Dealing with rare events in Cochrane reviews

Afroditi Kanellopoulou

Statistics Editor

Methods Support Unit

Cochrane CET

akanellopoulou@cochrane.org

Trusted evidence.
Informed decisions.
Better health.

Structure of session

- Background
- Rare events in Cochrane reviews
- Statistical approaches for analyzing rare outcomes
  - Standard meta-analytical models and their limitations
  - Alternative meta-analytical models
- Take home messages
- Discussion and questions

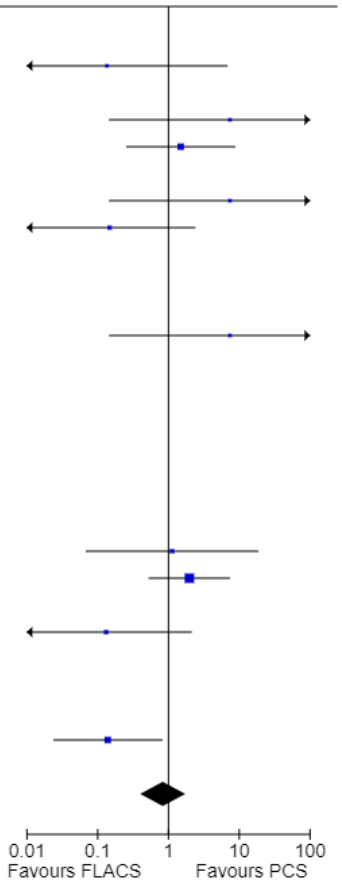
Background

- No globally accepted definition of what constitutes a rare event
  - Small number of events (even zero) is observed in the studies at hand
  - Outcome risk <1% (or, even <0.1%)
- Common issue when studying important safety dichotomous outcomes (e.g. different types of adverse effects)
- Meta-analysis (MA) is a powerful tool for synthesizing individual studies (usually underpowered to detect any treatment effects due to rare outcomes) and increase the overall statistical power

Background

Study or Subgroup	FLACS Events	FLACS Total	PCS Events	PCS Total	Weight	Peto odds ratio Peto, Fixed, 95% CI
Chee 2021	0	45	0	48		Not estimable
Conrad-Hengerer 2013 (1)	0	73	1	73	3.5%	0.14 [0.00 , 6.82]
Conrad-Hengerer 2014 (1)	0	104	0	104		Not estimable
Conrad-Hengerer 2015 (1)	1	100	0	100	3.5%	7.39 [0.15 , 372.38]
Day 2020	3	391	2	389	17.3%	1.49 [0.26 , 8.62]
Donnenfeld 2018	0	15	0	15		Not estimable
Dzhaber 2020 (1)	1	67	0	67	3.5%	7.39 [0.15 , 372.38]
Hansen 2020	0	64	2	71	6.9%	0.15 [0.01 , 2.39]
Hida 2017	0	200	0	200		Not estimable
Kovacs 2014	0	40	0	39		Not estimable
Kránitz 2012	0	20	0	25		Not estimable
Krarup 2021 (1)	1	34	0	34	3.5%	7.39 [0.15 , 372.38]
Liu 2021 (1)	0	78	0	78		Not estimable
Mursch-Edlmayr 2017 (1)	0	50	0	50		Not estimable
Nagy 2011	0	54	0	57		Not estimable
Nagy 2014	0	20	0	20		Not estimable
Pahlitzsch 2018	0	191	0	147		Not estimable
Pajic 2017	0	68	0	62		Not estimable
Panthier 2017 (1)	0	33	0	33		Not estimable
Reddy 2013	1	56	1	63	6.9%	1.13 [0.07 , 18.31]
Roberts 2019	6	200	3	200	30.8%	1.97 [0.53 , 7.39]
Schargus 2015 (1)	0	37	0	37		Not estimable
Schweitzer 2020	0	704	2	685	7.0%	0.13 [0.01 , 2.10]
Vasvada 2019	0	91	0	91		Not estimable
Yu 2015	0	25	0	29		Not estimable
Yu 2016	0	19	0	20		Not estimable
Zhang 2016	0	153	5	161	17.2%	0.14 [0.02 , 0.81]
Total (95% CI)		**2932**		**2898**	**100.0%**	**0.83 [0.40 , 1.72]**
Total events:	13		16			

Heterogeneity: Chi² = 13.66, df = 9 (P = 0.14); I² = 34%
Test for overall effect: Z = 0.50 (P = 0.62)
Test for subgroup differences: Not applicable



- 27 studies overall
- Maximum number of events per arm: 6 (Roberts 2019)
- 17 ‘double-zero’ studies
- 10 studies contributed to the summary estimate

Rare events in Cochrane reviews

- In a sample of 480 Cochrane reviews,
  - 35% did an adverse events MA
  - ~30% of the MAs had at least one study with zero events in one arm
  - Most common summary estimates:
    - Peto's odds ratio
    - Mantel-Haenszel odds ratio
    - Mantel-Haenszel risk ratio
    - Risk difference

Statistical Methods in Medical Research 2009; **18**: 421–432

Meta-analyses of safety data: a comparison of exact versus asymptotic methods

Ben Vandermeer, Liza Bialy, Nicola Hooton, Lisa Hartling, Terry P Klassen, University of Alberta Evidence Based Practice Centre, Alberta Research Centre for Health Evidence, **Bradley C Johnston** University of Alberta, Department of Medicine and **Natasha Wiebe** University of Alberta Clinical Nephrology Research Group

