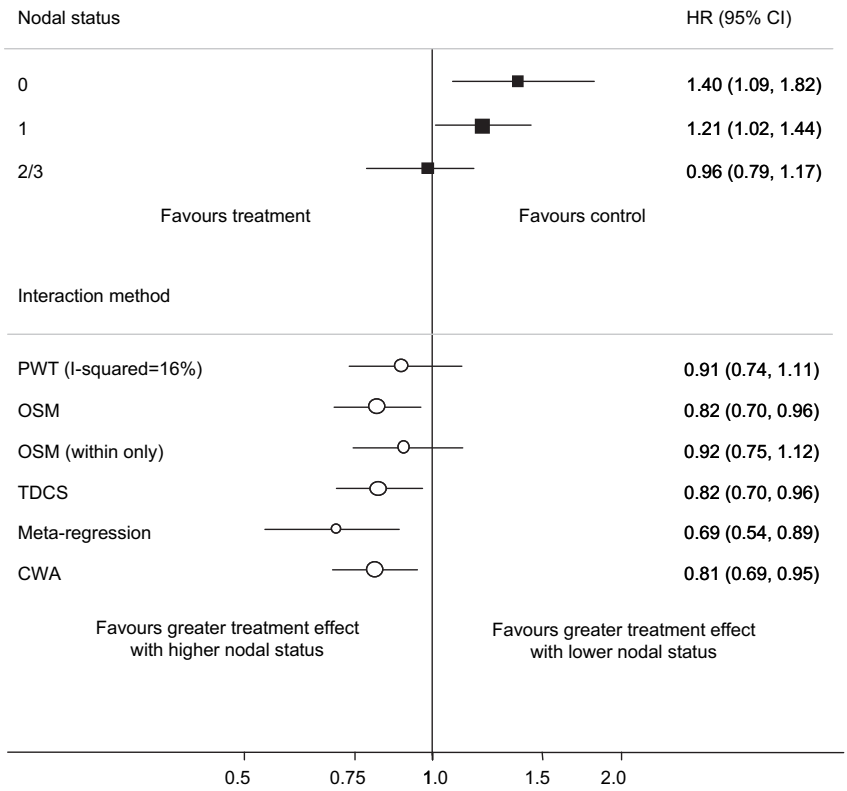


Fig. 4. Treatment effect by nodal status: PORT data set. Independently pooled results for each nodal stage subgroup, and covariate interaction estimates from each of the methods under discussion.

similar precision (HR = 0.69; 95% CI: 0.54, 0.89; $P = 0.003$ using meta-regression, Fig. 4). The combined estimate (by CWA) is significant at the 5% level (HR = 0.81; 95% CI: 0.69, 0.95; $P = .009$). The discrepancy between the PWT analysis and the original analysis using TDCS (or CWA) exemplifies that the inclusion and exclusion of across-trial information can lead to markedly different conclusions. It also illustrates the importance of a priori judgment as to whether across-trial information should be included, and the need for caution concerning possible ecological bias if combined estimates are reported.

7. Discussion

A well-established benefit of collecting IPD is the ability to investigate heterogeneity in treatment effects at the patient level, but various methods of analysis exist and no single method can be recommended for all scenarios. We suggest the choice may naturally be influenced by the objectives of the analysis, the data structure, and the resources and expertize available. Four main approaches have been presented here, each of which is either commonly used in practice or suggested in the literature; all can be fitted (at least at a basic level) using standard statistical software such as Stata. Their characteristics have been compared and discussed, and they have also been applied to real data: a selection of IPD meta-analysis data sets with time-to-event outcomes in the field of cancer.

Our primary conclusion is that method selection should be led initially by whether or not across-trial information is considered for inclusion in the analysis, and that this decision is likely to have the greatest impact on the subsequent findings. This will be a largely subjective decision, influenced by whether the risk of bias from its inclusion is considered to be offset by the potential gain in power. A risk of bias may be considered acceptable, for example, when many interactions are investigated to be identified for later confirmatory studies. Conversely, if an interaction has already been highlighted and definitive confirmation is required then it may be more natural to include only within-trial information concerning the interaction. It is always preferable to decide on the role of the across-trial information and any criteria for its inclusion in advance of analysis.

