

Meta-analysis for zero-cases studies

Department of population medicine
Qatar University

Chang Xu



Background

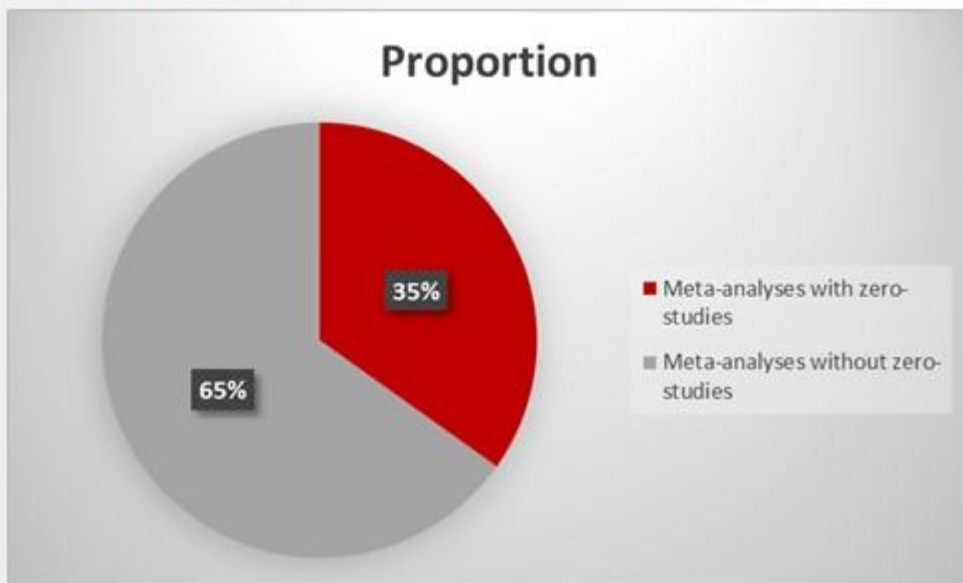
What is zero-cases studies? single-arm-zero vs. double-arm-zero

Study 1	Events	Non-events	Total
Intervention	0	b	n_1
Control	c	d	n_2
Study 2	Events	Non-events	Total
Intervention	a	b	n_1
Control	0	d	n_2
Study 3	Events	Non-events	Total
Intervention	0	b	n_1
Control	0	d	n_2

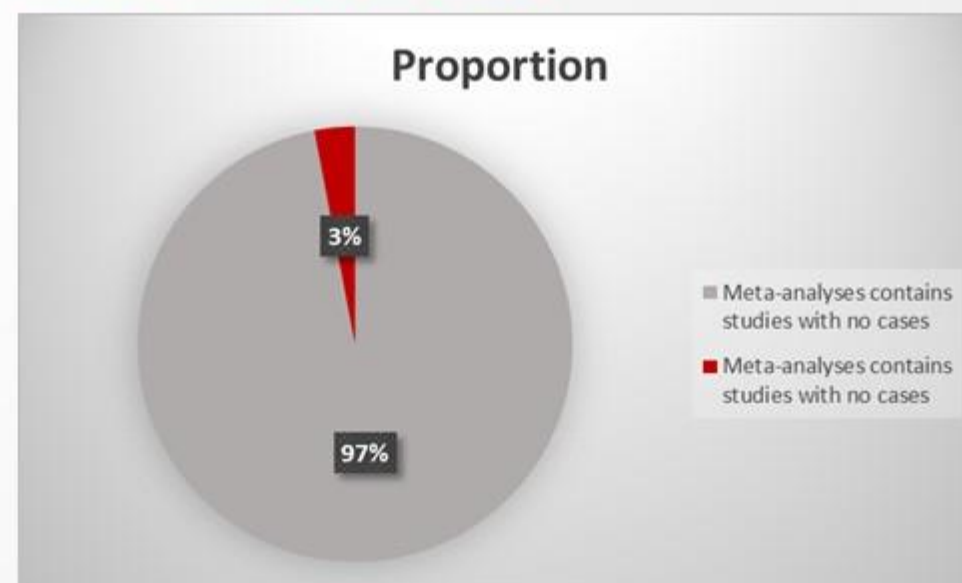
Background

Zero-cases studies are commonly seen in meta-analysis, especially for those with safety outcomes.

35% contains studies with zero cases
(21288/61090)



Of which, 3% contains studies with no cases
in both arms (658/21288)

