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Count outcome meta-analysis for comparing treatments by fusing mixed data sources

Comparing interventions using across report information

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Abstract Assessing interventions applied to target populations is a matter of prime interest. Studies are usually undertaken to see if an alternative intervention is superior (or at least equivalent) to a comparable standard intervention. This is typically achieved by comparing alternative and standard intervention *within* a given study and the developed meta-analytic methodology is building on this assumption. Very little work has been delivered when studies only report results on one of the interventions only, but not on both. This is the situation we consider here and it is motivated by study reports on two surgeries for treatment of asymptomatic antenatally diagnosed congenital lung malformations in young children. Reports are often only available for one of the two and restricting analysis on those with results on both surgeries will restrict data to 33% of the potential sources. We show in this paper how data sources can be fused and under which condition this fusion will provide valid results. Application to the case study shows the potential gain of the suggested approach in reaching a more conclusive analysis. We argue that studies should best allow within-study comparison, but if only one intervention information is available (for example, as the required surgery expertise for the comparative intervention is not deliverable at the respective site) harnessing one-group information can provide additional insights.

Keywords meta-analysis · data fusion · mixed information

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1 Introduction and motivation

This work is motivated by a meta-analysis using reported data comparing thoracoscopic, or *key-hole* surgery, and *open* surgery for treatment of asymptomatic antenatally diagnosed congenital lung malformations in young children. The mean age of the children involved in the studies is 15 months and both surgeries have no deaths reported. Thoracoscopy has become more widely used because it requires only a small incision in the chest wall. We consider the following question: how does key-hole perform vs. open w.r.t. *total complications*?

Adams *et al.* (2017) considered a meta-analysis of 12 reports comparing key-hole and open surgery as listed in Table 1. These data allow a standard meta-analysis as follows. For each study an effect measure, here the risk ratio, is calculated associated with an estimate of its standard error. This allows a calculation of a summary measure with 95% confidence interval. We use here the package `STATA15` (Stata 2017) in connection with an add-on package `metan` (see also Palmer and Sterne 2009) for delivery of the calculation. The results are displayed in Table 2. This is an example of a standard, two-stage meta-analysis where in the first stage for each study an effect measure is calculated and in the second stage the study-specific effect estimates are further analyzed. This approach is extensively described in the existing literature (Borenstein *et al.* 2009; Cooper *et al.* 2009; Schwarzer *et al.* 2015). In the application study here, there is a significant beneficial effect of key-hole surgery w.r.t. the number of complications (which includes bleeding, wound or chest infections, or tracheal injury among others) and the effect is homogeneous over the studies as the test of homogeneity is not significant. These results are also visualized in the forest plot in Figure 1. Note that all but one of the studies show non-significant results whereas the meta-analytic summary estimator clearly does. This demonstrates one of the benefits of a meta-analysis.

Table 1 Meta-analytic data comparing key-hole with open; given are the number of complications and number of children enrolled for each treatment group

	key-hole		open	
report	#complications	size	#complications	size
Vu 2008	2	12	14	24
Diamond 2007	4	12	6	24
Kunisaki 2014	7	49	4	13
Lau 2013	6	39	6	28
Rahman 2009	2	14	3	14
Cho 2012	0	7	1	27
Tolg 2005	1	5	1	4
Sundararajan 2007	5	20	3	9
Fascetti-Leon 2013	5	26	3	28
Fievet 2012	1	9	0	2
Laje 2015	9	100	9	188
Kulaylat 2015	11	112	37	146

Table 2 `metan`-output and analysis comparing key-hole with open

```
           Study     |     RR    [95% Conf. Interval]     % Weight
---------------------+-------------------------------------------------
Vu 2008              |  0.286       0.077     1.058         12.03
Diamond 2007         |  1.333       0.463     3.843          5.16
Kunisaki 2014        |  0.464       0.160     1.347          8.15
Lau 2013             |  0.718       0.258     1.995          9.00
Rahman 2009          |  0.667       0.131     3.398          3.87
Cho 2012             |  1.167       0.052    25.967          0.86
Tolg 2005            |  0.800       0.070     9.180          1.43
Sundararajan 2007    |  0.750       0.227     2.480          5.33
Fascetti-Leon 2013   |  1.795       0.476     6.774          3.72
Fievet 2012          |  0.900       0.048    16.839          0.99
Laje 2015            |  1.880       0.771     4.585          8.06
Kulaylat 2015        |  0.388       0.207     0.725         41.40
---------------------+-------------------------------------------------
M-H pooled RR        |  0.680       0.495     0.936        100.00
---------------------+-------------------------------------------------

  Heterogeneity chi-squared =  14.08 (d.f. = 11) p = 0.229
  I-squared (variation in RR attributable to heterogeneity) =  21.9%

  Test of RR=1 : z=   2.37 p = 0.018
```