We have given special prominence to the methods we have termed PWT and CWA, the pooling of within-trial effects possibly combined with a meta-regression, viewing these as natural first steps for an analysis. They are simple to apply and naturally separate the within- and across-trial information. We acknowledge that ‘‘one-stage’’ (OSM) approach will be attractive for some analysts, particularly those with greater resources and expertize. It may be that in due course, when some technical aspects of methodology and software have been addressed and suitable tutorial articles become available, this method will naturally become the dominant approach to IPD meta-analysis. This is not

the case yet, however. Further, particular difficulties remain such as estimating random treatment effects with time-to-event outcomes.

The method we have termed TDCS has been commonly used in the past, for analysis of time-to-event outcomes such as disease survival [27,28] or binary outcomes such as vascular event incidence [29,30]. The reason for its ubiquity appears historical, it being an extension of the Peto ''log-rank'' method for estimation of main effect HRs. This was favored in the past, due probably to its use of noniterative procedures able to be carried out by hand or in nonstatistical packages such as Excel. Indeed, its extension to *trial*-level covariate interaction analysis is methodologically sound and remains an option for those same reasons. However, although TDCS has the ability to detect *patient*-level covariate interactions, its estimates may contain both within- and across-trial information but does not allow the separation of the two sources, so that estimates are at risk of ecological bias.

In this article, we have assumed that we wish to test for interaction between a single treatment effect and a covariate, which is continuous or binary, or an ordered categorical variable whose interaction is to be represented by a linear slope coefficient. These are the simplest scenarios, in which the interactions are represented by a single parameter. In practice, however, the form of the data or the desires of the reviewer may be more complex. Firstly, there are various reasons why a meta-analysis estimating more than one parameter—that is, a multivariate meta-analysis [31,32]—might be desired. One such reason is the estimation of *absolute* effects (i.e., the treatment effect for an individual patient based on their covariate value) where a second parameter is required to represent the baseline treatment effect. Alternatively, the interaction between covariate and treatment may itself require more than one parameter because either the covariate is continuous or ordered but causes a complex nonlinear interaction, or the covariate is an unordered categorical covariate such as histological disease subtype. Of the methods critiqued here, only OSM naturally allows multiple parameters to be estimated simultaneously, and we believe that appropriate models can be formulated that allow separate estimation of within- and across-trial effects for most, if not all, forms of multiple-parameter interactions. The separation of the effects for an unordered categorical covariate is a complex problem in its own right and deserves separate exploration. However, accounting for trial heterogeneity if the outcome is time-to-event may be problematic. Although PWT does not allow such a range of options, it nevertheless allows nonlinearity in the interaction to be tested by comparing a quadratic to the equivalent linear effect, because this requires only one extra parameter. If the evidence for nonlinearity is weak, this is sometimes taken as reassurance that a linear interaction is an adequate summary, although the power to detect such an effect will often be limited. Alternatively, work is ongoing on strategies for combining within-trial interactions for continuous variables estimated using fractional polynomials [33].

A potentially important issue is imbalance in the covariate across the trials in the analysis. For example, if some trials have few or no patients in some covariate categories because of selective reporting [34] this may introduce bias into the within-trial estimate. Similarly, if some trials contain continuous covariate measurements largely from one section of the distribution, then bias may occur if the resulting interaction is not representative of the true effect. There may be little or no possibility of reliably investigating this within the data, and we suggest this would prove a fruitful area for further research. Informally, the analyst might perform a sensitivity analysis by excluding trials where the range of covariate values is limited. Covariate interaction tests cannot be guaranteed to be free from bias or confounding because they are not randomized. However, we feel bias and confounding is minimized by the use of RCTs and by following the guidance given here.

Another area for further work might be to explore an approach within CWA to include across-trial information only if the point estimate for the across-trial interaction effect is sufficiently similar to the within-trial effect point estimate by a priori defined criteria, that is, if the two effect estimates are *consistent*. This idea may be formalized using models incorporating data-driven estimates of consistency. A similar idea is sometimes used in multiple treatment comparison meta-analyses, which use a Bayesian approach [35], although the concept could also be implemented in a frequentist framework.

Overall, we examined a total of 19 covariates within 5 IPD meta-analyses (data not shown). We detected relatively few significant treatment-covariate interactions, which in our experience is a common finding. Nevertheless there were instances, such as that detailed in case study 3, where within- and across-trial effects differed, thus exhibiting ecological bias. In such circumstances, different methods may produce dissimilar estimates and so the selection of the method for analysis, following the guidance we present, may have a major impact on the findings.