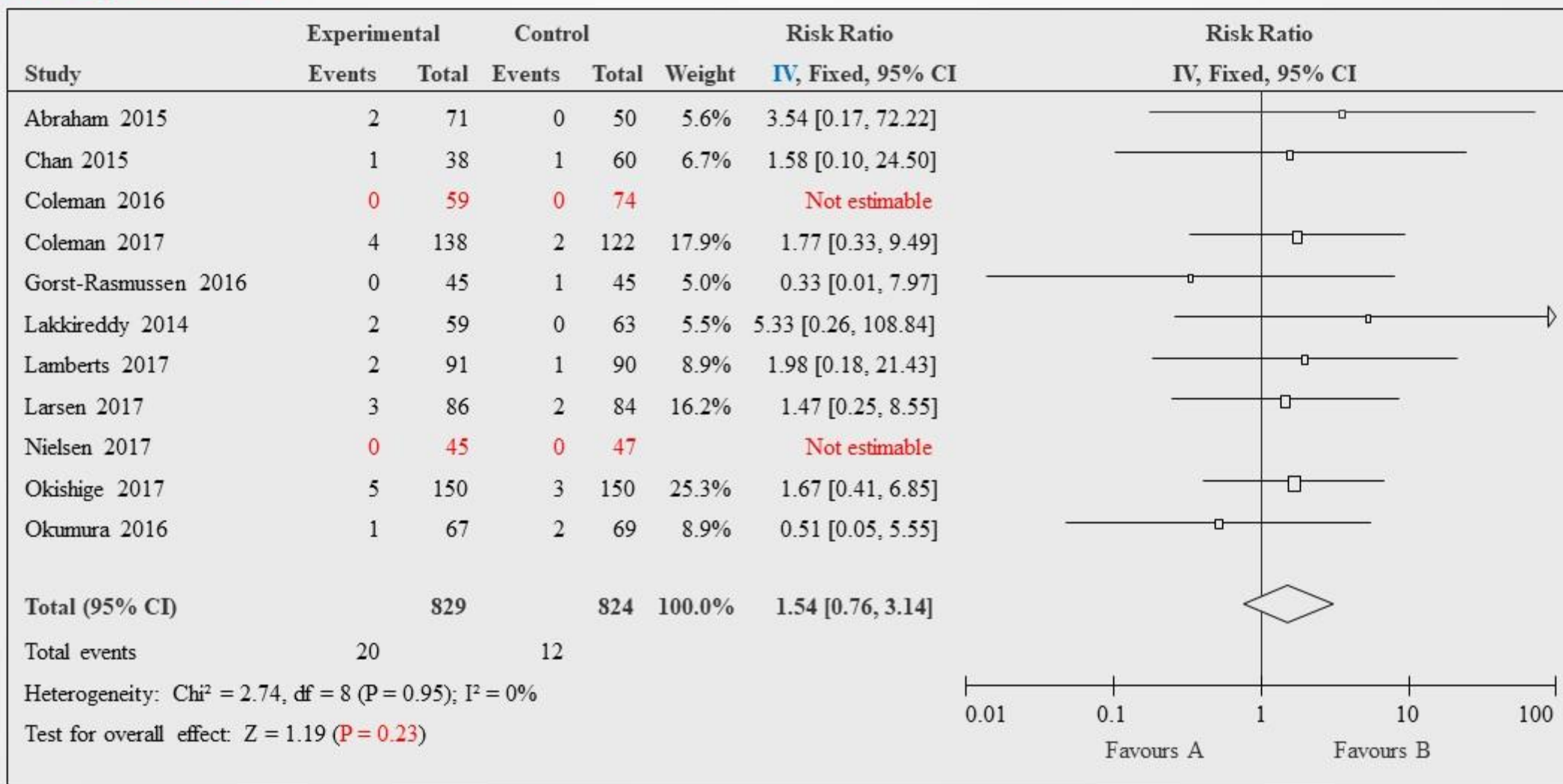


Data source: Cochrane database of systematic reviews (n=6781), 61090 meta-analyses



Background

For these meta-analyses, studies with no cases were routinely excluded from the synthesis.



Questions

Is this reasonable?



Whether studies with no cases are non-informative?

Yes



Excluding is reasonable

No



Excluding is reasonable too?



Q1: Whether studies with no cases are non-informative?

The identity of two meta-analytic likelihoods and the ignorability of double-zero studies

DANKMAR BÖHNING*

*Mathematical Sciences and Southampton Statistical Sciences Research Institute,
University of Southampton, Southampton SO17 1BJ, UK*

d.a.bohning@soton.ac.uk

PATARAWAN SANGNAWAKIJ

Department of Mathematics and Statistics, Thammasat University, Pathum Thani 12120, Thailand

SUMMARY

In meta-analysis, the conventional two-stage approach computes an effect estimate for each study in the first stage and proceeds with the analysis of effect estimates in the second stage. For counts of events as outcome, the risk ratio is often the effect measure of choice. However, if the meta-analysis includes many studies with no events the conventional method breaks down. As an alternative one-stage approach, a **Poisson regression model and a conditional binomial model** can be considered where no event studies do not cause problems. **The conditional binomial model** excludes double-zero studies, whereas this is seemingly not the case for the Poisson regression approach. However, **we show here that both models lead to the same likelihood inference and double-zero studies (in contrast to single-zero studies) do not contribute in either case to the likelihood.**