In addition to the 12 studies that have been used in Adams *et al.* (2017) as these included information on both treatment groups and, hence, allowing a conventional meta-analysis, there were 24 additional reports available, of which *15 had only information on key-hole* and *9 had only information on open surgery*. So, in total there are 36 reports with 12 studies having information on both, 15 on key-hole only, and 9 on open only. We list these additional studies in Table 3 and Table 4.

These additional 24 studies were ignored in Adams *et al.* (2017) as for any of these it is not possible to calculate a study-specific risk ratio estimate since a comparator treatment is missing. Hence this does not allow a conventional 2-stage meta-analysis where in the first stage a within-study effect is estimated and then this effect estimate is further analyzed in a second stage. This setting of having only one result per study available (with the comparator result missing) has not been considered in meta-analysis. To overcome this difficulty we suggest a 1-stage modelling approach which will allow to use the information from all 36 studies and which we will detail in the following section.

2 A count modelling approach using Poisson regression

We consider the number of complications X as a Poisson count with mean $E(X) = \mu n$ where n is the size of the study report. Clearly, $\mu = E(X)/n$ is the *incidence risk of complications*. We write for report i

$$E(X_{ij}) = \mu_j n_{ij} \tag{1}$$

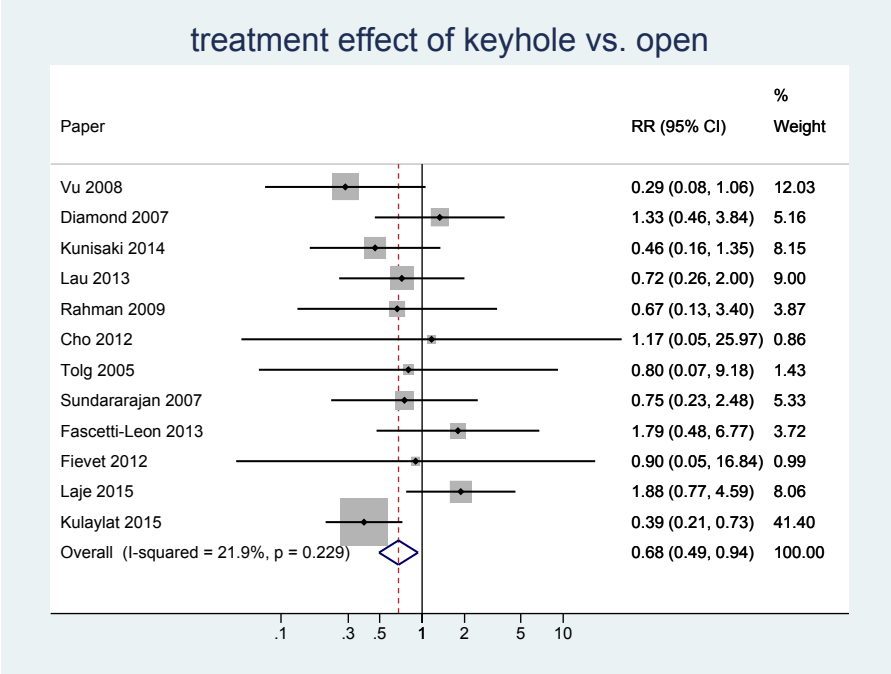

Fig. 1 Forest plot based on 12 studies with complication information in open and key-hole surgery

for $j = 1$ (treatment=key-hole) and $j = 0$ (comparison=open), so that the risk ratio $RR = \mu_1/\mu_0$, assumed to be independent of the study i, for the time being. Taking logarithms on both sides of (1) we yield

$$\log E(X_{ij}) = \log n_{ij} + \log \mu_j = \log n_{ij} + \alpha + \beta \times j \tag{2}$$

where $\beta = \log(\mu_1/\mu_0)$ is the *log-risk ratio*, α is the log-baseline risk, and $\log n_{ij}$ enters as *an offset* (a covariate with a fixed, known coefficient) into the modelling. Note that α and β are considered non-random and unknown. Finally, it is assumed that the count X_{ij} follows a Poisson distribution

$$X_{ij} \sim Po(x|n_{ij}\mu_j), \tag{3}$$

where $Po(x|\theta) = \exp(-\theta)\theta^x/x!$.