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collaborative groups or the trial groups listed. SMAC: Scandinavian Sarcoma Group, Sweden—SSG 81/1; Dana-Faber Cancer Institute, USA—DFCI 78/080; Intergroup Sarcoma Committee, USA—EST 1782; MD Anderson Cancer Center, USA; European Organization for Research and Treatment of Cancer, Belgium—EORTC 62771; National Cancer Institute, USA—NCI SB-S4, NCI SB-S5, NCI SB-S6; Mayo Clinic, USA—#75-77-01; Eastern Cooperative Oncology Group, USA—EST 2377; Istituti Ortopedici Rizzoli, Italy; Institut Bergonie, France; Gynecologic Oncology Group, USA—GOG 20; Swiss Group for Clinical Cancer Research, Switzerland—SAKK 57/87. CCCMAC: Gynecologic Oncology Group, USA—GOG0123, GOG0165; Yale University School of Medicine, USA—YALE HIC 5566; Cross Cancer Institute and University of Alberta, Canada—NCICCTG CX.2; Instituto de Radiología y Centro de Lucha Contra el Cancer, Uruguay—QTCON; University Medical Center Groningen and University of Groningen, Netherlands—DUY-KWF-CYKO 9407; Institute for Oncology and Radiology of Serbia—Project 1683; Toronto Sunnybrook Cancer Center, Canada; First Teaching Hospital, China; Acy'badem Oncology and Neurological Science Hospital, Turkey; Sanjay Gandhi Postgraduate Institute of Medical Sciences, India; Chiang Mai University, Thailand; and University of Yamanashi, Japan. PMT: Institut Jules Bordet and Hôpitaux St Pierre et Erasme, Belgium; Chinese Academy of Medical Sciences, China; European Organization for Research and Treatment of Cancer, Belgium—EORTC 08861; Groupe d'Etude et de Traitement des Cancers Bronchiques, France—GETCB 04CB86, GETCB 05CB88; Lung Cancer Study Group, USA—LCSG 773; Hôpital Calmette, CHRU, France; MRC Clinical Trials Unit, UK—MRC LU11; Institute of Oncology, Slovenia.

Appendix A

Results of literature search

MEDLINE search terms

meta AND (analys OR regression*) AND (subgroup* OR interaction* OR covariate* OR heterogen* OR (effect AND modif*))*

Limits: Year of publication 1966–2009; Title only; English language only.

The limitation to ''title only'' was used to filter out the large number of practical meta-analyses with heterogeneity assessments. It was felt that relevant methodological papers, whether theoretical or reviews of current use, should include the desired search terms in their titles.

Results (140 items)

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Appendix B

Mathematical description of the four methods discussed

For ease of comparison, each approach is presented as the fitting of a model relating a linear function of treatment x and covariate z to either an outcome Y (continuous, binary, or count) or a relative hazard (if the data are time to event). For generalized linear models (GLMs), this will be written as $\mu = g^{-1}(x, z)$, where $\mu = \mathrm{E(Y)}$. For time-to-event data, this becomes $h_j(t)/h_0(t) = \psi(x_j, z_j)$, where $h_j(t)$ is the hazard function for individual j and $h_0(t)$ is the baseline hazard.

For simplicity, the trial, treatment, covariate, and interaction effects are labeled as α, β, γ, and δ, respectively, in each approach, although these parameters have different values and interpretations across approaches. We use indices i for trial, j for patient and, where applicable, k for covariate level. Subscripts W and A are used to denote within- and across-trial effects, respectively. For simplicity, in this section we consider just two competing treatments (so x is binary) and a patient covariate z that is either binary, continuous, or ordered categorical. We assume that if z is not binary then the interaction can be adequately represented by a linear term so that δ is scalar.