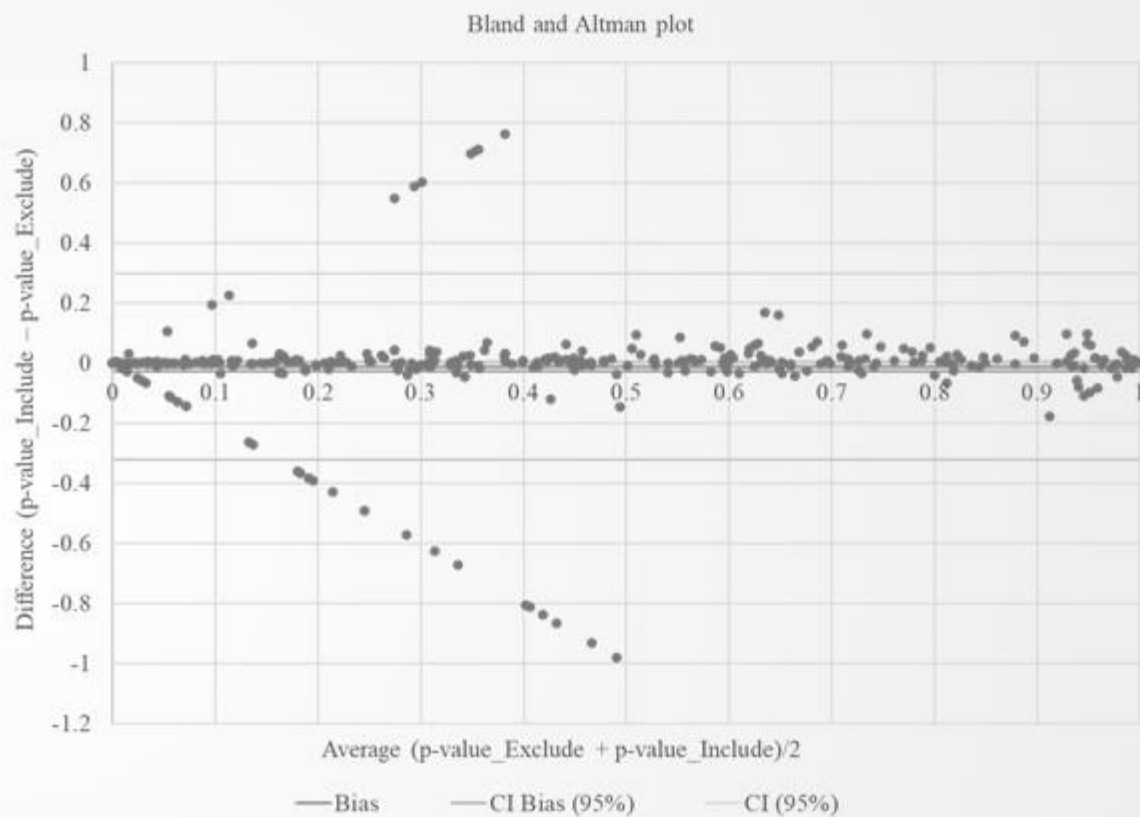
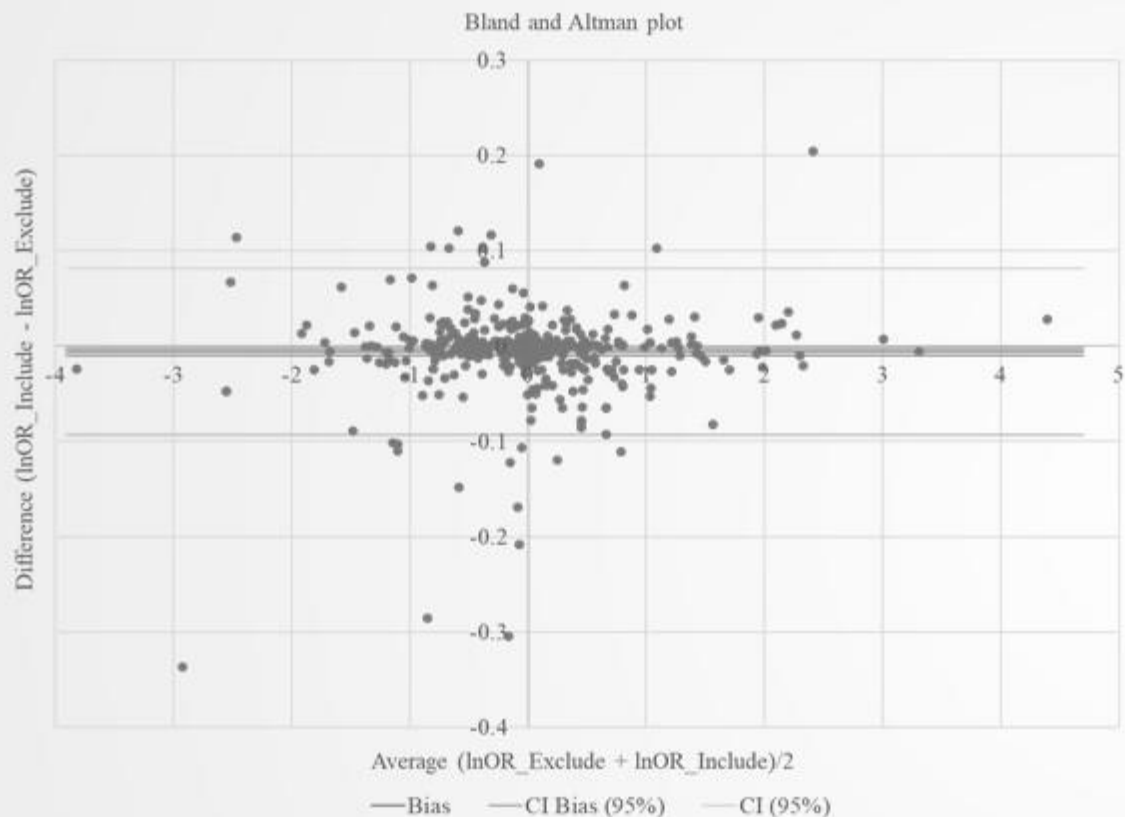
Q1: Whether studies with no cases are non-informative?

