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## Meta-analysis of Published Excess Relative Risk Estimates

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### Abstract

A meta-analytic summary effect estimate often is calculated as an inverse variance weighted average of study-specific estimates of association. The variances of published estimates of association often are derived from their associated confidence intervals under the assumptions typical of Wald-type statistics, such as normality of the parameter. However, in some research areas, such as radiation epidemiology, epidemiological results typically are obtained by fitting linear relative risk models, and associated likelihood-based confidence intervals are often asymmetric; consequently, reasonable estimates of variances associated with study-specific estimates of association may be difficult to infer from the standard approach based on the assumption of a Wald-type interval. We describe a novel method for meta-analysis of published results from linear relative risk models that uses a parametric transformation of published results to improve on the normal approximation used to assess confidence intervals. Using simulations,

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Availability of data and material (meta-analysis of published data only)

Code availability (software code provided in appendices)

we illustrate that the meta-analytic summary obtained using the proposed approach yields less biased summary estimates, with better confidence interval coverage, than the summary obtained using the more classical approach to meta-analysis. The proposed approach is illustrated using a previously published example of meta-analysis of epidemiological findings regarding circulatory disease following exposure to low-level ionizing radiation.

## Keywords

meta-analysis; cohort studies; excess relative risk; cancer

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In a meta-analysis of epidemiological study results, a summary effect estimate is obtained by combining information from a set of study-specific estimates. A common approach is to calculate an inverse variance weighted average of the study-specific estimates of association (e.g., (Sutton A.J., Abrams K.R. et al. 2000, United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2018)). This approach assigns more weight to studies with more precise study-specific estimates of association. In the context of unbiased linear sums of estimates this approach is justified by the Gauss-Markov theorem (Plackett 1949).

For epidemiological results obtained from fitting log-linear regression models, it is easy to recover reasonable estimates of the variances associated with study-specific estimates of association by using the information encoded in the confidence intervals. Standard meta-analytic techniques typically proceed by assuming that, given reported effect measures and associated confidence intervals, one can derive the variances of estimates of association based on the assumptions typical of Wald-type statistics; these estimates of study-specific variances are used to calculate the inverse-variance weighted average estimate of association which is reported as the summary effect estimate (Sutton A.J., Abrams K.R. et al. 2000).

However, such an approach is not straightforward for some estimators for which variances are rarely reported. In some application areas effect measures are typically obtained from fitting linear relative risk regression models. For example, in epidemiological studies of a variety of carcinogens, including asbestos (Hein, Stayner et al. 2007), benzene (Rinsky, Hornung et al. 2002), radon progeny (National Research Council (U.S.). Committee on the Biological Effects of Ionizing Radiations., United States. Environmental Protection Agency. et al. 1988, Lubin, Boice et al. 1995, Darby, Hill et al. 2005), and external ionizing radiation (Boice, Blettner et al. 1987, National Research Council (U.S.). Committee on the Biological Effects of Ionizing Radiations. 1990, Preston, Shimizu et al. 2003), investigators have modeled the relative risk per unit exposure as a linear function of exposure rather than an exponential function of exposure. In radiation research, this convention follows from a long history of use of the linear relative risk model in analyses of the Life Span Study of Japanese atomic bomb survivors (Preston, Ron et al. 2007, Pawel, Preston et al. 2008) for which there is a biophysical basis (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 1993, Little, Wakeford et al. 2009, Little 2010); and, in the contemporary epidemiological literature, the linear relative risk model has been applied in analyses of many radiation-exposed populations (Gilbert, Cragle et al. 1993, Cardis, Gilbert

et al. 1995, Cardis, Vrijheid et al. 2005, Muirhead, O'Hagan et al. 2009, Metz-Flamant, Laurent et al. 2013). The widespread use of the same model form has the advantage that it may facilitate comparison of results between studies. Unfortunately, a quantitative meta-analytic summarization of epidemiological results that have been quantified using linear relative risk models is more challenging than doing so with results that have been quantified using standard log-linear regression models.

An important challenge in meta-analyses of results that have been quantified using a linear relative risk model is deriving reasonable estimates of study-specific variances. The methodology developed for quantitative summaries of epidemiological findings has largely focused on log-linear model forms, where symmetric Wald-type confidence intervals are routinely reported (DerSimonian and Laird 1986). In contrast, likelihood-based confidence intervals are commonly reported for estimates of association derived from linear relative risk models, and often these intervals are asymmetric (Cox and Hinkley 1974, Meeker and Escobar 1995). Consequently, a reasonable estimate of the variance associated with a point estimate may be difficult to infer from the information encoded in the likelihood-based confidence bounds by simply leveraging the assumptions typical of Wald-type statistics.

In the current paper we describe a method to address these challenges to meta-analysis of published studies that report estimates of association derived from linear relative risk models. The approach is based on an algebraic transformation of published results to yield an estimator with a more symmetrical distributions than those reported in the literature, and then derive an expression of variance of this transformed estimator assuming that the reported profile-likelihood bounds for the estimate of association in the original scale conform well to a re-expression of Wald-type bounds of the transformed estimator. The effect on meta-analyses of non-normality in study-specific estimates has been recognized by prior authors (Jackson and White 2018); and, the Cochrane Handbook, for example, discusses transformation of results as an approach to reduce skew (Higgins and Cochrane Collaboration 2020). A meta-analytic summary and associated confidence interval are constructed and back transformed to the original scale. We address fixed effect and random effects meta-analyses; these approaches employ different assumptions (i.e., under a fixed effect model, it is assumed that there is one true association that underlies all the studies in the analysis; and, under the random effects model, it is assumed that there is an underlying distribution of true associations across studies). For illustration, the proposed methodology is implemented using an empirical example.