Pooling of within-trial covariate interactions (PWT)

First, the following model should be fitted within each trial i separately:

$$\text{GLM}: \quad g(\mu_{ij}) = \alpha_i + \beta_i x_{ij} + \gamma_i z_{ij} + \delta_i x_{ij} z_{ij} \tag{1a}$$

$$\text{Time to event}: \quad \psi^{-1}\left[h_j(t)/h_0(t)\right] = \alpha_i + \beta_i x_{ij} + \gamma_i z_{ij} + \delta_i x_{ij} z_{ij} \tag{1b}$$

The resulting treatment-covariate interaction effect estimates $\widehat{\delta}_i$ are then pooled using inverse-variance meta-analysis (fixed effects or random effects):

$$\widehat{\delta}_W = \frac{\sum_i w_i \widehat{\delta}_i}{\sum_i w_i}; \quad se\left(\widehat{\delta}_W\right) = \frac{1}{\sqrt{\sum_i w_i}} \tag{2}$$

for weights w_i defined as either $w_i = 1/se\left(\widehat{\delta}_i\right)^2$ (fixed effects) or $w_i = 1/\left(se\left(\widehat{\delta}_i\right)^2 + \tau^2\right)$ (random effects). τ^2 is the

across-trial variance, estimated as follows, where k is the number of studies and Q is defined as in Equation (4):

$$\tau^2 = \frac{Q-(k-1)}{\sum_i w_i - \left(\frac{\sum_i w_i^2}{\sum_i w_i}\right)} \tag{3}$$

Heterogeneity is assessed as for standard inverse-variance meta-analysis, that is:

$$Q = \sum_i w_i \left(\widehat{\delta}_i - \widehat{\delta}\right)^2 \tag{4}$$

distributed as χ^2 on $k-1$ degrees of freedom under the null hypothesis of no heterogeneity.

One-stage models with a covariate interaction term (OSM)

Treatment-covariate interaction is estimated using all available data in a single model. In its most usual form, it can be written as follows:

$$\text{GLM}: \quad g\left(\mu_{ij}\right) = \alpha_i + \beta x_{ij} + \gamma z_{ij} + \delta x_{ij} z_{ij} \tag{5a}$$

$$\text{Time to event}: \quad \psi^{-1}\left[h_j(t)/h_0(t)\right] = \alpha_i + \beta x_{ij} + \gamma z_{ij} + \delta x_{ij} z_{ij} \tag{5b}$$

The trial effect α_i consists of a vector of dummy variables representing trial membership—that is, as a "fixed" effect. The treatment effect β can either be "common" (i.e., a fixed value common to all trials) or "random," in which case $\beta = \beta_0 + u_i$ where $u_i \sim N(0, \tau^2)$. γ and δ are considered as "common" effects. Note that any of the coefficients could potentially be treated as common, fixed, or random depending on model assumptions. The model presented here is that which may be considered the most basic yet useful.

The interaction δ in Equations (5a) or (5b) will be a weighted average of across- and within-trial effects, but there is an alternative formulation of this model, described by Simmonds [1], that enables them to be separated. If we calculate trial mean covariate values $\overline{z}_i$ (i.e., the values that would be used for performing a meta-regression), then we can fit (for a GLM or time-to-event model, respectively):

$$g\left(\mu_{ij}\right) = \alpha_i + \beta x_{ij} + \gamma z_{ij} + \delta_W x_{ij}\left(z_{ij} - \overline{z}_i\right) + \delta_A x_{ij} \overline{z}_i \tag{6a}$$

$$\psi^{-1}\left[h_j(t)/h_0(t)\right] = \alpha_i + \beta x_{ij} + \gamma z_{ij} + \delta_W x_{ij}\left(z_{ij} - \overline{z}_i\right) + \delta_A x_{ij} \overline{z}_i \tag{6b}$$

The trial, treatment, and covariate coefficients α_i, β, and γ retain a similar interpretation to Equations (5a) or (5b), but δ is replaced by δ_W and δ_A. $\delta_A - \delta_W$ represents the "excess" across-trial relationship that exists over and above the within-trial relationship—that is, a quantification of the ecological bias [1]. Having estimated δ_W and δ_A separately using Equations (6a) or (6b), we may consider "combining" these estimates by presenting the estimate of interaction $\widehat{\delta}$ from Equations (5a) or (5b) if suitable criteria are satisfied.