But how about marginal likelihood?

- Real-world Data from Cochrane reviews, and 442 meta-analyses with studies with no cases were eligible for analysis
- Repeat the meta-analyses: Including VS. Excluding
- **Generalized linear mixed model** for meta-analyses

Hypothesis: If non-informative, the results of including = excluding

Q1: Whether studies with no cases are non-informative?



Conclusion: whether double-zero studies contains information depends on the methods and assumption.

Xu C, Li L, Lin L, Chu H, Thabane L, Zou K, Sun X. Exclusion of studies with no events in both arms in meta-analysis impacted the conclusions. *J Clin Epidemiol.* 2020;123:91-99.

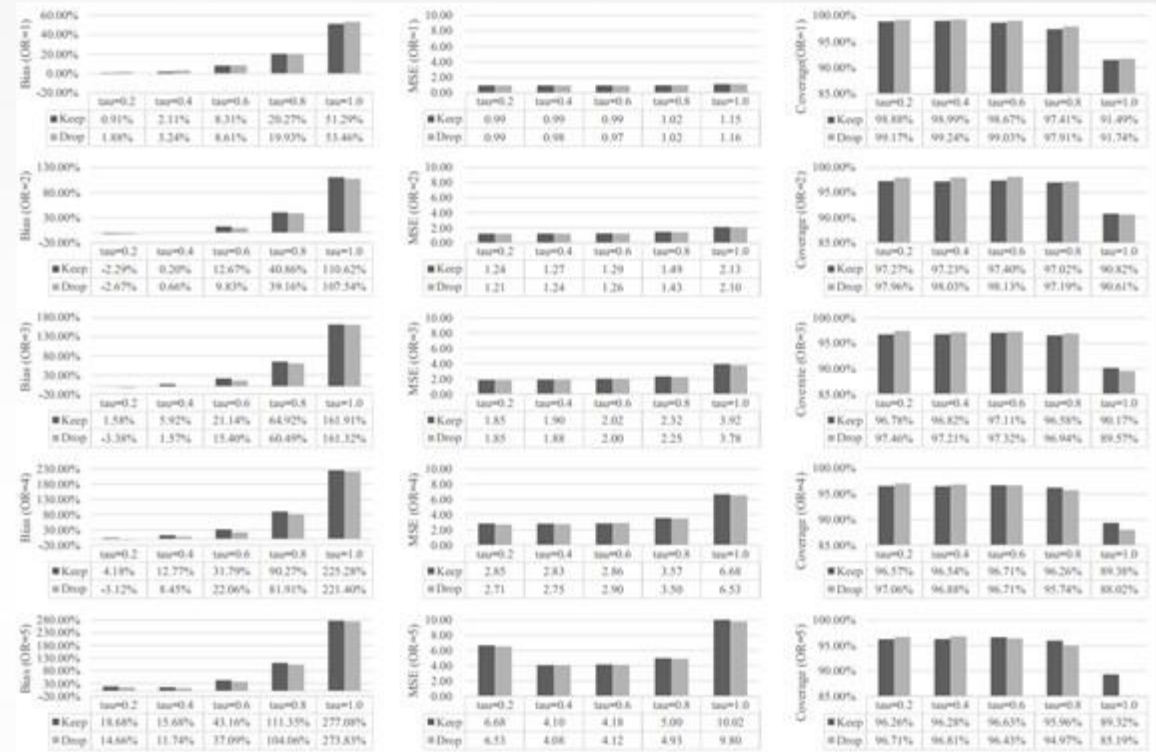
Q2: Exclusion is reasonable ?

One important concern

- **Double-zero studies facing large amount of random error.**
- **Suppose a trial with 1:1 design, the true incidence is 0.005 vs. 0.001 so the true OR is approach to 5.**
- **However, if the sample size is only 100 for each arm, then mostly the events observed in both arms are 0, which may biased the pooled results.**

Q2: Exclusion is reasonable ?

- Simulation
- 3 GLMMs (one-stage framework, without adding 0.5)
- Including VS. Excluding



Excluding DO NOT showed better performance than Including!

Xu C, Li L, Lin L, et al. Exclusion of studies with no events in both arms in meta-analysis impacted the conclusions. *J Clin Epidemiol.* 2020;123:91-99.

Xu C, Zhang C, Lin L, et al. The impact of studies with no events in both arms on meta-analysis of rare events: a simulation study using generalized linear mixed model. *Journal of Biopharmaceutical Statistics.* 2021, In Revision.

Q2: Exclusion is reasonable ?