Rare events in Cochrane reviews

- In a sample of 4,177 rare events MAs included in Cochrane reviews, only 12% had sufficient power (≥80%) to detect a relative risk reduction of 50%
- For MAs of rare events, a much larger number of studies was needed to ensure sufficient power

Journal of Clinical Epidemiology 131 (2021) 113–122

ORIGINAL ARTICLE

Many meta-analyses of rare events in the Cochrane Database of Systematic Reviews were underpowered

Pengli Jia[a], Lifeng Lin[b], Joey S.W. Kwong[c], Chang Xu[d,*]

[a]School of Management, Shanxi Medical University, Taiyuan, China
[b]Department of Statistics, Florida State University, Tallahassee, FL, USA
[c]Global Health Nursing, St. Luke's International University, Tokyo, Japan
[d]Department of Population Medicine, College of Medicine, Qatar University, Doha, Qatar

Accepted 23 November 2020; Published online 30 November 2020

Standard meta-analytical models

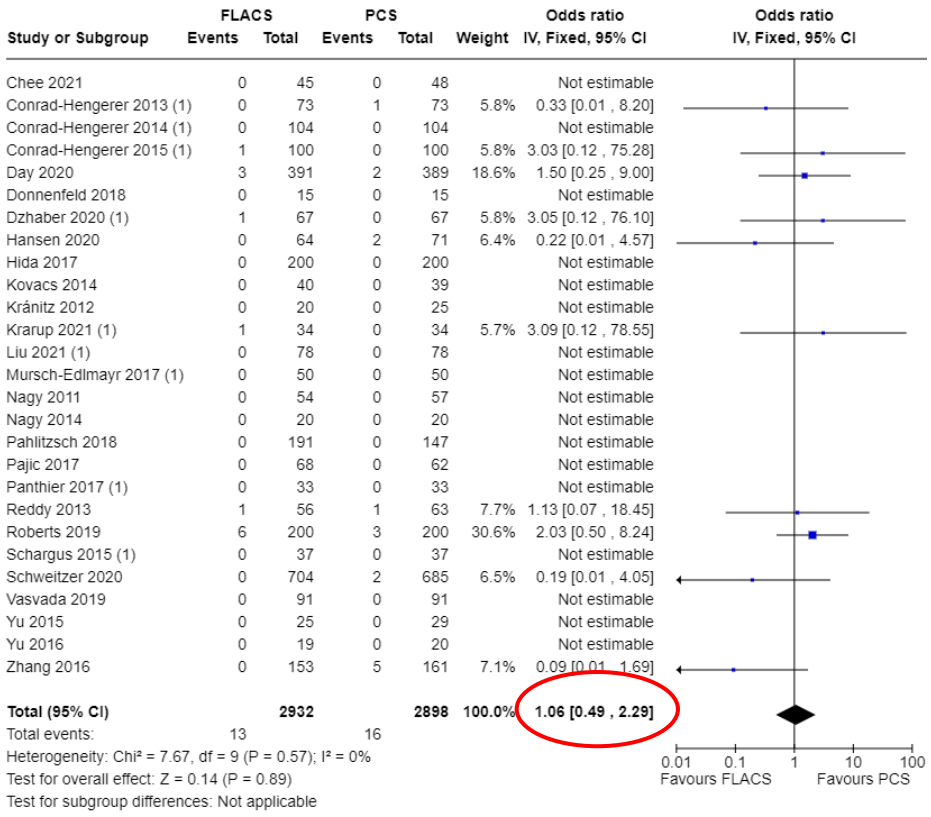
- Approaches available in RevMan:
  - Fixed- and random-effects inverse-variance (IV) methods
  - Mantel-Haenszel (MH) method
  - Peto's method

Cochrane

Fixed- and random-effects IV methods

- Estimate of the intervention effect and its standard error from each study
- A **fixed-effect MA** is valid under an assumption that all effect estimates are estimating the same underlying intervention effect
  - $\mu_{IV-FE} = \frac{\sum_{i=1}^{k} w_i y_i}{\sum_{i=1}^{k} w_i}$, where $w_i = \frac{1}{SE_i^2}$
- A **random-effects MA** (DerSimonian & Laird) assumes that the different studies are estimating different, yet related, intervention effects
  - $\mu_{IV-RE} = \frac{\sum_{i=1}^{k} w_{i*} y_i}{\sum_{i=1}^{k} w_{i*}}$, where $w_{i*} = \frac{1}{SE_i^2 + tau^2}$