3 Fusion of the Poisson likelihoods

According to the available data we have the following, three different likelihoods. The first likelihood appears for those studies where both, key-hole and open surgery, information is available:

$$L_0 = \prod_{i=1}^{k_0} \left[Po(x_{i0}|n_{i0}\exp(\alpha_i)) \times Po(x_{i1}|n_{i1}\exp(\alpha_i + \beta)) \right], \tag{4}$$

Table 3 Meta-analytic data comparing key-hole with open: reports from key-hole only

	key-hole		open	
report	#complications	size	#complications	size
Jesch 2005	0	5	.	.
de Lagausie 2005	0	8	.	.
Tanaka 2013	2	12	.	.
Rothenberg 2008	6	97	.	.
Rothenberg 2011	1	75	.	.
Seong 2013	8	50	.	.
Kaneko 2010	2	7	.	.
Muller 2012	0	12	.	.
Tarrado 2010	0	6	.	.
Truitt 2006	0	12	.	.
Zeidan 2009	1	6	.	.
Cano 2006	0	6	.	.
Boubnova 2011	11	30	.	.
Albanese 2007	4	144	.	.
Johnson 2011	5	15	.	.

Table 4 Meta-analytic data comparing key-hole with open: reports from open surgery only

	key-hole		open	
report	#complications	size	#complications	size
Tsai 2008	.	.	7	105
Raychaudhuri 2011	.	.	0	14
Nagata 2009	.	.	0	5
Sueyoshi 2008	.	.	0	8
Chow 2007	.	.	6	6
Aziz 2004a	.	.	2	6
Aziz 2004b	.	.	0	3
Aziz 2004c	.	.	0	9
Ferreira 2010	.	.	10	35

where k_0 are the reports involving both techniques.

The second likelihood occurs for those studies with only information on key-hole surgery:

$$L_1 = \prod_{i=k_0+1}^{k_0+k_1} \left[Po(x_{i1}|n_{i1} \exp(\alpha_i + \beta)) \right], \tag{5}$$

where k_1 are the reports involving only key-hole. Finally, the third likelihood occurs for those studies with only open surgery information:

$$L_2 = \prod_{i=k_0+k_1+1}^{k_0+k_1+k_2} \left[Po(x_{i0}|n_{i0} \exp(\alpha_i)) \right], \tag{6}$$

where k_2 are the reports involving only open surgery. This leads to the *joint likelihood*

$$L(\theta) = L_0(\theta) L_1(\theta) L_2(\theta) \tag{7}$$

where θ stands for a generic parameter.

Table 5 Some results comparing key-hole with open

type of study (k)	RR	SE	z	$P > \|z\|$	95% CI
both arm information (12)	0.6895	0.1240	-2.07	0.039	0.4847 – 0.9809
mixed arm information (36)	0.6596	0.1130	-2.43	0.015	0.4715 – 0.9229

4 Poisson likelihoods with random effect for `study`

It appears reasonable to capture the baseline variation across studies with a random effect. Hence, let $\alpha_i \sim N(\alpha, \sigma_\alpha^2)$ be a normal random effect with mean α and variance σ_α^2. Then the likelihood for studies with information on key-hole and open surgery becomes:

$$L_0 = \prod_{i=1}^{k_0} \int_{\alpha_i} [Po(x_{i0}|n_{i0}\exp(\alpha_i)) \times Po(x_{i1}|n_{i1}\exp(\alpha_i+\beta))]\phi(\alpha_i|\alpha,\sigma_\alpha^2)d\alpha_i, \quad (8)$$

where $\phi(\alpha_i|\alpha,\sigma_\alpha^2)$ is a normal density with mean α and variance σ_α^2 with similar expressions for the other likelihoods:

$$L_1 = \prod_{i=k_0+1}^{k_0+k_1} \int_{\alpha_i} [Po(x_{i1}|n_{i1}\exp(\alpha_i+\beta))]\,\phi(\alpha_i|\alpha,\sigma_\alpha^2)d\alpha_i, \quad (9)$$

and

$$L_2 = \prod_{i=k_0+k_1+1}^{k_0+k_1+k_2} \int_{\alpha_i} [Po(x_{i0}|n_{i0}\exp(\alpha_i))]\,\phi(\alpha_i|\alpha,\sigma_\alpha^2)d\alpha_i. \quad (10)$$