Treating double-zero studies as non-informative leads to other problem

- **Systematic review authors routinely ignore double-zero studies.**
- **But double-zero studies may be caused by non-reporting bias, say, stakeholders tend to less report the adverse events.**
- **Which dismissed review authors to make efforts to get the true data.**

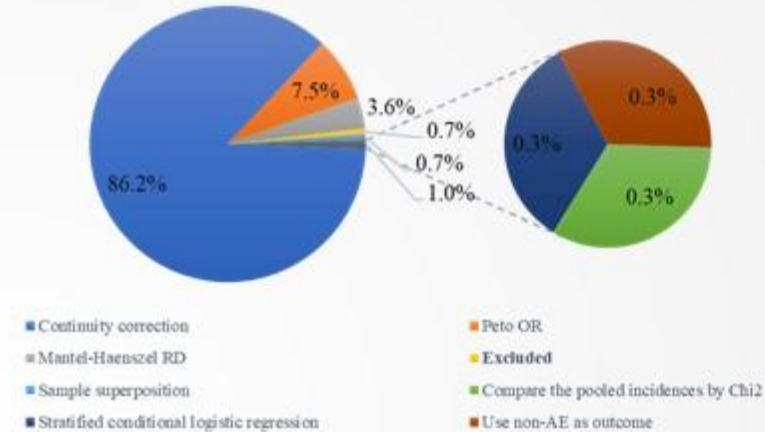
Saini P, Loke YK, Gamble C, Altman DG, Williamson PR, Kirkham JJ. Selective reporting bias of harm outcomes within studies: findings from a cohort of systematic reviews. *BMJ*. 2014; 349: g6501.

Empirical investigation

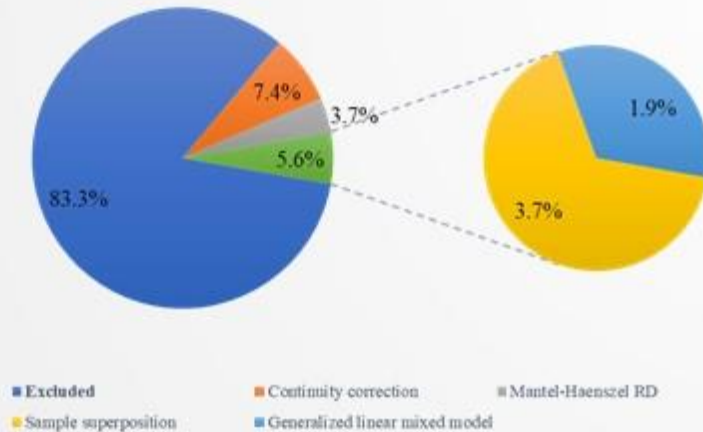
Methods dealing with single-arm-zero-events (2008-2011)



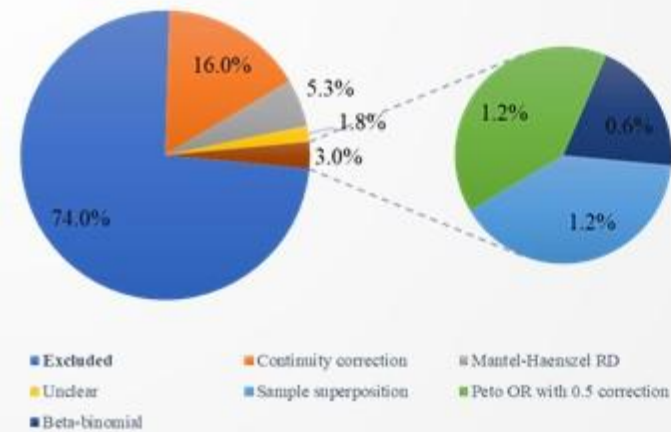
Methods dealing with single-arm-zero-events (2015-2020)



Methods dealing with double-arm-zero-events (2008-2011)



Methods dealing with double-arm-zero-events (2015-2020)



The majority (80%) of the systematic reviews authors treat studies with no events as non-informative, and simply excluded them from meta-analysis.



Sectional conclusions

- **Studies with no cases are not necessarily non-informative, which depends on the methods and assumptions.**
- **Simply treating studies with no cases is unreasonable, and things need to change**



What is the solution?

- ❑ **Conduct sensitivity analysis with different methods and assumptions, and use at least one method that can make use of the information from double-zero studies.**
- ❑ **Measuring the potential impact of studies with no cases on the results before the synthesis**



Q3: How to make full use of the evidence?

A framework for meta-analysis with zero-events studies



Type 1. MA-SZ

Zero-events only occur in single arm and no double-arm-zero-events studies exist; the total event count in each arm is non-zero



Type 2. MA-MZ

Both single-arm-zero-events studies and double-arm-zero-events studies were included; the total event count in each arm is non-zero



Type 3. MA-DZ

Only double-arm-zero-events studies were included, without single-arm-zero studies; the total event count in each arm is non-zero



Type 4. MA-CSZ

Zero-events only occur in a single arm and no double-arm-zero-events studies exist, but the total event count in one arm is zero



Type 5. MA-CMZ

Both single-arm-zero-events studies and double-arm-zero-events studies were included, but the total event count one arm is zero



Type 6. MA-CDZ

All included studies were double-arm-zero-events studies and the total event counts in both arms are zero

1

Single-arm-zero-events (MA-SZ)				
Study	r1	n1	r2	n2
1	1	50	0	50
2	0	50	1	50
⋮	⋮	⋮	⋮	⋮
k	1	50	0	50

2

Mixed zero-events (MA-MZ)				
Study	r1	n1	r2	n2
1	1	50	0	50
2	0	50	0	50
⋮	⋮	⋮	⋮	⋮
k	1	50	1	50

