Interval estimation of risk differences based upon independent interval estimates of the relative risk and the baseline risk

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Outline

- Background:
  Interval estimation of RD based upon RR and BR

- Currently used approaches: Cochrane, GRADE

- (Enhanced) MOVER-R

- Example

- Discussion

- Conclusions

- References

Background

- Relative and absolute effect measures are used to assess the effect of interventions

- Binary data:
Relative measures: **RR**, OR, (RRR, ROR)
Absolute measures: **RD** (ARR), NNT (NNTB, NNTH)

- Adverse binary outcome:
Risk in control group: Baseline risk (**BR**)
Risk in intervention group: Intervention risk (IR)

- **RR = IR / BR**

- $\textbf{RD} = \text{IR} - \text{BR} = \textbf{BR} \times \textbf{(RR} - \textbf{1)}$

- Beneficial intervention: RR < 1 , RD < 0
Harmful intervention: RR > 1 , RD > 0

Background

Cochrane Handbook for
Systematic Reviews of Interventions

Version 5.1.0
[updated March 2011]
Editors: Julian PT Higgins and Sally Green

THE COCHRANE COLLABORATION®

- "... relative measures of effect are more consistent than absolute measures of effect ..."

- "… meta-analyses should generally use either a risk ratio or an odds ratio as a measure of effect …"

- "For any assumed control group risk, it is possible to estimate a corresponding intervention group risk from the meta-analytic risk ratio or odds ratio."

- "… Upper and lower confidence limits for the corresponding intervention risk are obtained by replacing RR or OR by their upper and lower confidence limits …"

'Summary of findings' table:

Outcome	Relative effect (95% CI)	Assumed risk control group	Corresponding risk intervention group (95% CI)	Absolute effect (95% CI)	…
Pain	RR 1.02 (0.85 to 1.22)	Low risk[1] 280 per 1000	Low risk[1] 286 per 1000 (238 to 342)	RD=0.006 (−0.042 to 0.062)	…
		High risk[2] 480 per 1000	High risk[2] 490 per 1000 (408 to 586)	RD=0.01 (−0.072 to 0.106)	
…	…	…	…	…	…

- The confidence intervals of IR and RD take only the uncertainty of the RR estimate into account

- OK, if BR is considered as fixed constant

- However, if BR is estimated from data, the corresponding uncertainty should be taken into account!

Currently used approach by GRADE

BMJ

RESEARCH METHODS & REPORTING

Uncertainties in baseline risk estimates and confidence in treatment effects

The GRADE system provides a framework for evaluating how risk of bias, publication bias, imprecision, inconsistency, and indirectness may reduce confidence in estimates of relative effects of interventions on outcomes. However, GRADE and all other systems for rating confidence in effect estimates do not fully address uncertainty in baseline risk and its impact on confidence in absolute estimates of treatment effect. In this article the authors examine factors that may reduce confidence in estimates of baseline risk and thus estimates of absolute treatment benefit

Currently used approach by GRADE

- Usual calculation of confidence intervals for RD take into account the uncertainty of RR estimate only

- Spencer et al. (2012) suggest that the confidence in estimates of baseline risks is subject to the same issues as evidence for relative effects of a treatment strategy

- For illustration, Spencer et al. (2012) used an ad hoc approach of directly combining the confidence limits for BR and RR, i.e. combining LL of BR with UL of RR and vice versa

- *"We are not yet ready to offer specific guidance on how to rate down confidence in estimates of baseline risk."*

MOVER-R

- To describe the confidence in absolute treatment effects use of qualitative down-rating procedures is NOT required

- For the calculation of confidence intervals for RD taking the uncertainties of both the RR and BR estimates into account, a quantitative procedure is available: **MOVER-R**