Again we can form the joint likelihood

$$L(\theta) = L_0(\theta)L_1(\theta)L_2(\theta).$$

In Table 5 we find the analysis for the studies with information on both groups, hence using L_0, and for the studies including mixed arm information, in other words using the joint likelihood L. We note that the latter analysis shifts the borderline significance of the risk ratio to a clearly significant result. For both analyses the baseline random effect α_i for study is significant, more precisely has a positive variance, significantly different from zero.

The model is easily extendible to allow heterogeneity of effect across studies

$$\beta_i \sim N(\beta, \sigma_\beta^2)$$

where β_i is now a normal random effect for study report i. For example, the likelihood for studies with only information on key-hole becomes

$$L_1 = \prod_{i=k_0+1}^{k_0+k_1} \int_{\beta_i} \left[\int_{\alpha_i} Po(x_{i1}|n_{i1}\exp(\alpha_i+\beta))\phi(\alpha_i|\alpha,\sigma_\alpha^2)d\alpha_i \right] \phi(\beta_i|\beta,\sigma_\beta^2)d\beta_i, \quad (11)$$

with similar expressions for the other likelihoods corresponding to the available study information. It is now possible to investigate effect heterogeneity in more detail. The two models under comparison would be $M_0 : \sigma^2_\beta = 0$ and $M_1 : \sigma^2_\beta \neq 0$. In Table 6, a model evaluation is provided which shows that there is no evidence for heterogeneity of effect across studies. This can be seen by looking at the likelihood ratio $2 \log \lambda = 2(105.29 - 104.86) = 0.86$ with associated p-value of 0.18. Note that $2 \log \lambda$ has $\frac{1}{2}\chi^2_{(0)} + \frac{1}{2}\chi^2_{(1)}$ as asymptotic null-distribution ($\chi^2_{(k)}$ is the chi-squared distribution with k degrees of freedom with $k = 0$ denoting the distribution putting all its mass at zero) due to the boundary condition that M_0 is on the boundary of M_1. In addition, both information criteria, Akaike (AIC) and the Bayesian (BIC) information criterion, favor M_0 which we take as evidence for the lack of effect heterogeneity.

Table 6 Model evaluation comparing key-hole with open: log-likelihood, Akaike and Bayesian information criteria are given for the model with and without treatment random effect

variance component	Log L	AIC	BIC
$\sigma^2_\beta = 0$	-105.29	216.58	222.19
$\sigma^2_\beta \neq 0$	-104.86	217.73	225.21

5 Simulation study

We evaluated the performance of the two Poisson regression methods, one based only on the studies with information on both arms and the other based additionally on the studies including mixed arm information, by means of simulation. We consider a Poisson model that allows a random effect for `study`. In the simulation study, the data were generated from two, potentially different, Poisson distributions for the treatment and comparison groups, respectively. The number of studies (k) was chosen as 20, 40, 60, and 80. Furthermore, the simulated meta-analytic data included 50% of all studies with information in two arms and 50% of all studies with information in one arm, the latter having an equal split on treatment and comparison group. The settings were set to mimic the data on comparing open and key-hole surgery. We used $\alpha = -2, \sigma^2_\alpha = 0.7$, and $\beta = -0.5$ and 0.5, leading to the true risk ratios of 0.61 and 1.65, respectively. For each situation, 1000 simulation replications were used.