Fixed- and random-effects IV methods



Study or Subgroup	FLACS Events	FLACS Total	PCS Events	PCS Total	Weight	Odds ratio IV, Fixed, 95% CI
Chee 2021	0	45	0	48		Not estimable
Conrad-Hengerer 2013 (1)	0	73	1	73	5.8%	0.33 [0.01 , 8.20]
Conrad-Hengerer 2014 (1)	0	104	0	104		Not estimable
Conrad-Hengerer 2015 (1)	1	100	0	100	5.8%	3.03 [0.12 , 75.28]
Day 2020	3	391	2	389	18.6%	1.50 [0.25 , 9.00]
Donnenfeld 2018	0	15	0	15		Not estimable
Dzhaber 2020 (1)	1	67	0	67	5.8%	3.05 [0.12 , 76.10]
Hansen 2020	0	64	2	71	6.4%	0.22 [0.01 , 4.57]
Hida 2017	0	200	0	200		Not estimable
Kovacs 2014	0	40	0	39		Not estimable
Kránitz 2012	0	20	0	25		Not estimable
Krarup 2021 (1)	1	34	0	34	5.7%	3.09 [0.12 , 78.55]
Liu 2021 (1)	0	78	0	78		Not estimable
Mursch-Edlmayr 2017 (1)	0	50	0	50		Not estimable
Nagy 2011	0	54	0	57		Not estimable
Nagy 2014	0	20	0	20		Not estimable
Pahlitzsch 2018	0	191	0	147		Not estimable
Pajic 2017	0	68	0	62		Not estimable
Panthier 2017 (1)	0	33	0	33		Not estimable
Reddy 2013	1	56	1	63	7.7%	1.13 [0.07 , 18.45]
Roberts 2019	6	200	3	200	30.6%	2.03 [0.50 , 8.24]
Schargus 2015 (1)	0	37	0	37		Not estimable
Schweitzer 2020	0	704	2	685	6.5%	0.19 [0.01 , 4.05]
Vasvada 2019	0	91	0	91		Not estimable
Yu 2015	0	25	0	29		Not estimable
Yu 2016	0	19	0	20		Not estimable
Zhang 2016	0	153	5	161	7.1%	0.09 [0.01 , 1.69]
Total (95% CI)		**2932**		**2898**	**100.0%**	**1.06 [0.49 , 2.29]**
Total events:	13		16			

Odds ratio IV, Fixed, 95% CI

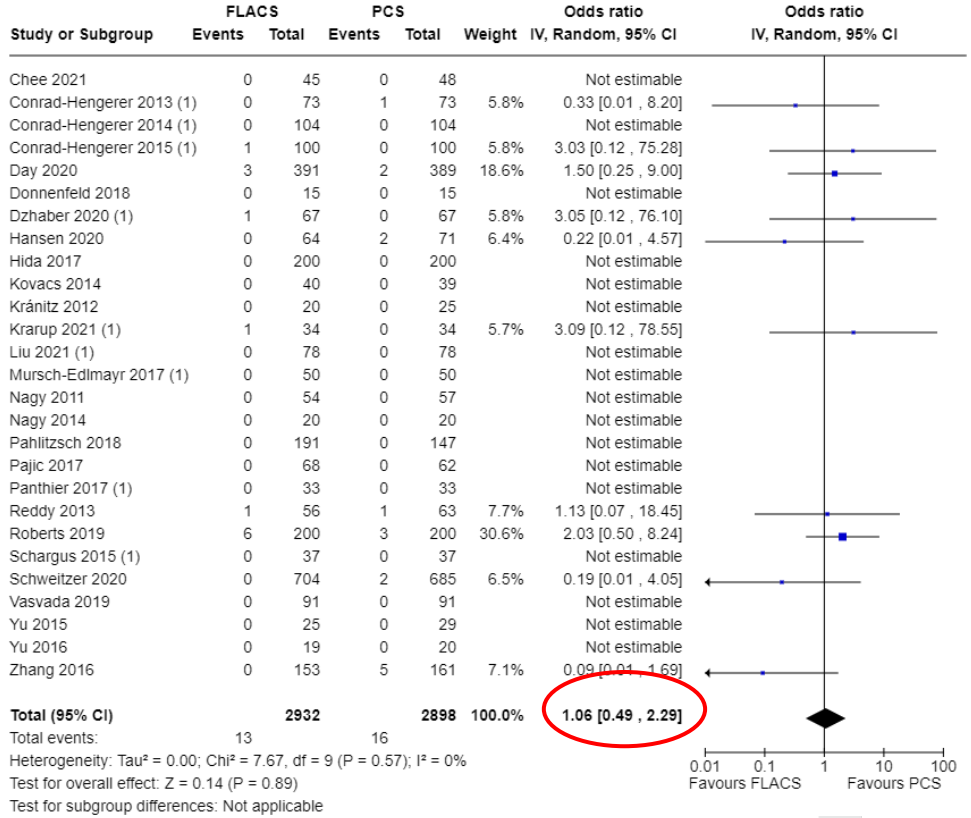
0.01 0.1 1 10 100

Favours FLACS Favours PCS

Heterogeneity: Chi² = 7.67, df = 9 (P = 0.57); I² = 0%

Test for overall effect: Z = 0.14 (P = 0.89)

Test for subgroup differences: Not applicable



Study or Subgroup	FLACS Events	FLACS Total	PCS Events	PCS Total	Weight	Odds ratio IV, Random, 95% CI
Chee 2021	0	45	0	48		Not estimable
Conrad-Hengerer 2013 (1)	0	73	1	73	5.8%	0.33 [0.01 , 8.20]
Conrad-Hengerer 2014 (1)	0	104	0	104		Not estimable
Conrad-Hengerer 2015 (1)	1	100	0	100	5.8%	3.03 [0.12 , 75.28]
Day 2020	3	391	2	389	18.6%	1.50 [0.25 , 9.00]
Donnenfeld 2018	0	15	0	15		Not estimable
Dzhaber 2020 (1)	1	67	0	67	5.8%	3.05 [0.12 , 76.10]
Hansen 2020	0	64	2	71	6.4%	0.22 [0.01 , 4.57]
Hida 2017	0	200	0	200		Not estimable
Kovacs 2014	0	40	0	39		Not estimable
Kránitz 2012	0	20	0	25		Not estimable
Krarup 2021 (1)	1	34	0	34	5.7%	3.09 [0.12 , 78.55]
Liu 2021 (1)	0	78	0	78		Not estimable
Mursch-Edlmayr 2017 (1)	0	50	0	50		Not estimable
Nagy 2011	0	54	0	57		Not estimable
Nagy 2014	0	20	0	20		Not estimable
Pahlitzsch 2018	0	191	0	147		Not estimable
Pajic 2017	0	68	0	62		Not estimable
Panthier 2017 (1)	0	33	0	33		Not estimable
Reddy 2013	1	56	1	63	7.7%	1.13 [0.07 , 18.45]
Roberts 2019	6	200	3	200	30.6%	2.03 [0.50 , 8.24]
Schargus 2015 (1)	0	37	0	37		Not estimable
Schweitzer 2020	0	704	2	685	6.5%	0.19 [0.01 , 4.05]
Vasvada 2019	0	91	0	91		Not estimable
Yu 2015	0	25	0	29		Not estimable
Yu 2016	0	19	0	20		Not estimable
Zhang 2016	0	153	5	161	7.1%	0.09 [0.01 , 1.69]
Total (95% CI)		**2932**		**2898**	**100.0%**	**1.06 [0.49 , 2.29]**
Total events:	13		16			