## METHODS

We assume that a systematic literature search was performed, study results (in terms of point estimates and associated confidence intervals) extracted, and study quality appraised. We do not address these important steps in a meta-analysis. Rather, here we focus on the stage of data synthesis during which a quantitative summary of the study findings is calculated. We focus on a setting where epidemiological results have been obtained by fitting a model of the form

$$\psi = 1 + \beta D,$$

where  $\psi$  denotes the risk ratio or odds ratio,  $D$  denotes the continuous exposure of interest, and the parameter of primary interest in the meta-analysis,  $\beta$ , denotes the excess relative risk or excess odds ratio per unit  $D$  (e.g., the excess relative risk per sievert (Sv) in a radiation epidemiology study), and likelihood-based confidence intervals have been reported. For simplicity we will henceforth assume 95% confidence intervals but the approach is readily adapted to other bounds. First, we describe a standard approach to meta-analytic summarization of epidemiological study results. Second, we describe the proposed alternative approach to meta-analytic summarization of epidemiological study results. Third, we address how to proceed with a meta-analysis of results that have been quantified using a linear risk ratio model when a lower confidence bound was not determined for the reported estimate.

### A standard approach to meta-analysis of published linear relative risk estimates

The data structure for a standard approach to summarization of epidemiological findings in a meta-analysis is a table of point estimates and associated confidence intervals. Let  $i = 1 \dots k$  index the  $k$  studies to be summarized in the meta-analysis. Let  $\hat{\beta}_i$  denote the estimated excess relative risk or excess odds ratio per unit  $D$  for study  $i$ ; and, let  $L_i$  and  $U_i$  denote the associated lower and upper confidence limits for  $\hat{\beta}_i$ .

For each study,  $i$ , we derive the standard error of the reported estimate of association, denoted  $se(\hat{\beta}_i)$  given the reported associated confidence intervals  $L_i, U_i$  for the published results, by the following calculation:  $se(\hat{\beta}_i) = (U_i - L_i) / (2 \times 1.96)$ .

This approach to estimation of the study-specific standard error follows from considering the framework typical of a linear regression model fitting that yields a point estimate ( $\hat{\beta}_i$ ) and associated Wald-type confidence bounds ( $L_i, U_i$ ). Given this information, an estimate of  $se(\hat{\beta}_i)$  can be derived under the conditions typical of Wald-type statistics:  $L_i = \hat{\beta}_i - 1.96 \times se(\hat{\beta}_i)$  and  $U_i = \hat{\beta}_i + 1.96 \times se(\hat{\beta}_i)$ . With simple rearrangement we get,  $L_i + 1.96 \times se(\hat{\beta}_i) = U_i - 1.96 \times se(\hat{\beta}_i)$ , and it follows that  $(U_i - L_i) = 2 \times (1.96 \times se(\hat{\beta}_i))$ , leading to the above expression for  $se(\hat{\beta}_i)$  as a function of  $(L_i, U_i)$ .

Little *et al* (Little, Azizova et al. 2012) described an approach to deriving a fixed effect inverse-variance weighted estimate of the excess relative risk per unit exposure, where the meta-analytic summary is calculated as the sum of the study-specific estimates divided by its

variance, over the sum of the inverse of the study-specific variances,  $\hat{\beta}_{tot}^{Fixed} = \frac{\sum_{i=1}^k \hat{\beta}_i / se(\hat{\beta}_i)^2}{\sum_{i=1}^k 1 / se(\hat{\beta}_i)^2}$ .

This inverse-variance weighted average estimate of association is reported as the summary estimate of association.

Confidence intervals for this fixed effect summary estimate of association are derived by calculation of an estimate of the standard error for the meta-analytic summary association. The estimate of the standard error is simply the reciprocal of the square-root of the sum of the study-specific variances,

$$se(\hat{\beta}_{tot}^{Fixed}) = \frac{1}{\left[ \sum_{i=1}^k \frac{1}{se(\hat{\beta}_i)^2} \right]^{0.5}}; \text{ and,}$$

a Wald-type confidence interval for the summary estimate of association is derived as,

$$95\% \text{ CI}(\hat{\beta}_{tot}^{Fixed}) = \hat{\beta}_{tot}^{Fixed} \pm 1.96 \times se(\hat{\beta}_{tot}^{Fixed}).$$

A random-effects summary estimate of association may also be derived. Little *et al* (Little, Azizova et al. 2012) described how to calculate a random effects summary estimate of association based on the method proposed by Dersimonian and Laird (DerSimonian and Laird 1986) for a one-step estimation of the variance of the random effect, where the summary meta-analytic estimate of the association based on a random effects model is calculated as,

$$\hat{\beta}_{tot}^{Random} = \frac{\sum_{i=1}^k \hat{\beta}_i / \left[ se(\hat{\beta}_i)^2 + \Delta^2 \right]}{\sum_{i=1}^k \frac{1}{\left[ se(\hat{\beta}_i)^2 + \Delta^2 \right]}}$$

where

$$\Delta^2 = \max \left[ 0, \frac{Q - (I - 1)}{\sum_{i=1}^k \frac{1}{\left[ se(\hat{\beta}_i)^2 \right]} - \frac{\sum_{i=1}^k \frac{1}{\left[ se(\hat{\beta}_i)^4 \right]}}{\sum_{i=1}^k \frac{1}{\left[ se(\hat{\beta}_i)^2 \right]}}} \right],$$

and

$$Q = \sum_{i=1}^I \left[ \left( \hat{\beta}_i - \hat{\beta}_{tot}^{Fixed} \right) / se(\hat{\beta}_i) \right]^2.$$