The performance of the estimators in the Poisson model with baseline random effect was evaluated in terms of bias and root mean squared error (RMSE). As seen in Tables 7 and 8, the bias of the log-risk ratio ($\hat{\beta}$) and the bias of the variance of baseline risk ($\hat{\sigma}^2_\alpha$) were closer to zero when using the studies with mixed arm information in comparison to the respective bias obtained from the method using the studies with information on both arms

Table 7 The performance of estimators for meta-analysis using mixed arm information

		Average Bias			Average RMSE		
k	β	$\hat{\alpha}$	$\hat{\beta}$	$\hat{\sigma}^2_\alpha$	$\hat{\alpha}$	$\hat{\beta}$	$\hat{\sigma}^2_\alpha$
20	-0.5	-2.0328	-0.0067	-0.0349	0.3690	0.4041	0.5189
	0.5	-2.0334	0.0146	-0.0758	0.3371	0.3157	0.4045
40	-0.5	-2.0098	-0.0032	-0.0373	0.2484	0.2761	0.3444
	0.5	-1.9990	-0.0042	-0.0240	0.2339	0.2181	0.2782
60	-0.5	-2.0066	-0.0045	-0.0255	0.1999	0.2177	0.2629
	0.5	-2.0031	-0.0006	-0.0258	0.1953	0.1790	0.2196
80	-0.5	-2.0036	0.0022	-0.0087	0.1782	0.1833	0.2276
	0.5	-2.0085	0.0042	-0.0204	0.1610	0.1533	0.1901

Table 8 The performance of estimators for meta-analysis using both arm information

		Average Bias			Average RMSE		
k	β	$\hat{\alpha}$	$\hat{\beta}$	$\hat{\sigma}^2_\alpha$	$\hat{\alpha}$	$\hat{\beta}$	$\hat{\sigma}^2_\alpha$
20	-0.5	-2.0955	0.0301	-0.0301	1.2452	1.1924	0.7946
	0.5	-2.0454	0.0221	-0.1018	0.4313	0.3545	0.5158
40	-0.5	-2.0157	-0.0045	-0.0521	0.3131	0.3164	0.4227
	0.5	-2.0040	-0.0037	-0.0321	0.2936	0.2398	0.3552
60	-0.5	-2.0018	-0.0052	-0.0377	0.2544	0.2524	0.3422
	0.5	-2.0040	-0.0012	-0.0230	0.2459	0.1929	0.2871
80	-0.5	-1.9947	-0.0038	-0.0270	0.2224	0.2113	0.2843
	0.5	-2.0077	0.0038	-0.0276	0.1966	0.1632	0.2426

only, in almost all cases. The RMSEs of $\hat{\beta}$ and the RMSEs of $\hat{\sigma}^2_\alpha$ computed from the method based on mixed arm information were smaller than those of the compared method in all cases. Our results emphasize that Poisson regression analysis using all available information can provide a benefit in a meta-analysis. At least in the situation studied here, it yields good performance in terms of bias and mean squared error of the estimated parameters of interest.

6 Diagnostics

Clearly, the approach suggested here goes beyond the conventional within-study comparison to estimate the treatment effect. Hence, we must be considerate that comparing treatment across studies might lead to a different result than comparing treatment within studies. In the following we outline a strategy to diagnose a potential discrepancy between study estimates using both arm information and study estimates using one arm information only. The strategy is as follows:

- fit the model M_0 for all reports using $\theta = (\alpha, \sigma^2_\alpha, \beta)$,
- fit the model M_1 with $\theta_1 = (\alpha_1, \sigma^2_{\alpha_1}, \beta_1)$ for the subset of reports with both surgeries and with $\theta_2 = (\alpha_2, \sigma^2_{\alpha_2}, \beta_2)$ for the subset with only one surgery,
- evaluate

$$2\log\lambda = 2\log\left[\frac{L(\hat{\theta}_1)L(\hat{\theta}_2)}{L(\hat{\theta})}\right]$$

on a χ^2-scale with 3df as M_1 has 6 and M_0 3 parameters,
– in the case here, $2\log\lambda = 6.14$ with associated `p-value = 0.1051` which is above the conventionally used threshold of 0.05, so that we do not reject the common parameter model.

A more direct (but also more limited) approach is as follows: define the indicator variable

$$S = \begin{cases} 1 & \text{if report contains info on both surgeries} \\ 0 & \text{otherwise} \end{cases}$$

and the effect variable

$$T = \begin{cases} 1 & \text{if key-hole} \\ 0 & \text{open} \end{cases}$$

and assess treatment×both/mixed information interaction $S \times T$ by means of investigating the coefficient γ for significance in the model (12)

$$\log E(X_{it}) = \log n_{it} + \log \mu_j = \log n_{it} + \alpha + \beta \times t + \gamma(s \times t), \qquad (12)$$

where the treatment $t = 0, 1$ indicates open and key-hole surgery, respectively, and $s = 0, 1$ indicates whether the study has only one type of surgery (0) or both (1). Clearly, if the interaction parameter γ is needed in the model (12) it would imply that the relative risk estimate varies depending whether the report includes both surgeries or only one.