3

Double-arm-zero-events (MA-DZ)				
Study	r1	n1	r2	n2
1	0	50	0	50
2	1	50	1	50
⋮	⋮	⋮	⋮	⋮
k	1	50	1	50

4

Completely single-arm-zero-events (MA-CSZ)				
Study	r1	n1	r2	n2
1	1	50	0	50
2	1	50	0	50
⋮	⋮	⋮	⋮	⋮
k	1	50	0	50

5

Completely mixed zero-events (MA-CMZ)				
Study	r1	n1	r2	n2
1	1	50	0	50
2	0	50	0	50
⋮	⋮	⋮	⋮	⋮
k	1	50	0	50

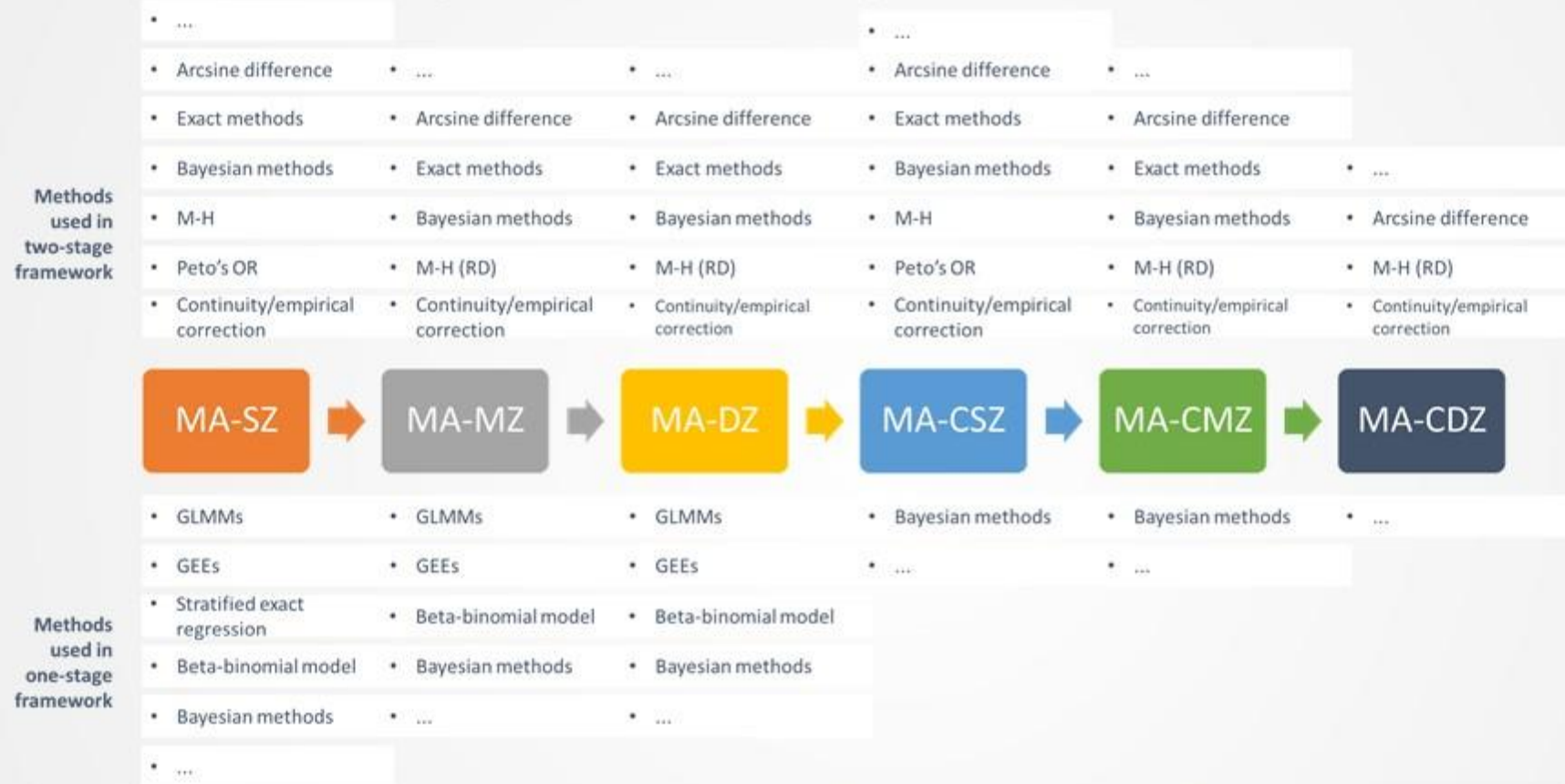
6

Completely double-arm-zero-events (MA-CDZ)				
Study	r1	n1	r2	n2
1	0	50	0	50
2	0	50	0	50
⋮	⋮	⋮	⋮	⋮
k	0	50	0	50



Q3: How to make full use of the evidence?

Flow diagram to deal with meta-analysis with zero-events studies



Abbreviations: 1. M-H: Mantel-Haenszel; 2. GLMMs: Generalized linear mixed models; 3. GEEs: Generalized Estimating Equations; 4. RD: risk difference. It should be noted that M-H method generally refers to the two-stage method in meta-analysis. For zero-events measured by OR/RR, M-H uses the add 0.5, therefore it is not a method to deal with zero-events for OR and RR. But it is a valid method to deal with zero-events when measured by RD.