The associated standard error is calculated as,

$$se(\hat{\beta}_{tot}^{Random}) = \frac{1}{\left[ \sum_{i=1}^k \frac{1}{\left[ se(\hat{\beta}_i)^2 + \Delta^2 \right]} \right]^{0.5}}.$$

## An alternative approach to meta-analysis of published linear relative risk estimates

In most contemporary epidemiological analyses that quantify associations under a linear relative risk model the reported confidence interval is derived from likelihood-based methods rather than calculated as a Wald-type interval (McCullagh and Nelder 1989). This is because, in a given study, the distribution of maximum likelihood estimators for the parameter  $\beta$  may be far from normal unless the sample size is large. When maximum likelihood estimators are not approximately normal (e.g. in small or moderate samples), Wald-type intervals may not have nominal coverage (Cox and Hinkley 1974, Meeker and Escobar 1995); for this reason, it has become common practice for published results for fittings of linear relative risk models to report likelihood-based confidence intervals rather than Wald-type intervals (Prentice and Mason 1986, Moolgavkar and Venzon 1987). By extension, meta-analytic summaries that proceed under the assumption that typical Wald-type statistical assumptions hold may not yield an appropriately inverse-variance weighted average estimate of association or confidence interval.

We describe an alternative approach to meta-analytic summarization of epidemiological study results that have been obtained from fitting of linear relative risk regression models. The data structure for the proposed approach is a table of point estimates, associated confidence intervals, and maximum observed doses. Letting  $i = 1 \dots k$  index study,  $\hat{\beta}_i$  denote the point estimate of interest, and  $L_i$  and  $U_i$  denote the associated lower and upper confidence bounds for the point estimate reported for study  $i$ . Further, let  $x_i$  denote the maximum value of the dose reported in published study  $i$ , noting that the value of  $x_i$  is often known and reported in an epidemiological study (or may be obtained from the authors).

For each study, we derive a transformed metric of the estimate of association,

$$\hat{A}_i = \ln(c\hat{\beta}_i + 1) \dots \dots \dots \quad \text{Equation 1}$$

and associated standard error, denoted  $se(\hat{A}_i)$ , as a function of reported values  $L_i$  and  $U_i$ ,

$$se(\hat{A}_i) = \ln\left(\frac{cU_i + 1}{cL_i + 1}\right) / (2 \times 1.96) \dots \dots \dots \quad \text{Equation 2}$$

where  $c = \min[x_i: 1 \leq i \leq k]$ , to ensure that  $\left(\frac{cU_i + 1}{cL_i + 1}\right) > 0$   $1 \leq i \leq k$  and therefore we can calculate  $se(\hat{A}_i)$  for all studies in the meta-analysis. The proposed approach derives a variance estimate for this transformed quantity that is based on the reported likelihood-based confidence interval for the estimate of association on its original scale; however, estimates of the transformed quantity  $\hat{A}_i$  will tend to more closely approximate a normal distribution than  $\hat{\beta}_i$ .

The justification for the proposed approach follows from considering that parameter transformations can improve asymptotic distributional approximations, as discussed in the context of the linear relative risk model by Barlow (Barlow 1985) and by Prentice and Mason (Prentice and Mason 1986). Criteria for selecting such transformations have been

discussed previously (Sprott 1974) and include removal of range restriction on  $\hat{\beta}_i$  and reduction of the asymmetry of the log-likelihood about  $\hat{\beta}_i$ .

The transformation  $\hat{A}_i = \ln(c\hat{\beta}_i + 1)$  can remove the range restriction on the excess relative risk parameters  $\hat{\beta}_i$ . Consider study  $i$  in which the dose variable,  $D_i$ , has compact support  $C_i$ , for which  $x_i = \sup[C_i]$ . Consequently, the possible range of the estimate of dose-response association,  $\hat{\beta}_i$ , under a model  $RR_i = 1 + \beta_i D_i$ , is  $1 / -x_i$ , infinity). Preston and Mason proposed the simple transformation  $\alpha = \ln(\beta + \beta_0)$ , where  $\beta_0 = \frac{1}{x_i}$  to remove the range restriction; when  $c = x_i$ , that simple transformation is equivalent to our proposed expression  $\ln(c\beta + 1)$ .