Table 9 Assessing treatment-mixed information interaction

term	RR	SE	z	$P > \|z\|$	95% CI
$S \times T$	1.4956	0.5870	1.03	0.305	0.6930 – 3.2277

We conclude from the analysis in Table 9 that there is no evidence that key-hole/open effect is differential in reports with both surgeries reported to reports with only one surgery (the treatment effect is not affected by the type of study report), so that conclusions might be based upon the total of 36 reports.

7 Discussion

The paper is based on the idea of fusing several likelihoods. Here we used mixed Poisson likelihoods. This model is often used for rates where events occur within a given person-time. If the person-time is identical for all individuals under risk, the person-time reduces to the sample size. In the latter case, the binomial model would then occur as alternative. However, we should point out that in the present case study a child could have multiple complications leading to a count of total complications per child. Hence, the outcome per child is not

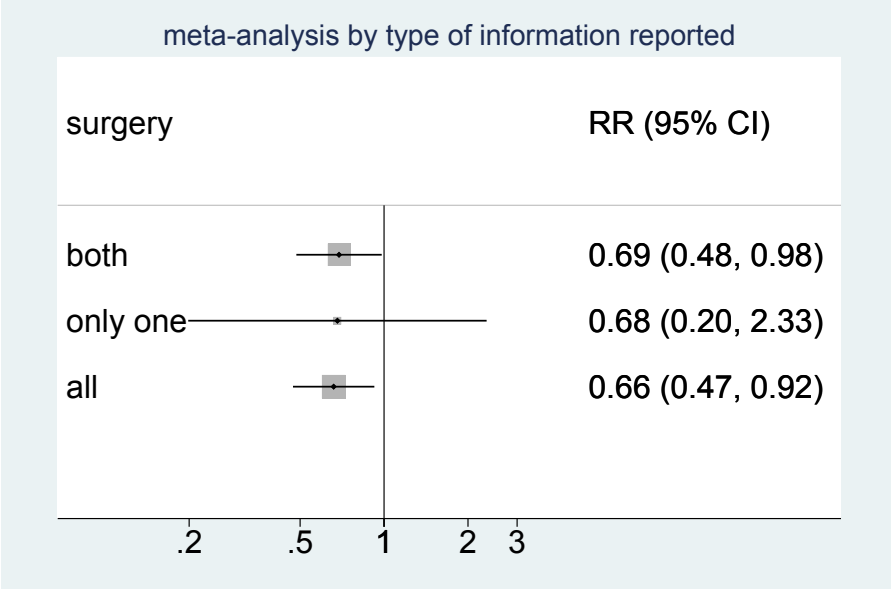

Fig. 2 Summary plot: "both" is based on all studies with complication information in open and key-hole surgery, "only one" is based on those study with reports only in one of the two groups (open or key-hole surgery), and "all" is a merger of "both" and "only one"

binary and the outcome per study report not a proportion but rather a rate. This suggests to have the binomial or beta-binomial not the primary choice although it may be so in other applications. Of course, the Poisson model is not the only possible rate model for offset settings; here an alternative could be the negative-binomial distributions. In any case, the arguments of fusing likelihoods would be identical. In addition, we argue that the mixed Poisson model that we have used here and which uses a random effect for the factor study, provides quite a flexible model.

Another issue is how the situation studied here relates to network-meta-analysis. In the latter we are looking at a collection of studies which provide different treatment or intervention comparisons such as treatment A with treatment B, treatment B with treatment C or treatment A with treatment C. In our situation here, we have reports which provide outcome information on one treatment but *no* comparison to the comparator which is the crucial difference.

It remains in the debate how much information can be gained from reports providing only one intervention outcome, in particular, for comparative analysis. We have indicated that gain can be reached, but it is limited. In addition, it is more appropriate from the statistical perspective to have all available information included in the analysis. Clearly, there is no doubt to use all report information if interest is in *absolute risk*, whether there is one-group information or two-group information per study. Of course, there is then

also the question how this information could be combined, but we leave this for another discussion.

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