Interval estimation of risk differences based upon independent interval estimates of the relative risk and the baseline risk
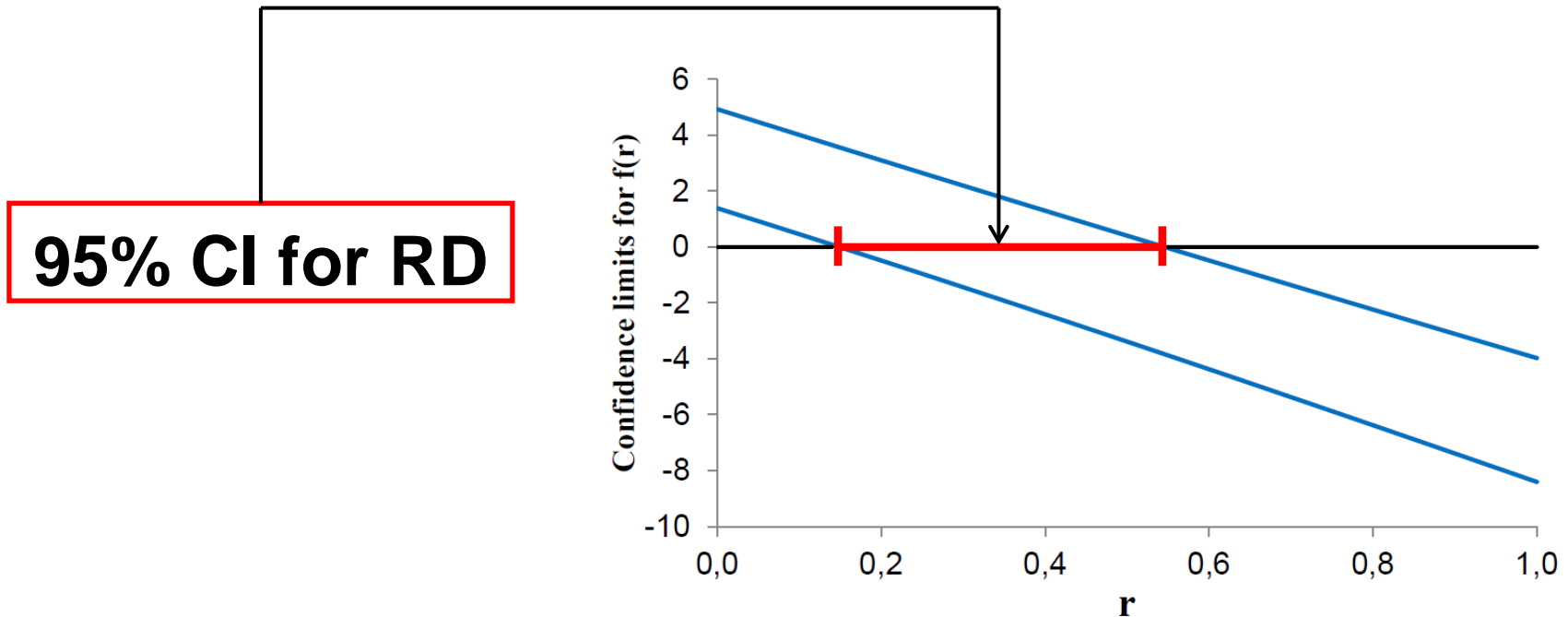
MOVER

- MOVER: Method of variance estimates recovery

- General approach to calculate confidence intervals (CIs) for sums and differences of 2 independently estimated quantities (Zou & Donner 2008, Newcombe 2012)

- 2 independently estimated parameters: $\hat{\theta}_1, \hat{\theta}_2$

- 95% CIs for θ_1, θ_2: $[L_1, U_1]$, $[L_2, U_2]$

- 95% CI for $\theta_1 + \theta_2$: $[L, U]$ with

$$L = \hat{\theta}_1 + \hat{\theta}_2 - \sqrt{\left(\hat{\theta}_1 - L_1\right)^2 + \left(\hat{\theta}_2 - L_2\right)^2}$$

$$U = \hat{\theta}_1 + \hat{\theta}_2 + \sqrt{\left(U_1 - \hat{\theta}_1\right)^2 + \left(U_2 - \hat{\theta}_2\right)^2}$$

MOVER-R

- Different versions of general MOVER approach (Newcombe 2012):

  - MOVER-S for sums
  - MOVER-D for differences
  - MOVER-L for applications with log transformation
  - MOVER-R for ratios and products

- MOVER-R developed by Donner & Zou (2012) yields meaningful results only if RR and corresponding confidence limits are below 1 or above 1

- A enhanced version of MOVER-R yielding meaningful results also if the CI of RR spans 1 is developed by Newcombe (2013)

MOVER-R

- MOVER-R according to Newcombe (2013) complex

- $\theta_1 = RR - 1, \ \theta_2 = 1/BR \ \Rightarrow \ RD = \theta_1/\theta_2$

- $f(r) = \theta_1 - r\theta_2 \ , \ r = RD \Rightarrow f(r) = 0$

- CI for RD = range of r-values for which the interval includes 0

95% CI for RD

MOVER-R

- Complete MOVER-R approach according to Newcombe (2013) is of closed form

- But contains a lot of formulae with square roots etc. ...