The transformation  $\hat{A}_i = \ln(c\hat{\beta}_i + 1)$  also may reduce log-likelihood skewness, and therefore improve symmetry of confidence bounds on the transformed metric. The standard approach assumes that typical Wald-type statistical assumptions hold. Prentice and Mason illustrated that the simple transformation  $A = \ln(\beta + \beta_0)$ , yields nearly complete symmetry about the transformed metric (Prentice and Mason 1986); and, when  $c = x_i$ , that simple transformation is equivalent to our proposed expression  $A = \ln(c\beta + 1)$ . Using Sprott's index as a measure of the normality of the likelihood function, Barlow demonstrated that the transformation  $\hat{\beta}_i = \exp(\hat{A}_i) - 1$ , improves the normality of estimates (Barlow 1985). Our proposed transformation,  $c\hat{\beta}_i = \exp(\hat{A}_i) - 1$ , is equivalent to the transformation proposed by Barlow (1985) when  $c = 1$ . It follows that the proposed transformation will tend to improve the symmetry of the likelihood-based confidence bounds on the transformed scale, and upon applying this transformation to the reported bounds,  $L$  and  $U$ , we can better approximate the variance by employing assumptions of Wald-type intervals to the likelihood-based bounds on this transformed  $\hat{A}_i$  scale than when applied to these bounds on their original scale.

A fixed effect inverse-variance weighted summary of this estimated quantity is calculated as

$$\text{follows, } \hat{A}_{tot}^{Fixed} = \frac{\sum_{i=1}^k \hat{A}_i / se(\hat{A}_i)^2}{\sum_{i=1}^k 1 / se(\hat{A}_i)^2}.$$

The standard error of  $\hat{A}_{tot}^{Fixed}$  is given by  $se(\hat{A}_{tot}^{Fixed}) = \frac{1}{\left[ \sum_{i=1}^k 1 / se(\hat{A}_i)^2 \right]^{0.5}}$ .

We then re-transform to the original scale and obtain the summary fixed effect meta-analytic estimate of the association  $\hat{\beta}_{tot}^{Fixed}$ , and associated confidence interval. This summary estimate is calculated as:

$$\hat{\beta}_{tot}^{Fixed} = \frac{\exp(\hat{A}_{tot}^{Fixed}) - 1}{c},$$

and it is this form of the inverse-variance weighted average estimate of association that is reported as the meta-analytic summary estimate of association.

A Wald-type confidence interval for the summary estimate of association is derived based on the estimate of  $se(\hat{A}_{tot}^{Fixed})$ ,

$$95\% CI(\hat{\beta}_{tot}^{Fixed}) = \frac{\exp(\hat{A}_{tot}^{Fixed} \mp 1.96se(\hat{A}_{tot}^{Fixed})) - 1}{c}.$$

A similar approach can be used to calculate a random effects summary meta-analytic estimate and associated confidence interval. Let  $\hat{A}_{tot}^{Random}$  denote the random effects inverse-variance weighted summary, calculated as follows,

$$\hat{A}_{tot}^{Random} = \frac{\sum_{i=1}^k \hat{A}_i / [se(\hat{A}_i)^2 + \Delta^2]}{\sum_{i=1}^k 1 / [se(\hat{A}_i)^2 + \Delta^2]}, \text{ where}$$

$$\Delta^2 = \max \left[ 0, \frac{Q - (I - 1)}{\sum_{i=1}^k \frac{1}{[se(\hat{A}_i)^2] \frac{\sum_{i=1}^k 1 / [se(\hat{A}_i)^4]}{\sum_{i=1}^k 1 / [se(\hat{A}_i)^2]}} \right] \text{ and}$$

and

$$Q = \sum_{i=1}^I \left[ (\hat{A}_i - \hat{A}_{tot}^{Fixed}) / se(\hat{A}_i) \right]^2.$$

The associated standard error for this meta-analytic summary of the transformed estimates is,

$$se(\hat{A}_{tot}^{Random}) = \frac{1}{\left[ \sum_{i=1}^k \frac{1}{[se(\hat{A}_i)^2 + \Delta^2]} \right]^{0.5}}.$$

We then re-transform to the original scale, and obtain the summary random effects meta-analytic estimate of association and associated confidence interval, calculated as:

$$\hat{\beta}_{tot}^{Random} = \frac{\exp(\hat{A}_{tot}^{Random}) - 1}{c},$$

with a Wald-type confidence interval for this random effects summary estimate of association is derived,



$$95\% \text{ CI}(\hat{\beta}_{tot}^{Random}) = \frac{\exp(\hat{A}_{tot}^{Random} \mp 1.96se(\hat{A}_{tot}^{Random})) - 1}{c}.$$

Simple computer code written for the SAS and R statistical packages is provided that calculates fixed and random effects meta-analytic summary estimates as well as associated confidence intervals (Appendix).

### Meta-analysis when a lower confidence bound was not determined in a published report

Sometimes a likelihood-based lower confidence bound,  $L_i$ , is not determined in a particular analysis because, at the lower constraint on the parameter range (i.e.,  $1/x_i$ ), the likelihood-based statistic that defines the lower confidence bound has not reached the specified critical value. In such instances, a lower bound is typically not reported; rather, authors may indicate that the bound is simply  $< 1/x_i$ .

To-date practice for how to address this has not been well described in the literature. It appears that what is done in standard meta-analyses of linear relative risk estimates is to impute a lower bound by assuming that the confidence bounds are symmetrical on the original scale (Little, Azizova et al. 2012), such that the imputed lower bound is  $L_i = \hat{\beta}_i - (U_i - \hat{\beta}_i)$ . The standard approach then proceeds using  $L_i$  in place of the missing  $L_i$ .