Odds ratio IV, Random, 95% CI

0.01 0.1 1 10 100

Favours FLACS Favours PCS

Heterogeneity: Tau² = 0.00; Chi² = 7.67, df = 9 (P = 0.57); I² = 0%

Test for overall effect: Z = 0.14 (P = 0.89)

Test for subgroup differences: Not applicable

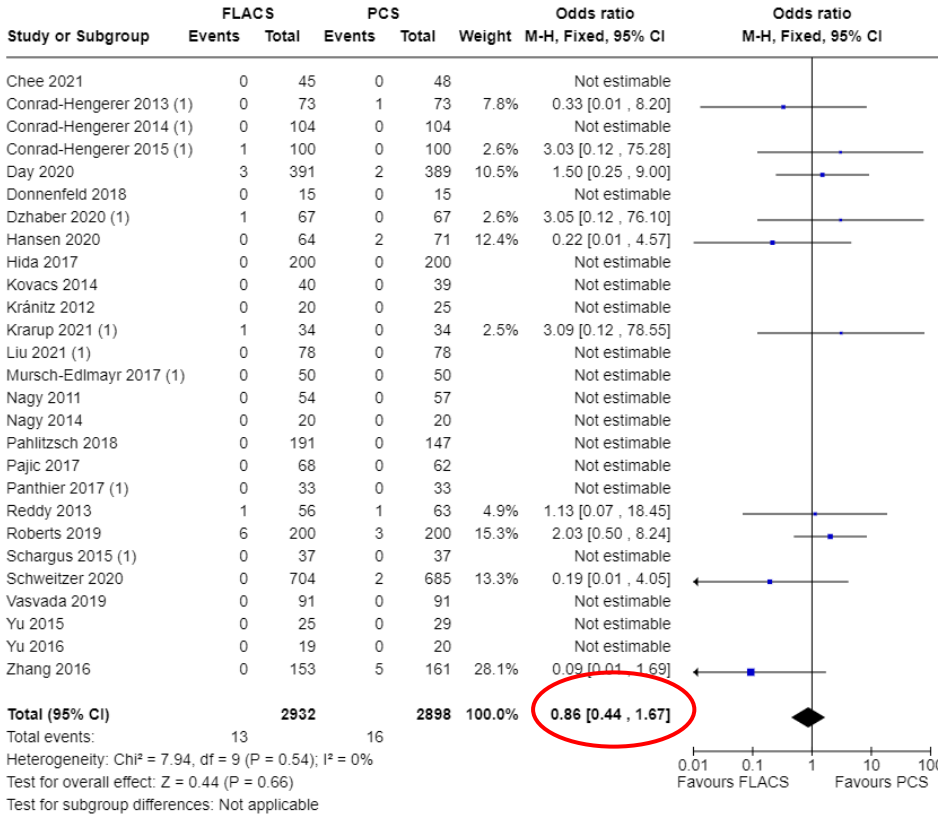
Mantel-Haenszel (MH) method

- A fixed-effect approach using a different weighting scheme that depends on which effect measure (e.g. risk ratio, odds ratio, risk difference) is being used
- No distributional assumption (i.e. a non-parametric approach)

	No. of events	No. of non- events	Total
Intervention	a	b	a+b
Control	c	d	c+d
Total	a+c	b+d	n=a+b+c+d

- $OR_i = \frac{a/b}{c/d} = \frac{ad}{bc}$, $OR_{MH} = \frac{\sum_{i=1}^{k} \frac{a_i d_i}{n_i}}{\sum_{i=1}^{k} \frac{b_i c_i}{n_i}}$