- Excel spreadsheet **"RD from BR and RR.xls"** available

- http://medicine.cf.ac.uk/primary-care-public-health/resources/

- http://ebm.bmj.com/content/early/2013/08/22/eb-2013-101340

RD from BR and RR.xls

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	Arbeitsmappenansichten		Anzeigen		Zoom		Fe

B34	▼	f_x	0,041			

	A	B	C	D	E	F	G
23	Error codes are displayed for the confidence limits if these conditions are violated.						
24	Entered confidence limits for BR below 0 or above 1 are truncated to 0 or 1.						
25							
26	Also, when BR and RR are large, the calculated RD and its confidence limits may be >=1.						
27	If this is a possibility, the RR based model may be inappropriate and an OR based model may be preferable.						
28	If the calculated RD >= 1, a warning is displayed and error codes are displayed for both confidence limits.						
29	Otherwise, a calculated upper limit >=1 is truncated and a warning displayed.						
30							
31	To perform these calculations, replace values in **bold** as appropriate.						
32							
33	**Input data:**	Estimate	Lower limit	Upper limit			
34	Baseline risk (BR)	0,041	0,011	0,137			
35	Relative risk (RR)	0,36	0,2	0,67			
36							
37	Input data validity check	WAHR					
38							
39	**Results:**	Estimate	Lower limit	Upper limit			
40	Risk difference (RD)	-0,0262	-0,0888	-0,0058			
41							

Methods for example

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(1) Accounting only for **uncertainty of RR** estimate
(as currently used by Cochrane and GRADE)

(2) Accounting only for **uncertainty of BR** estimate

(3) MOVER-R
(takes uncertainties of RR and BR estimates into account)

(4) Ad hoc approach of directly combining the confidence limits for BR and RR
(as used by Spencer et al. (2012) for illustration)

Example

Beneficial intervention (Spencer et al. 2012)

- Use of low dose, low molecular heparin (LMWH) to prevent venous thromboembolytic events in women undergoing assisted reproduction who develop severe ovarian hyperstimulation syndrome

- From a meta-analysis:
  RR = 0.36 with 95% CI $[\mathbf{0.20}, \mathbf{0.67}]$

- From an independent small study (Wilson score method):
  BR = 2/49 = **0.041** with 95% CI $[\mathbf{0.011}, \mathbf{0.137}]$

- **RD =** $0.041 \times (0.36 - 1) = -\mathbf{0.026}$

- Use of LMWH is estimated to prevent **26** venous thromboembolytic events **per 1000 women** treated