When using the proposed alternative method, a lower bound may be imputed by assuming symmetry on the transformed scale. If the transformation improves normality as compared to the original scale this should be advantageous. For study  $i$  with no reported lower bound  $L_i$ , impute the value

$L_i = \frac{\exp(\hat{A}_i - (\ln(cU_i + 1) - \hat{A}_i)) - 1}{c}$ . The data set can proceed with analysis described above using the imputed lower bound.

### Sensitivity to observed exposure ranges

The proposed transformation involves selection of a constant,  $c$ , to ensure that we can calculate  $se(\hat{A}_i)$  for all studies in the meta-analysis. Our proposed approach defines  $c = \min[x_i; 1 \leq i \leq k]$ . The sensitivity of results to choice of  $c$  can be assessed by recalculating the meta-analytic summary measure under an alternative value,  $c'$  under the constraint  $0 < c' \leq \min[x_i; 1 \leq i \leq k]$ , to ensure calculation of  $se(\hat{A}_i)$ . This permits investigation of sensitivity of results, for example, to outliers or extreme values of the exposure variable in study samples. We suggest such sensitivity analyses proceed by calculating results under a value such as,  $c' = 0.9c$ .

### Simulations

We compare the proposed approach to meta-analytic summaries to the standard fixed effect and random effects approaches in simulated data examples. We simulated 1000

meta-analyses under scenarios in which the number of individuals in each study was small (1000-1500), moderate (2000-2500), large (4000-4500), or variable size (1000-4500); and, we considered examples in which the number of studies in a simulated meta-analysis was set to 5, 10, or 15 studies. In each simulation, the number of people in a study was drawn from a uniform distribution over the specified range of study size; for each cohort member, we generated an independent standard normal covariate  $Z$ . We generated an exposure,  $E$ , by sampling from a uniform distribution (0,5). We generated a binary outcome,  $Y$ , with dependence of  $Y$  on  $Z$  and  $E$  encoded by specifying that  $Y$  took a value of 1 with odds =  $\exp(\log(\alpha) + 0.1Z) \times (1 + \eta E)$ , where the parameter describing the baseline odds of the outcome,  $\alpha$ , was set to 0.15, 0.2, or 0.25, and the parameter describing the excess odds ratio per unit  $E$ ,  $\eta$  was set to 1.0, 0.75, or 0.50. The excess odds ratio model was used for data generation to avoid numerical issues with generating data from a linear relative risk model. We estimated the coefficients associated with  $E$  for each study using maximum likelihood and obtained profile likelihood confidence bounds. We calculate fixed effect and random effects meta-analyses using the standard approach; and, we calculate fixed effect and random effects meta-analyses using the proposed approach described above. To summarize the results we calculate the average meta-analyzed estimate as well as the percentage of associated confidence intervals that cover the specified true effect.

### Empirical examples

We illustrate the calculation of a meta-analytic summary using both the standard approach and the proposed alternative approach in an empirical data example based on data reported in a prior systematic review and meta-analysis of ischemic heart disease following exposure to low-level ionizing radiation (Little, Azizova et al. 2012).

## RESULTS

### Simulations: Fixed effect meta-analyses

Table 1 reports the results of simulations in which we estimated a meta-analytic summary estimate of the excess odds ratio per unit exposure using the standard fixed effect meta-analytic approach and our proposed approach; in table 1 the baseline odds of the outcome was set to 0.2 and the excess relative odds of the outcome was set to 1.0. In all simulation scenarios, the standard fixed effect meta-analytic approach yielded summary effect measures that were null biased and had less than nominal confidence interval coverage. In simulations of meta-analyses of large cohorts (i.e., 4000-4500 people per study), the standard fixed effect meta-analysis yield a slightly biased meta-analytic summary results with 95% confidence interval coverage that was closest to nominal. In simulation scenarios involving meta-analyses of smaller cohorts, the standard fixed effect meta-analysis exhibited greater null bias and the summary effect measure had less than nominal confidence interval coverage. As the number of studies per meta-analysis increased from 5 to 15 studies per meta-analysis, and other parameters remained unchanged, the bias in the standard fixed effect meta-analysis remained unchanged; however, the confidence interval coverage for the standard meta-analytic summary worsened and was substantially less than the nominal level.

In all simulation scenarios, the proposed approach yielded fixed effect meta-analytic summary results that were approximately unbiased and the confidence interval coverage for the proposed fixed effect meta-analytic summary measure was close to the nominal 95% value in all simulation scenarios. Even in simulation scenarios involving meta-analyses of small cohorts (N=1000-1500), the proposed meta-analytic summary was approximately unbiased and associated confidence interval coverage was close to the nominal 95% value. Figure 1 illustrates that the transformed metric of the estimate of association,  $\hat{A}_t$ , appears more normally distributed than the excess odd ratio estimates.

### **Simulations: Random effects meta-analyses**

Table 1 also reports the results of simulations in which we estimated a meta-analytic summary estimate of the excess odds ratio per unit exposure using the standard random effects meta-analytic approach and our proposed approach. Similar to the conclusions drawn for the fixed effect meta-analyses, the standard random effects meta-analytic approach yielded summary effect measures that were null biased and tended to have less than nominal confidence interval coverage. In simulations of meta-analyses of large cohorts (i.e., 4000-4500 people per study), the standard random effects meta-analysis yield a slightly biased meta-analytic summary results with 95% confidence interval coverage that was close to nominal. In simulation scenarios involving meta-analyses of smaller cohorts, the standard random effects meta-analysis exhibited greater null bias and the summary effect measure had less than nominal confidence interval coverage. As the number of studies per meta-analysis increased from 5 to 15 studies per meta-analysis, and other parameters remained unchanged, the confidence interval coverage for the standard random effects meta-analytic summary worsened and was substantially less than the nominal level.