Mantel-Haenszel (MH) method



Study or Subgroup	FLACS Events	FLACS Total	PCS Events	PCS Total	Weight	Odds ratio M-H, Fixed, 95% CI
Chee 2021	0	45	0	48		Not estimable
Conrad-Hengerer 2013 (1)	0	73	1	73	7.8%	0.33 [0.01 , 8.20]
Conrad-Hengerer 2014 (1)	0	104	0	104		Not estimable
Conrad-Hengerer 2015 (1)	1	100	0	100	2.6%	3.03 [0.12 , 75.28]
Day 2020	3	391	2	389	10.5%	1.50 [0.25 , 9.00]
Donnenfeld 2018	0	15	0	15		Not estimable
Dzhaber 2020 (1)	1	67	0	67	2.6%	3.05 [0.12 , 76.10]
Hansen 2020	0	64	2	71	12.4%	0.22 [0.01 , 4.57]
Hida 2017	0	200	0	200		Not estimable
Kovacs 2014	0	40	0	39		Not estimable
Kránitz 2012	0	20	0	25		Not estimable
Krarup 2021 (1)	1	34	0	34	2.5%	3.09 [0.12 , 78.55]
Liu 2021 (1)	0	78	0	78		Not estimable
Mursch-Edlmayr 2017 (1)	0	50	0	50		Not estimable
Nagy 2011	0	54	0	57		Not estimable
Nagy 2014	0	20	0	20		Not estimable
Pahlitzsch 2018	0	191	0	147		Not estimable
Pajic 2017	0	68	0	62		Not estimable
Panthier 2017 (1)	0	33	0	33		Not estimable
Reddy 2013	1	56	1	63	4.9%	1.13 [0.07 , 18.45]
Roberts 2019	6	200	3	200	15.3%	2.03 [0.50 , 8.24]
Schargus 2015 (1)	0	37	0	37		Not estimable
Schweitzer 2020	0	704	2	685	13.3%	0.19 [0.01 , 4.05]
Vasvada 2019	0	91	0	91		Not estimable
Yu 2015	0	25	0	29		Not estimable
Yu 2016	0	19	0	20		Not estimable
Zhang 2016	0	153	5	161	28.1%	0.09 [0.01 , 1.69]
Total (95% CI)		**2932**		**2898**	**100.0%**	**0.86 [0.44 , 1.67]**
Total events:	13		16			

Odds ratio M-H, Fixed, 95% CI

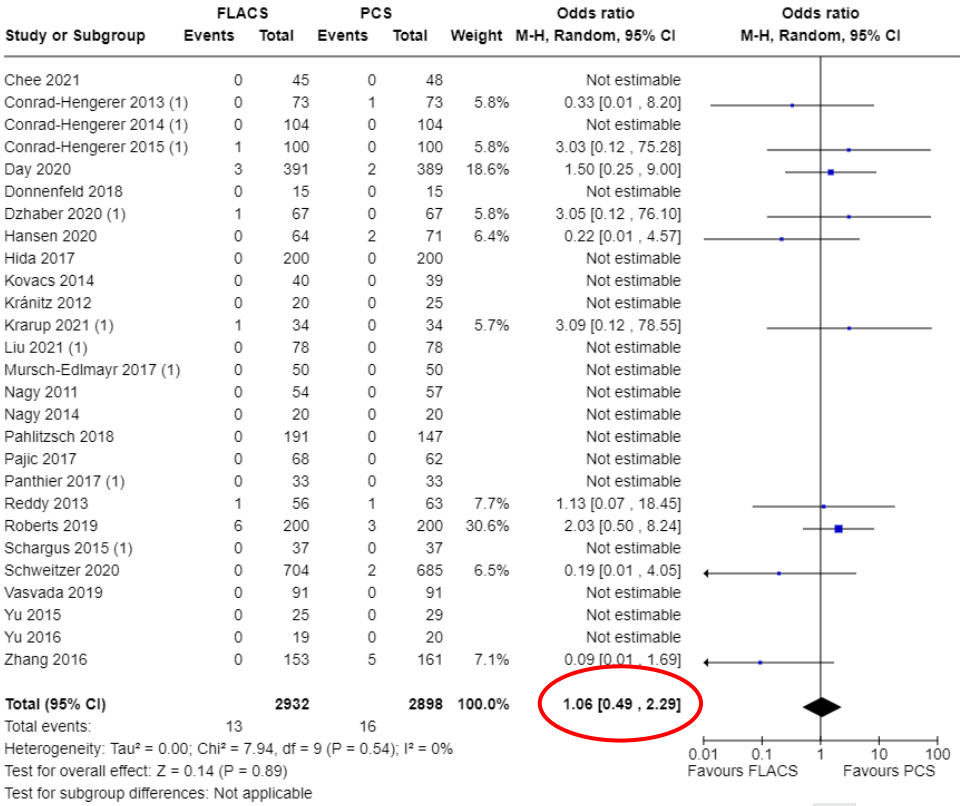
0.01 0.1 1 10 100

Favours FLACS Favours PCS

Heterogeneity: Chi² = 7.94, df = 9 (P = 0.54); I² = 0%

Test for overall effect: Z = 0.44 (P = 0.66)