Q3: How to make full use of the evidence?

Statistical methods for meta-analyses including information from studies without any events—add nothing to nothing and succeed nevertheless

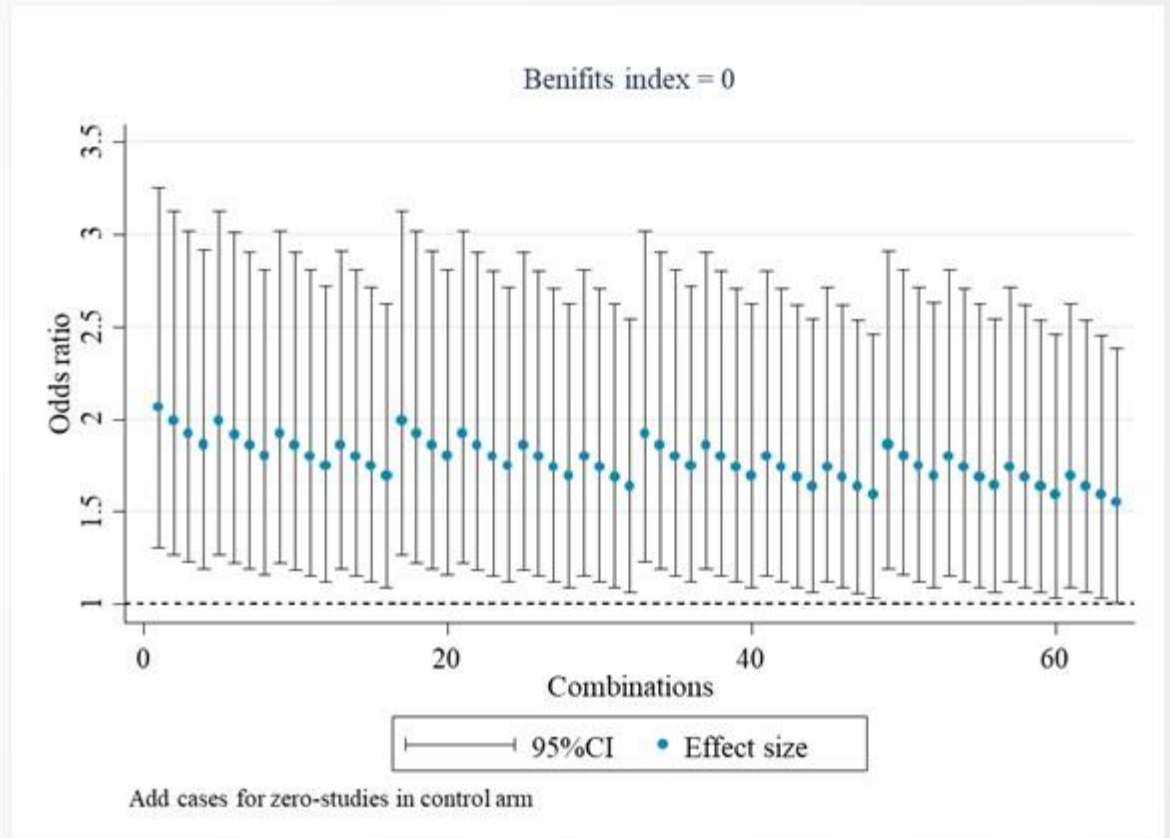
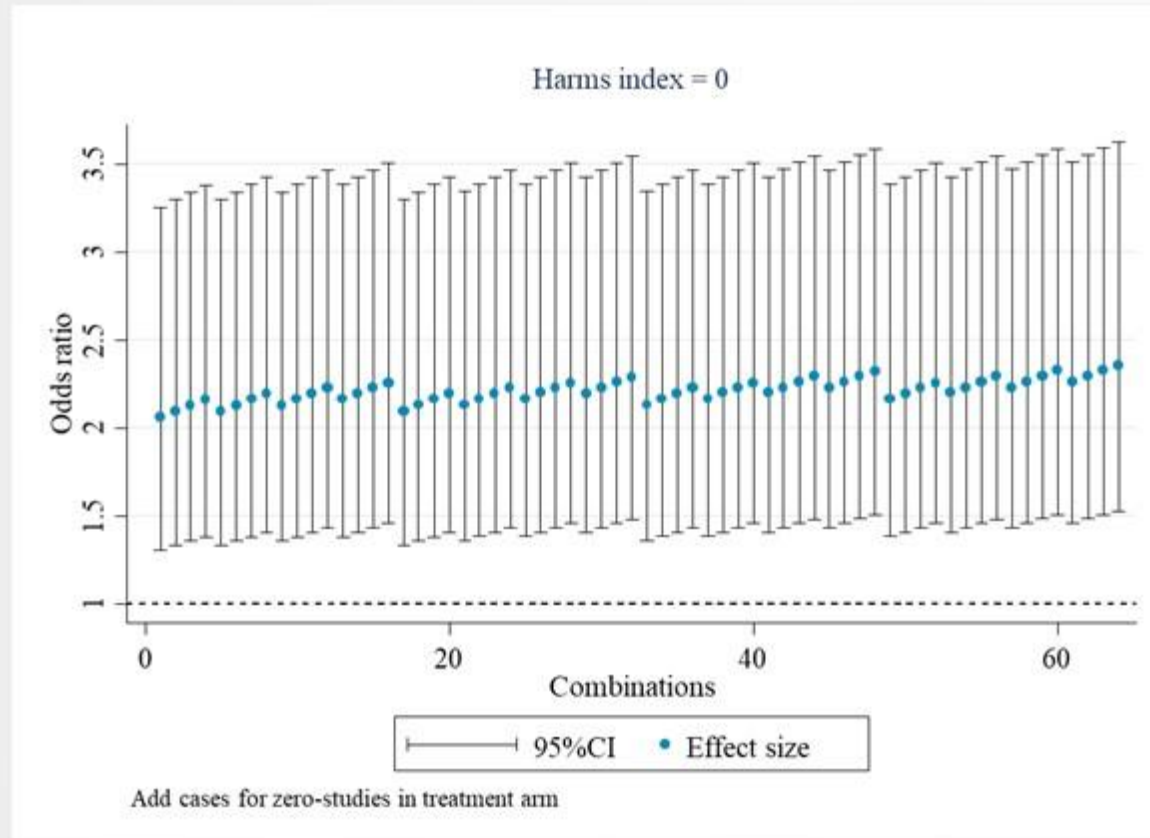
O. Kuss*[†]