The proposed approach yielded random effects meta-analytic summary results that were approximately unbiased and the confidence interval coverage for the proposed meta-analytic summary effect measure was slightly conservative yet very close to the nominal 95%.

### **Simulation results: Sensitivity analyses**

Simulations also were conducted under scenarios in which baseline odds of the outcome,  $\alpha$ , was 0.15 and 0.25; again, under those simulation scenarios, the proposed approach yielded fixed effect and random effects meta-analytic summary results that were approximately unbiased and the confidence interval coverage for the proposed fixed effect and random effects meta-analytic summary measures were close to the nominal 95% value (Appendix Table A1). In addition, simulations were conducted in which we varied the excess relative odds of the outcome per unit exposure was 0.75 and 0.5; under those simulation scenarios we also observed that the proposed approach yielded fixed effect and random effects meta-analytic summary results that were approximately unbiased and the confidence interval coverage for the proposed fixed effect and random effects meta-analytic summary measures were close to the nominal 95% value (Appendix Table A2). Finally, simulations were conducted in which the number of subjects per study varied from 1000-2500 and from 1000-4500; under those simulation scenarios we also observed that the proposed approach yielded fixed effect and random effects meta-analytic summary results that were approximately unbiased and the confidence interval coverage for the proposed fixed effect

and random effects meta-analytic summary measures were close to the nominal 95% value (Appendix Table A3).

Sensitivity of the simulation results to the value  $c = \min[\max(x)]$  was assessed by re-calculating values under the condition  $c' = 0.9c$  and  $c' = 0.8c$ ; these sensitivity analyses yielded essentially equivalent quantitative values (Appendix Table A4).

### Empirical example.

While high doses of ionizing radiation have a fairly well-established association with circulatory disease, evidence for an association at lower doses (e.g., <0.5 Sv) remains more controversial. Little et al. reported on a meta-analysis of epidemiological findings of association between radiation exposure and circulatory disease involving moderate- or low-dose whole-body exposure to ionizing radiation (Little, Azizova et al. 2012). Table 2 shows the point estimates and associated lower and upper confidence bounds for each study considered in the meta-analysis of radiation and ischemic heart disease, where the estimates represent the estimated excess relative rate per Sv whole-body dose (noting that the studies expressed radiation dose in Sv). The standard approach yields a fixed effect estimate  $\hat{\beta}_{tot}^{Fixed} = 0.10$  (95% CI: 0.05, 0.15). The proposed alternative approach yields a fixed effect estimate  $\hat{\beta}_{tot}^{Fixed} = 0.10$  (95% CI: 0.05, 0.15), similar to the results obtained using the standard approach to calculation of a fixed effect estimate. These results correspond to the fixed effect meta-analytical result reported by Little et al. (0.10; 95% CI: 0.05, 0.15) (Little, Azizova et al. 2012). The similarity of the results is expected given the large sample sizes of the studies included in this meta-analysis, demonstrating that the proposed approach is not influential in the case when conditions suggest the normality assumption is tenable (Table 2).

We also report results derived under a random-effects meta-analysis. A standard approach to estimation of a random effects estimate  $\hat{\beta}_{tot}^{Random} = 0.10$  (95% CI: 0.04, 0.15). The proposed alternative approach yields a random-effects estimate  $\hat{\beta}_{tot}^{Random} = 0.10$  (95% CI: 0.04, 0.16). Again, these results correspond closely to the random effects meta-analytical result reported by Little *et al* (0.10; 95% CI: 0.04, 0.15).

Sensitivity of these results to the value  $c = \min[\max(x)]$  was assessed by re-calculating values under the condition  $c' = 0.9c$  and  $c' = 0.8c$ . These sensitivity analyses yielded essentially equivalent quantitative values under these conditions, the proposed fixed effect meta-analytic summary was  $\hat{\beta}_{tot}^{Fixed} = 0.10$  (95% CI: 0.05, 0.15) and the proposed random effects meta-analytic summary was  $\hat{\beta}_{tot}^{Random} = 0.10$  (95% CI: 0.04, 0.16).

## DISCUSSION

Non-linear regression models fitted via maximum likelihood methods are known to suffer problems when data are sparse (Greenland, Mansournia et al. 2016). For example, the commonly-used logistic and Cox regression models are susceptible to bias in small samples (Greenland, Schwartzbaum et al. 2000). These biases translate into bias of meta-analyses based on them (Greenland, Mansournia et al. 2016). Maximum likelihood estimates of the

linear odds ratio or linear risk ratio per unit exposure are much more prone to bias in small samples than standard log-linear regression models (Prentice and Mason 1986); and, unless the study size is very large, the resultant parameter estimates may have a profile likelihood-based confidence intervals that differ substantially from Wald-type intervals (Moolgavkar and Venzon 1987).