Test for subgroup differences: Not applicable



Study or Subgroup	FLACS Events	FLACS Total	PCS Events	PCS Total	Weight	Odds ratio M-H, Random, 95% CI
Chee 2021	0	45	0	48		Not estimable
Conrad-Hengerer 2013 (1)	0	73	1	73	5.8%	0.33 [0.01 , 8.20]
Conrad-Hengerer 2014 (1)	0	104	0	104		Not estimable
Conrad-Hengerer 2015 (1)	1	100	0	100	5.8%	3.03 [0.12 , 75.28]
Day 2020	3	391	2	389	18.6%	1.50 [0.25 , 9.00]
Donnenfeld 2018	0	15	0	15		Not estimable
Dzhaber 2020 (1)	1	67	0	67	5.8%	3.05 [0.12 , 76.10]
Hansen 2020	0	64	2	71	6.4%	0.22 [0.01 , 4.57]
Hida 2017	0	200	0	200		Not estimable
Kovacs 2014	0	40	0	39		Not estimable
Kránitz 2012	0	20	0	25		Not estimable
Krarup 2021 (1)	1	34	0	34	5.7%	3.09 [0.12 , 78.55]
Liu 2021 (1)	0	78	0	78		Not estimable
Mursch-Edlmayr 2017 (1)	0	50	0	50		Not estimable
Nagy 2011	0	54	0	57		Not estimable
Nagy 2014	0	20	0	20		Not estimable
Pahlitzsch 2018	0	191	0	147		Not estimable
Pajic 2017	0	68	0	62		Not estimable
Panthier 2017 (1)	0	33	0	33		Not estimable
Reddy 2013	1	56	1	63	7.7%	1.13 [0.07 , 18.45]
Roberts 2019	6	200	3	200	30.6%	2.03 [0.50 , 8.24]
Schargus 2015 (1)	0	37	0	37		Not estimable
Schweitzer 2020	0	704	2	685	6.5%	0.19 [0.01 , 4.05]
Vasvada 2019	0	91	0	91		Not estimable
Yu 2015	0	25	0	29		Not estimable
Yu 2016	0	19	0	20		Not estimable
Zhang 2016	0	153	5	161	7.1%	0.09 [0.01 , 1.69]
Total (95% CI)		**2932**		**2898**	**100.0%**	**1.06 [0.49 , 2.29]**
Total events:	13		16			

Odds ratio M-H, Random, 95% CI

0.01 0.1 1 10 100

Favours FLACS Favours PCS

Heterogeneity: Tau² = 0.00; Chi² = 7.94, df = 9 (P = 0.54); I² = 0%

Test for overall effect: Z = 0.14 (P = 0.89)

Test for subgroup differences: Not applicable

Cochrane

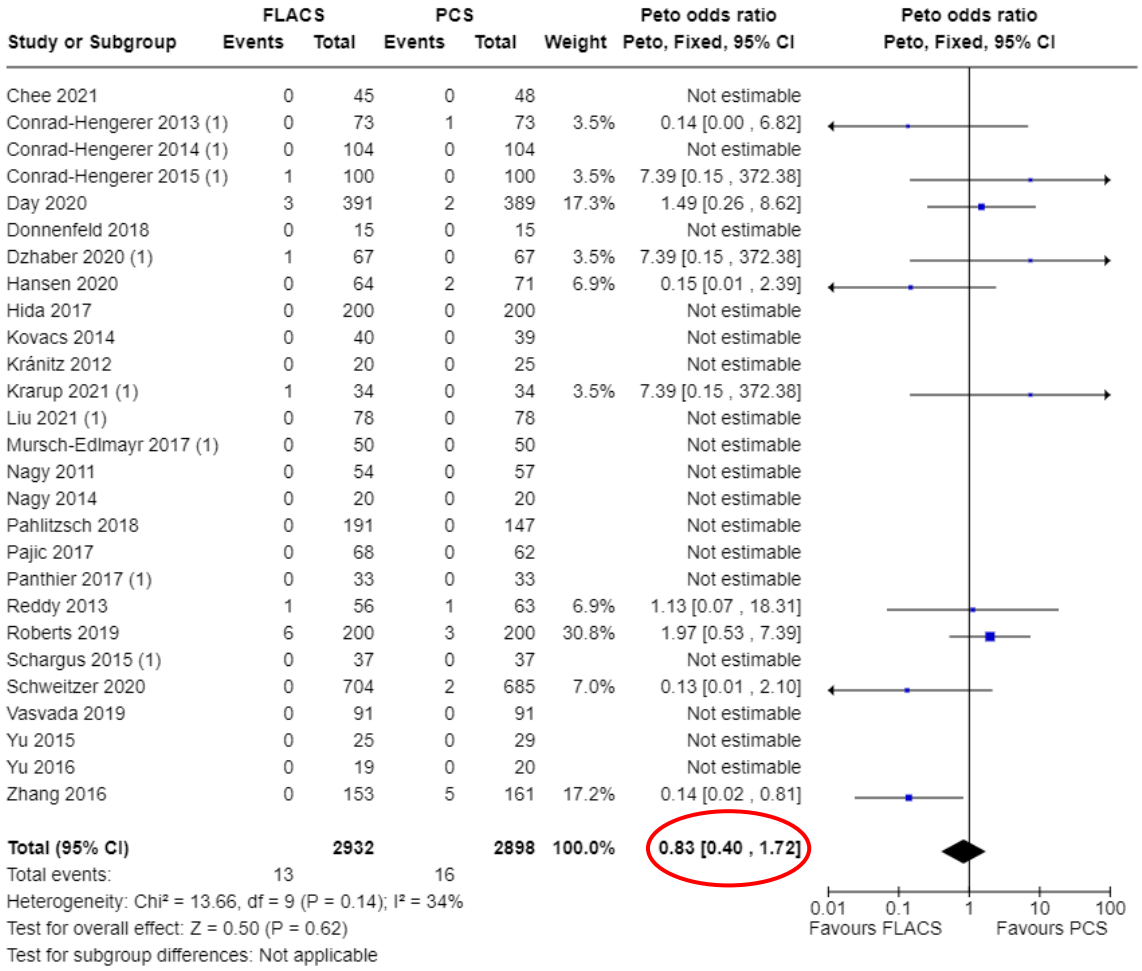
Peto's method

- A fixed-effect IV approach to combine odds ratios only
- Again, no distributional assumption

	No. of events	No. of non- events	Total
Intervention	a	b	a+b
Control	c	d	c+d
Total	a+c	b+d	n=a+b+c+d