Example

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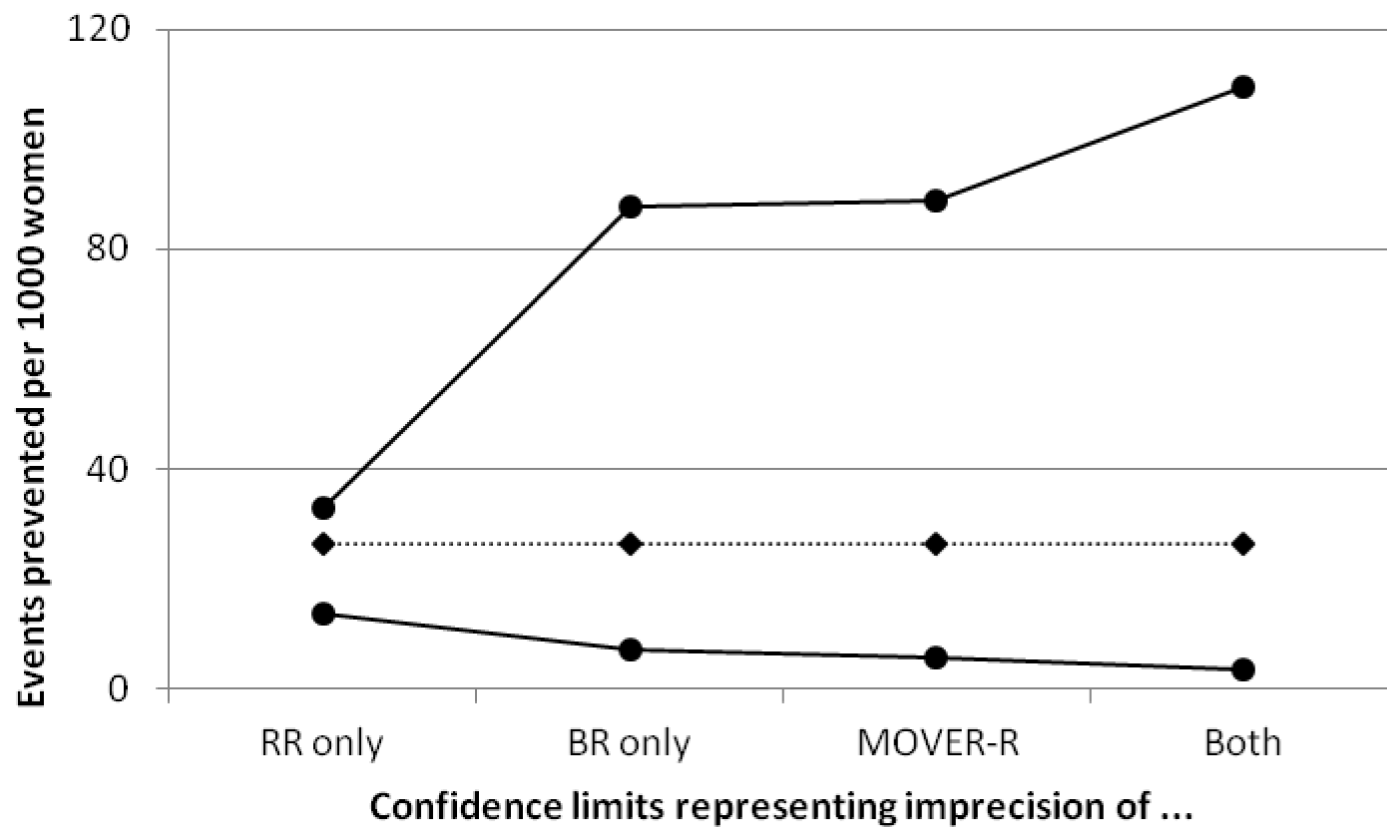Institute for Quality and Efficiency in Health Care

95% CIs for number of prevented events:

- Method (1): 13 to 32 events   (RR only)

- Method (2):   7 to 88 events   (BR only)

- **Method (3): 6 to 89 events   (MOVER-R)**

- Method (4):   4 to 110 events   (ad hoc approach)

In this example, the BR estimate is the dominant source of imprecision.

Example

- Method (1) inadequate (CI much too narrow)
- Method (4) unnecessarily too wide

Discussion 1

- MOVER-R appropriately accounts for the estimation uncertainties of RR and BR (Newcombe & Bender, 2013)

- Can be used if RR and BR are estimated independently

- Situations where RR and BR estimates are not independent:

- One single study:

  - MOVER-R should not be used

  - CI for RD should be calculated directly from 2×2 table (i.e. by means of the Wilson score method)

- Meta-analysis without independent BR estimate:

  - If appropriate: Use RD as effect measure

  - Use meta-analytic methods to calculate a pooled RD

Discussion 2

- <u>Difficult situation:</u>
    - RR from meta-analysis
    - BR is the median or mean of control group risks of the same studies

- MOVER-R cannot be used

- Calculate CI for RD by means of resampling methods

- Consider BR as fixed constant and use method (1) as currently applied by Cochrane and GRADE

- Present the results with clear information that BR is considered as fixed

Discussion 3

- <u>Effect measure is OR rather that RR:</u>

  - OR from meta-analysis
  - BR from independent study

- MOVER-R cannot be used
  (because OR and BR are interlocked)

- If adequate and possible:
  Meta-analysis with RR and apply MOVER-R

- If use of OR is the only choice:
  Iterative procedure "Propagating Imprecision" (PropImp)
  can be used (Newcombe 2012)

- Implementation of PropImp in Excel possible
  (Newcombe 2012)

Conclusions

- Neglecting the uncertainty of BR or RR estimates leads to confidence intervals which are too narrow

- If RR and BR are independently estimated the enhanced MOVER-R approach according to Newcombe (2013) should be used in practice

- A free Excel spreadsheet is available for the required MOVER-R computations

- If OR is used as effect measure the PropImp procedure according to Newcombe (2012) can be used

- No simple solution is yet available for the situation that RR (or OR) is estimated by a meta-analysis and BR is given by the median of the control group risks of the same studies

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