In the current paper we focus on the implications for meta-analytic summarization of epidemiological study results derived from maximum likelihood fittings of linear relative risk models. Using simulations, we illustrate the potential for bias and lack of appropriate confidence interval coverage in meta-analyses of linear odds ratio models that employ a standard approach to fixed effect meta-analysis. We observed that bias increased as the size of the studies included in meta-analyses diminished. We further noted that as the number of studies included in meta-analyses increased from 5 to 15, while other parameters remained unchanged, the bias in the meta-analytic summary remained similar but the confidence interval coverage for the meta-analytic summary decreased. This is likely because confidence intervals for meta-analytic summary estimates become tighter as the number of studies in a meta-analysis increases while the bias remains; a similar phenomenon has been reported in simulations of sparse data bias in ordinary (i.e., loglinear) logistic regression (Lin 2018).

Barlow (Barlow 1985), and Prentice and Mason (Prentice and Mason 1986), proposed reparameterizations of linear relative risk models that substantially reduced bias and improved approximations of confidence intervals to those predicted by the asymptotic normal distribution. This prior body of work suggested that a transformation applied for conducting a meta-analysis of published study results should lead to a distribution of estimators for  $A$  that tend to more closely approximate a normal density than the maximum likelihood estimators for the excess relative risk per unit  $D$  (Prentice and Mason 1986). We apply a similar transformation to existing estimates of excess relative risk to better approximate the normality of the meta-analyzed parameter, which is a necessary assumption underlying typical inverse-variance weighted meta-analyses. The proposed approach is based on the known improved symmetry of the confidence interval for the transformed metric relative to the untransformed (Prentice and Mason 1986). When  $\hat{A}_i$  and  $sd(\hat{A}_i)$  better conform to normal distributions than  $\hat{\beta}_i$  and  $sd(\hat{\beta}_i)$  the proposed analytical approach to deriving a meta-analytic summary based on inverse-variance weighting of the transformed quantities should improve estimation as the underlying assumptions will be better approximated (Barlow 1985, Prentice and Mason 1986). In principle, this should provide improved approximations of parameters with asymptotic normal distributions for meta-analysis when working with reported results from linear relative risk models than working directly with the published values, which may will not conform well to underlying distributional assumptions in small and moderately-sized studies (Barlow 1985).

In contrast to standard meta-analytic approaches, the proposed approach requires information on the maximum exposure range in each study included in the meta-analysis. Often this value is reported; if not, often it can be ascertained from the study authors

or inferred (e.g., from the range of observed data in an exposure-response plot, or from substantive knowledge about exposure conditions).

We have illustrated the proposed approach with an empirical example. In the example, the study sizes are very large and the published likelihood-based confidence intervals are highly symmetrical. The empirical example illustrates the important point that when the assumption of normality approximately holds, our proposed approach yields essentially equivalent results to those of the standard approach. Our simulations using larger sample sizes support the finding from our empirical example that this transformation does not distort estimates when it is used in settings where normality may be a tenable assumption. The situations under which the proposed approach is likely to perform much better than the standard approach will tend to be meta-analyses that encompass many small studies, as opposed to a few large studies. The simulations illustrate that when data are sparse the approaches may yield somewhat different meta-analytic summaries of a set of estimates of excess relative risk per unit exposure, with substantially different means and associated confidence intervals (Table 1). Our simulations demonstrate that the proposed transformation improved performance of meta-analyses in terms of bias and confidence interval coverage.

It is common in epidemiological analyses that use the linear relative risk model to encounter settings in which the lower likelihood-based confidence bound was not determined. This poses a challenge for meta-analysis in which published results of point estimates and confidence bounds are the basis for deriving estimates of variance that underpin inverse-variance weighted meta-analytic summaries. It appears that a standard practice in meta-analysis of excess relative risk per unit dose estimates has been to impute a lower bound by assuming that the bounds are symmetrical on the original scale, so that given just the reported upper bound and point estimate a lower bound is imputed. In the proposed approach, we suggest that a lower bound may be imputed by assuming symmetry on the transformed scale. If the transformation does improve normality as compared to the original scale, as illustrated in Figure 1, this should be advantageous and improve practice for meta-analysis of radiation epidemiology results in settings where a profile likelihood-based lower confidence interval is not defined.

The simple approach we describe, that follows from the transformation proposed in Barlow (Barlow 1985) and Prentice and Mason (Prentice and Mason 1986), may offer a useful complement to standard methods that can be employed when undertaking meta-analysis of reported results based on linear relative risk models.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Abbreviations:

<b>RR</b>	relative rate
<b>CI</b>	confidence interval

<b>ERR</b>	excess relative risk
<b>Sv</b>	sievert

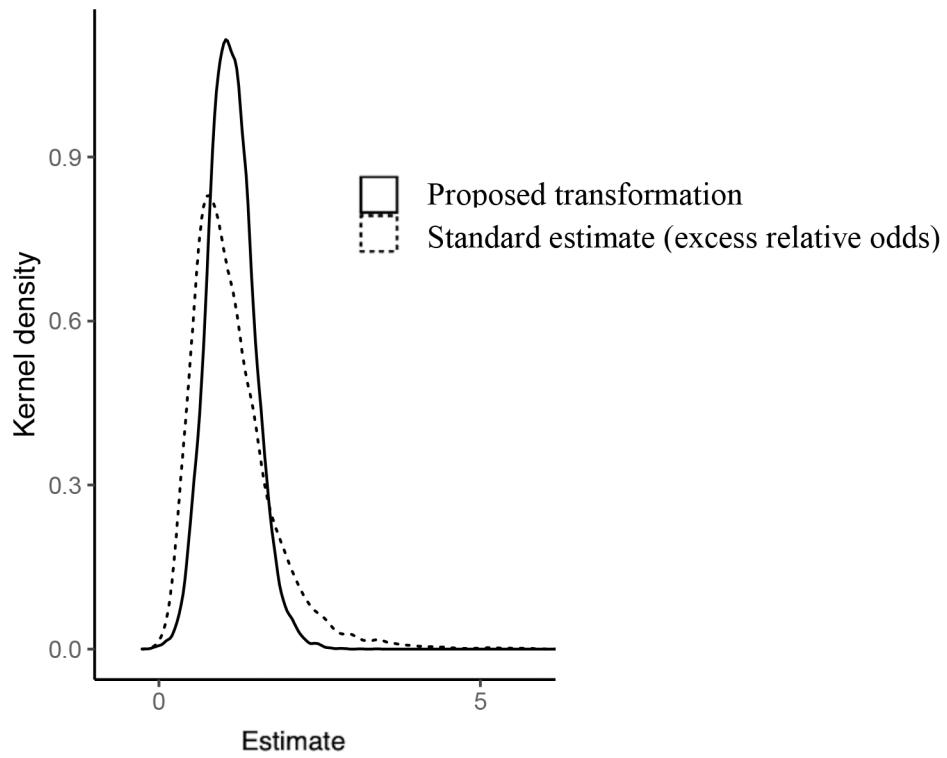
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**Figure 1.** Probability density functions of excess relative odds and the proposed transformed metric,  $A$ , across simulated studies with 500-750 subjects per study and 15 studies per meta-analysis.

**Table 1**

Results for simulations, reporting the average of the standard fixed effect and random effects meta-analytic results, proposed fixed effect and random effects meta-analytic results, and confidence interval coverages.

$\eta$	Simulation setup	Studies per meta-analysis	Subjects per study	Fixed effect meta-analysis				Random effects meta-analysis				
				Standard approach	Proposed approach	Standard approach	Proposed approach	Standard approach	Proposed approach	Standard approach	Proposed approach	
			Mean estimate	CI coverage %	Mean estimate	CI coverage %	Mean estimate	CI coverage %	Mean estimate	CI coverage %	Mean estimate	CI coverage %
1	15	4000-4500	0.96	0.80	0.99	0.95	0.96	0.88	0.99	0.96	0.96	
			2000-2500	0.92	0.71	0.98	0.94	0.93	0.76	0.99	0.96	
			1000-1500	0.86	0.60	0.97	0.94	0.86	0.62	0.97	0.95	
10	15	4000-4500	0.96	0.88	0.99	0.94	0.97	0.92	1.00	0.96		
			2000-2500	0.92	0.80	0.98	0.95	0.93	0.85	0.99	0.96	
			1000-1500	0.87	0.71	0.97	0.94	0.87	0.75	0.98	0.95	
5	15	4000-4500	0.97	0.91	0.99	0.95	0.97	0.95	1.00	0.96		
			2000-2500	0.94	0.86	0.99	0.95	0.95	0.92	1.00	0.96	
			1000-1500	0.89	0.83	0.99	0.96	0.91	0.88	1.00	0.97	

the baseline odds of the outcome,  $\alpha = 0.2$ .

**Table 2.**

Meta-analysis of epidemiological findings regarding associations between ischemic heart disease and exposure to low-level radiation. Reported coefficients ( $\beta_i$ ) refer to estimates of excess relative risk per Sv and are indicated along with associated lower ( $L_i$ ) and upper ( $U_i$ ) 95% confidence intervals, and maximum dose ( $x_i$ ). Illustration of data and fixed effect, and random effects, estimates derived in a standard approach to calculation and in the proposed alternative approach.

$i$	$\beta_i$	$L_i$	$U_i$	$x_i$	Persons
1	0.12	0.051	0.186	5.92	12,210
2	0.41	0.05	0.78	0.50	61,017
3	0.15	-0.14	0.58	0.12	16,236
4	4.10	-2.9	13.7	0.60	22,393
5	0.26	-0.05	0.61	0.40	174,541
6	0.02	-0.1	0.15	4.00	86,611
7	-0.01	-0.59	0.69	0.50	275,312
8	0.05	-0.05	0.16	4.00	10,399

	Standard approach		Proposed approach	
Meta-analytic summary	Fixed effect	Random effects	Fixed effect	Random effects
Estimate (95% CI)	0.10 (0.05, 0.15)	0.10 (0.04, 0.15)	0.10 (0.05, 0.15)	0.10 (0.04, 0.16)

Study citations, in numerical order: Azizova et al. 2010 (Azizova, Muirhead et al. 2010), Ivanov et al. 2006 (Ivanov, Maksiourov et al. 2006), Lane et al. 2010 (Lane, Frost et al. 2010), Laurent et al. 2010 (Laurent, Metz-Flamant et al. 2010), Muirhead et al. 2009 (Muirhead, O'Hagan et al. 2009), Shimizu et al. 2010 (Shimizu, Kodama et al. 2010), Vrijheid et al. 2007 (Vrijheid, Cardis et al. 2007), Yamada et al. 2004 (Yamada, Wong et al. 2004), as reported in Little et al. 2012 (Little, Azizova et al. 2012).