- $\mu_{Peto} = exp\left(\frac{\sum_{i=1}^{k}(O_i - E_i)}{\sum_{i=1}^{k} V_i}\right)$, where $O_i = a$, $E_i = \frac{(a+b)(a+c)}{n}$, $V_i = \frac{(a+b)(c+d)(a+c)(b+d)}{n}$

Peto's method



Study or Subgroup	FLACS Events	FLACS Total	PCS Events	PCS Total	Weight	Peto odds ratio Peto, Fixed, 95% CI
Chee 2021	0	45	0	48		Not estimable
Conrad-Hengerer 2013 (1)	0	73	1	73	3.5%	0.14 [0.00 , 6.82]
Conrad-Hengerer 2014 (1)	0	104	0	104		Not estimable
Conrad-Hengerer 2015 (1)	1	100	0	100	3.5%	7.39 [0.15 , 372.38]
Day 2020	3	391	2	389	17.3%	1.49 [0.26 , 8.62]
Donnenfeld 2018	0	15	0	15		Not estimable
Dzhaber 2020 (1)	1	67	0	67	3.5%	7.39 [0.15 , 372.38]
Hansen 2020	0	64	2	71	6.9%	0.15 [0.01 , 2.39]
Hida 2017	0	200	0	200		Not estimable
Kovacs 2014	0	40	0	39		Not estimable
Kránitz 2012	0	20	0	25		Not estimable
Krarup 2021 (1)	1	34	0	34	3.5%	7.39 [0.15 , 372.38]
Liu 2021 (1)	0	78	0	78		Not estimable
Mursch-Edlmayr 2017 (1)	0	50	0	50		Not estimable
Nagy 2011	0	54	0	57		Not estimable
Nagy 2014	0	20	0	20		Not estimable
Pahlitzsch 2018	0	191	0	147		Not estimable
Pajic 2017	0	68	0	62		Not estimable
Panthier 2017 (1)	0	33	0	33		Not estimable
Reddy 2013	1	56	1	63	6.9%	1.13 [0.07 , 18.31]
Roberts 2019	6	200	3	200	30.8%	1.97 [0.53 , 7.39]
Schargus 2015 (1)	0	37	0	37		Not estimable
Schweitzer 2020	0	704	2	685	7.0%	0.13 [0.01 , 2.10]
Vasvada 2019	0	91	0	91		Not estimable
Yu 2015	0	25	0	29		Not estimable
Yu 2016	0	19	0	20		Not estimable
Zhang 2016	0	153	5	161	17.2%	0.14 [0.02 , 0.81]
Total (95% CI)		**2932**		**2898**	**100.0%**	**0.83 [0.40 , 1.72]**
Total events:	13		16			

Heterogeneity: Chi² = 13.66, df = 9 (P = 0.14); I² = 34%
Test for overall effect: Z = 0.50 (P = 0.62)
Test for subgroup differences: Not applicable

Cochrane

Summary of methods

Method	OR (95% CI)
Fixed-effect IV	1.06 (0.49-2.29)
Random-effects IV (DerSimonian & Laird)	1.06 (0.49-2.29)
Fixed-effect MH	0.86 (0.44-1.67)
Random-effects MH	1.06 (0.49-2.29)
Peto	0.83 (0.40-1.72)
CI; confidence interval, OR; odds ratio	

Poll: Which method would you choose for this review?

Limitations of standard meta-analytical models

- **In general, IV methods are not appropriate for MAs of rare events**
  - Use of a normal approximation of the true binomial likelihood (the 'large sample approximation') which does not work well when event rates are low
  - The estimation of the variance of random effects (heterogeneity) may be biased, which may lead to spuriously narrow confidence intervals

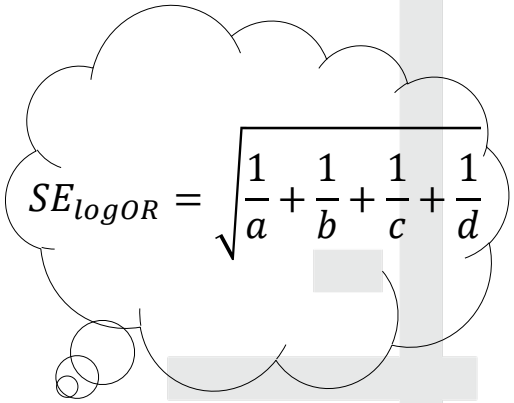
Limitations of standard meta-analytical models

- In simulations studies, Peto method gave the least biased summary estimate and best confidence interval coverage if:
  - There was no substantial imbalance between intervention and control group sizes
  - Treatment effects were not exceptionally large
- Peto is problematic when zero events occur in all arms of all studies

Limitations of standard meta-analytical models

- In other circumstances (i.e. event risks above 1%, very large effects, and meta-analyses where many studies are substantially imbalanced), the MH fixed-effect method should be preferred
  - But MH is also problematic when zero events exist for the same arm across the studies

Limitations of standard meta-analytical models



- Studies with zero events are excluded since calculation of treatment effects and their corresponding standard errors becomes impossible (it involves division by zero)
  - By default, RevMan does a continuity correction (adding 0.5) to studies with zero events *in only one arm*