Meta-analyses with rare events, especially those that include studies with no event in one ('single-zero') or even both ('double-zero') treatment arms, are still a statistical challenge. In the case of double-zero studies, researchers in general delete these studies or use continuity corrections to avoid them. A number of arguments against both options has been given, and statistical methods that use the information from double-zero studies without using continuity corrections have been proposed. In this paper, we collect them and compare them by simulation. This simulation study tries to mirror real-life situations as completely as possible by deriving true underlying parameters from empirical data on actually performed meta-analyses. It is shown that for each of the commonly encountered effect estimators valid statistical methods are available that use the information from double-zero studies without using continuity corrections. Interestingly, all of them are truly random effects models, and so also the current standard method for very sparse data as recommended from the Cochrane collaboration, the Yusuf-Peto odds ratio, can be improved on. For actual analysis, we recommend to use beta-binomial regression methods to arrive at summary estimates for the odds ratio, the relative risk, or the risk difference. Methods that ignore information from double-zero studies or use continuity corrections should no longer be used. We illustrate the situation with an example where the original analysis ignores 35 double-zero studies, and a superior analysis discovers a clinically relevant advantage of off-pump surgery in coronary artery bypass grafting. Copyright © 2014 John Wiley & Sons, Ltd.

Kuss O. Statistical methods for meta-analyses including information from studies without any events-add nothing to nothing and succeed nevertheless. Stat Med. 2015; 34(7):1097-1116.

Q3: How to measure the impact of studies with no cases?

Harms index (Hi) and Benefits index (Bi)



Xu C, Furuya-Kanamori L, Lin L, et al. Measuring the impact of zero-cases studies in evidence synthesis practice using the harms index and benefits index (Hi-Bi). *Journal of clinical epidemiology*. 2021. In Review.

Q3: How to measure the impact of studies with no cases?

- If studies with no cases do not impact the results, we may exclude them from the synthesis, **just like a rapid synthesis**
- If studies with no cases may impact the results, it is not recommended to exclude them from the synthesis

Xu C, Furuya-Kanamori L, Lin L, et al. Measuring the impact of zero-cases studies in evidence synthesis practice using the harms index and benefits index (Hi-Bi). *Journal of clinical epidemiology*. 2021. In Review.

Q3: How to deal with studies with no cases

User-friendly Stata Module for Hi-Bi

Stata/SE 14.0 - D:\日常工作\当前研究\证合方法\零事件系列\Zero-study index\Code and data\2x2 example.dta

File Edit Data Graphics Statistics User Window Help

Notes:

1. Unicode is supported; see [help unicode_advice](#).
2. Maximum number of variables is set to 5000; see [help set_maxvar](#).

running D:\Program Files (x86)\Stata14\profile.do ...

```
. use "D:\日常工作\当前研究\证合方法\零事件系列\Zero-study index\Code and data\2x2 example.dta", clear
```

```
. hibi a b c d, or
```

Note: two-stage peto's OR, Effect size =OR
Note: Number of double-arm-zero-events studies = 3
Doubld-zero-events studies may have little impact on the results:

Meta_Hi = 0
Meta_Bi = 8

Command

D:\Program Files (x86)\Stata14

Variables

Name	Label
id	
dis	
no_dis	
a	
c	
b	
d	
ob	

Properties

Variables	
Name	id
Label	
Type	byte
Format	%8.0g
Value label	
Notes	

Data

Filename	2x2 example.dta
Label	
Notes	

CAP NUM OVR



My further interests

- **Rapid review methods**
- **Individual participant data meta-analysis**
- **Cumulative evidence for the robustness**
- **Dose-response meta-analysis/Meta-regression (2015-2018)**
- **New concepts of this area: e.g. prediction interval**

<https://www.researchgate.net/profile/Chang-Xu-30>