To assess heterogeneity here, each term in the model needs to be allowed to vary with trial membership using fixed effects. That is (for a GLM or time-to-event model, respectively):

$$g\left(\mu_{ij}\right) = \alpha_i + \beta_0 x_{ij} + \beta_{1i} x_{ij} + \gamma_0 z_{ij} + \gamma_{1i} z_{ij} + \delta_0 x_{ij} z_{ij} + \delta_{1i} x_{ij} z_{ij} \tag{7a}$$

$$\psi^{-1}\left[h_j(t)/h_0(t)\right] = \alpha_i + \beta_0 x_{ij} + \beta_{1i} x_{ij} + \gamma_0 z_{ij} + \gamma_{1i} z_{ij} + \delta_0 x_{ij} z_{ij} + \delta_{1i} x_{ij} z_{ij} \tag{7b}$$

where β_0, γ_0, and δ_0 retain the interpretations of β, γ, and δ in Equations (5a) or (5b), and β_1, γ_1, and δ_1 are "fixed" effect variables. Models (7a) and (5a) (or (7b) and (5b)) should then be compared using a log-likelihood test [2].

The same approach can be taken if model (6a) is used. A log-likelihood test should be used to compare that model with the following:

$$g\left(\mu_{ij}\right) = \alpha_i + \beta_0 x_{ij} + \beta_{1i} x_{ij} + \gamma_0 z_{ij} + \gamma_{1i} z_{ij} + \delta_{W0} x_{ij}\left(z_{ij} - \overline{z}_i\right) + \delta_{W1i} x_{ij}\left(z_{ij} - \overline{z}_i\right) + \delta_{A0} x_{ij} \overline{z}_i + \delta_{A1i} x_{ij} \overline{z}_i \tag{8a}$$

Similarly, model (6b) should be compared with the following:

$$\psi^{-1}\left[h_j(t)/h_0(t)\right] = \alpha_i + \beta_0 x_{ij} + \beta_{1i} x_{ij} + \gamma_0 z_{ij} + \gamma_{1i} z_{ij} + \delta_{W0} x_{ij}\left(z_{ij} - \overline{z}_i\right) + \delta_{W1i} x_{ij}\left(z_{ij} - \overline{z}_i\right) + \delta_{A0} x_{ij} \overline{z}_i + \delta_{A1i} x_{ij} \overline{z}_i \tag{8b}$$

Testing for treatment-effect differences across covariate subgroups (TDCS)

A two-stage approach, in which inverse-variance pooled treatment effects $\widehat{\beta}_k$ are first estimated within each patient subgroup defined by $z = k$. In the second stage, a trend line or ANOVA is fitted to these $\widehat{\beta}_k$. We assume that a linear interaction term is appropriate. In GLM form, this is:

$$\widehat{\beta}_k = \beta_0 + \delta k + \epsilon_k, \epsilon_k \sim N\left(0, se\left(\widehat{\beta}_k\right)^2\right) \tag{9}$$

where δ is the interaction effect of interest.

Both the initial estimates $\widehat{\beta}_k$ and the interaction effect δ can be estimated using either fixed effects or random effects, although fixed effects are almost exclusively used in practice.

Because δ is defined across subgroups, a direct assessment of trial heterogeneity in the treatment-covariate interaction effect cannot be performed. However, the trial heterogeneity of each of the $\widehat{\beta}_k$ is straightforward to assess using the Peto method [3].

"Manually" combining separately calculated within- and across-trial effects (CWA)

The PWT method involves calculating an interaction effect within each trial independently and therefore estimates only the within-trial effect, while meta-regression estimates only the *across*-trial effect. The CWA method combines these two interaction effect estimates using a further weighted average.

The meta-regression model to estimate across-trial interaction δ_A is

$$\widehat{\beta}_i = \beta_0 + \delta_A \overline{z}_i + \epsilon_i,\ \epsilon_i \sim N\left(0, \widehat{\sigma}_i^2 + \tau^2\right) \tag{10}$$

where $\widehat{\beta}_i$ is the estimate of treatment effect for trial i with variance $\widehat{\sigma}_i^2$, $\overline{z}_i$ is the mean value of the covariate, and $\tau^2 > 0$ specifies a random-effect meta-regression.

We then combine Equations (10) with (2) as follows:

$$\widehat{\delta} = \frac{w_W \widehat{\delta}_W + w_A \widehat{\delta}_A}{w_W + w_A};\ se\left(\widehat{\delta}\right) = \frac{1}{\sqrt{w_W + w_A}} \tag{11}$$

where $w_W = 1/se\left(\widehat{\delta}_W\right)^2$ and $w_A = 1/se\left(\widehat{\delta}_A\right)^2$.

Assessment of treatment-covariate interaction effect heterogeneity cannot be done for the combined estimate. Conclusions must be based on the heterogeneity assessment from PWT.

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