Possible remedies

- Continuity correction
- Use of risk differences

Cochrane

Continuity correction

Method	Non-zero events in both arms (3 studies)	+Zero events in one arm (10 studies)	+Zero events in both arms (27 studies)
Fixed-effect IV	1.70 (0.61-4.74)	1.06 (0.49-2.29)	1.04 (0.57-1.90)
Random- effects IV	1.7 [illegible] 4)	1.06 (0.49-2.29)	1.04 (0.57-1.90)
Fixed-effect MH	0.83 ([illegible] .73)	0.86 (0.44-1.67)	0.91 (0.53-1.56)
Random-effects MH	1.7 [illegible] .61 [illegible] 4)	1.06 (0.49-2.29)	1.04 (0.57-1.90)
Peto	1.68 (0.63-4.52)	0.83 (0.40-1.72)	0.89 (0.50-1.59)

Continuity correction

- Simulation studies report excessively biased estimates after applying a 0.5 continuity correction, especially in fixed- and random-effects models
- Another method is to use non-fixed corrections (the continuity correction is different for each treatment arm of each study, and is inversely related to the size of the treatment arm) but it has been criticized as well

Cochrane

Use of risk differences

Method	OR (95% CI) (10 studies)	RD (95% CI) (27 studies)
Fixed-effect IV	1.06 (0.49-2.29)	-0.001 (-0.005-0.002)
Random-effects IV (DerSimonian & Laird)	1.06 (0.49-2.29)	-0.001 (-0.005-0.002)
Fixed-effect MH	0.86 (0.44-1.67)	-0.001 (-0.006-0.004)
Random-effects MH	1.06 (0.49-2.29)	-0.001 (-0.005-0.002)
Peto	0.83 (0.40-1.72)	-

CI; confidence interval, OR; odds ratio, RD: risk difference

- In the presence of rare events, risk difference methods have poor statistical properties (too wide intervals and low power), which makes them unsuitable for MA

Cochrane

Alternative meta-analytical models

- MA models using simple or penalized logistic regression
- Bayesian methods
- MA models using arcsine difference
- Beta-binomial model with correlated responses
- Exact methods based on combining CIs and p-value functions
- Bivariate binomial-normal model
- Non-central hypergeometric model
- Poisson-gamma models

Alternative meta-analytical models

- Simulation studies show:
  - Simple logistic regression performs similarly with the MH method with no continuity correction
  - In a Bayesian meta-analysis of rare events, the choice of prior distributions is very important as non-informative priors may dominate results
  - Beta-binomial with correlated responses can include studies with zero events in one or both arms, without continuity correction. It has been shown to perform well in various settings, when studies are balanced.

Alternative meta-analytical models

- Simulation studies show:
  - The use of arcsine difference as an effect measure tackles all problems associated with rare events in meta-analysis. But, difficult to interpret in clinical terms
  - Heterogeneity plays a significant role but this should not be a concern now!

Cochrane

Take home messages

- In presence of rare events,
  - MA might be the only way to investigate relevant outcomes
  - The IV models should be avoided
    - Assumption of within-studies normality does not hold
    - Biased estimates
  - Continuity correction should not be performed
  - Calculation of risk differences should be avoided
  - Peto's method and fixed-effect MH without continuity correction seem to work well under certain circumstances

Cochrane

Take home messages

- In presence of rare events,
  - Alternative meta-analytical models have been proposed which incorporate studies with zero events in one or both arms
  - Estimates will be inevitably imprecise
    - Results may be very sensitive to the choice of method used to analyze data
    - Sensitivity analyses should be done using a variety of pre-defined methods
    - Relative effects should be presented along with absolute event rates

Take home messages

- In presence of rare events,
  - When different methods lead to results with different clinical implications, results should be interpreted with caution. In such cases, results should be considered as hypothesis generating
  - Talk with a statistician!

Acknowledgments

Special thanks to Dr. Anna Chaimani and Dr. Theodoros Evrenoglou for the 2023 Cochrane Colloquium workshop on rare events MA

References

Deeks JJ, Higgins JPT, Altman DG (editors). Section 10.4.4 Meta-analysis of rare events. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.

Narayan A, Evans JR, O'Brart D, Bunce C, Gore DM, Day AC. Laser-assisted cataract surgery versus standard ultrasound phacoemulsification cataract surgery. Cochrane Database of Systematic Reviews 2023, Issue 6. Art. No.: CD010735. DOI: 10.1002/14651858.CD010735.pub3.

Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.

Efthimiou O. Practical guide to the meta-analysis of rare events. Evid Based Ment Health. 2018 May;21(2):72-76. doi: 10.1136/eb-2018-102911. Epub 2018 Apr 12.

Cochrane

References

Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med. 2004 May 15;23(9):1351-75. doi: 10.1002/sim.1761. Erratum in: Stat Med. 2006 Aug 15;25(15):2700.

Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Stat Med. 2007 Jan 15;26(1):53-77. doi: 10.1002/sim.2528.

Beisemann M, Doebler P, Holling H. Comparison of random-effects meta-analysis models for the relative risk in the case of rare events: A simulation study. Biom J. 2020 Nov;62(7):1597-1630. doi: 10.1002/bimj.201900379. Epub 2020 Jun 8.

Lane PW. Meta-analysis of incidence of rare events. Stat Methods Med Res. 2013 Apr;22(2):117-32. doi: 10.1177/0962280211432218. Epub 2012 Jan 4.

Kuss O. Statistical methods for meta-analyses including information from studies without any events-add nothing to nothing and succeed nevertheless. Stat Med. 2015 Mar 30;34(7):1097-116. doi: 10.1002/sim.6383. Epub 2014 Dec 1.

Efthimiou O. Statistics in pills: meta-analysis of rare events. Evid Based Ment Health. 2019 Aug;22(3):102. doi: 10.1136/ebmental-2019-300103. Epub 2019 Jul 13.

Cochrane

Discussion and questions