Stepwise-Hierarchical Pooled Analysis for Synergistic Interpretation of Meta-analyses Involving Randomized and Observational Studies: Methodology Development

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Introduction

- **Challenges in meta-analysis with observational studies**

- **Improving accuracy of the effect estimates of the meta-analysis combining observational studies and RCTs**

Overview

Introduction

- RCTs helps determine the efficacy of a treatment or intervention "**under ideal conditions**" and "**provide high-level evidence**" because they can minimize threats to internal validity, but they likely **lack generalizability**
- However, it is **difficult to conduct RCTs in certain situations**, such as with participants with serious complications, interventions with ethical constraints (e.g. surgical procedures) and serious adverse effects
- Studies of observational designs are often used to measure the effectiveness of an intervention in "**real world**" scenarios, but it is known to have "**limited internal validity**" as it is subject to both bias and confounding

In the field of interventional cardiology or oncology, randomization is difficult but a large body of single-arm clinical databases and registries are often available

Black N; BMJ 1996
Egger M et al.; BMJ 1998
Barton S; BMJ 2000

Challenges in meta-analysis with observational studies

Challenging facts

- **In meta-analysis of observational studies, it is always challenging or even impossible to assess the risk of bias both within and across studies**

- **Prior to synthesis, investigators should carefully consider whether all observational studies at hand are able to answer the same clinical question**

- **Synthesis should be guided through examination of the amount of**
  - Clinical and methodological heterogeneity
  - Possible biases

Metelli S & Chaimani A;
Evid Based Ment Health 2020

Spurious inferences might arise when combining effect estimates from observational studies

- **Observational studies usually have larger sample sizes than RCTs and might yield highly precise results**

- This phenomenon might lead to spurious inferences because usually the more precise the summary effects, the stronger the conclusions of the investigators.

- When observational and randomized studies are synthesized using typical methods (e.g., classical fixed or random effects meta-analysis), **the weight of observational studies would be larger than that of the RCTs**, although the latter usually give more reliable results

Metelli S & Chaimani A;
Evid Based Ment Health 2020

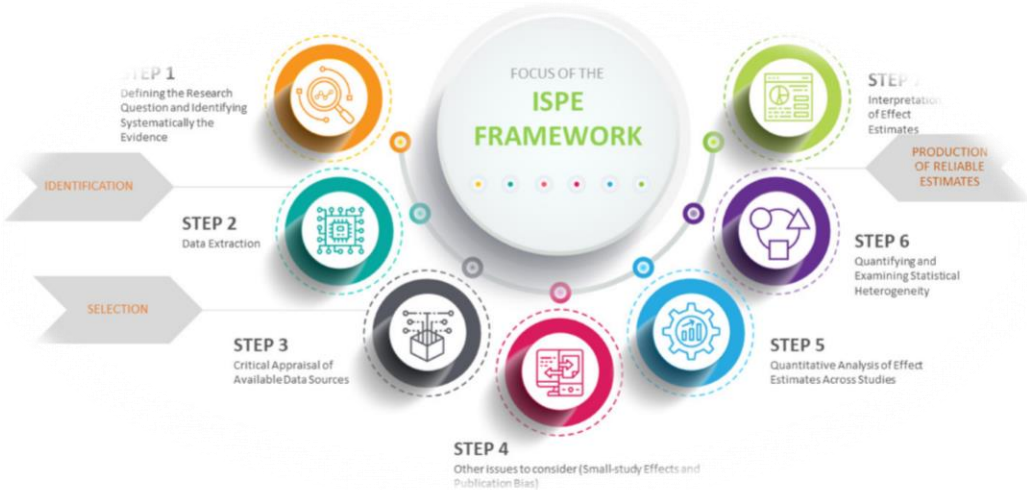
Improving accuracy of the effect estimates of the meta-analysis combining observational studies and RCTs

Evidence synthesis

Framework for the synthesis of non-randomised studies and randomised controlled trials: a guidance on conducting a systematic review and meta-analysis for healthcare decision making

Grammati Sarri ,[1] Elisabetta Patorno ,[2] Hongbo Yuan,[3] Jianfei (Jeff) Guo,[4] Dimitri Bennett ,[5] Xuerong Wen,[6] Andrew R Zullo ,[7] Joan Largent,[8] Mary Panaccio,[9] Mugdha Gokhale,[10] Daniela Claudia Moga,[11] M Sanni Ali,[12,13,14] Thomas P A Debray [15,16]

International Society for Pharmacoepidemiology (ISPE)



BMJ Evidence-Based Medicine 2020

Every step of a meta-analysis involving observational studies should be comprehensively conducted

- **In particular, at the step of the quantitative synthesis, in terms of handling heterogeneity and biases**

- **Some sophisticated synthesis methods, which may allow for more flexible modelling approaches than common meta-analysis models**

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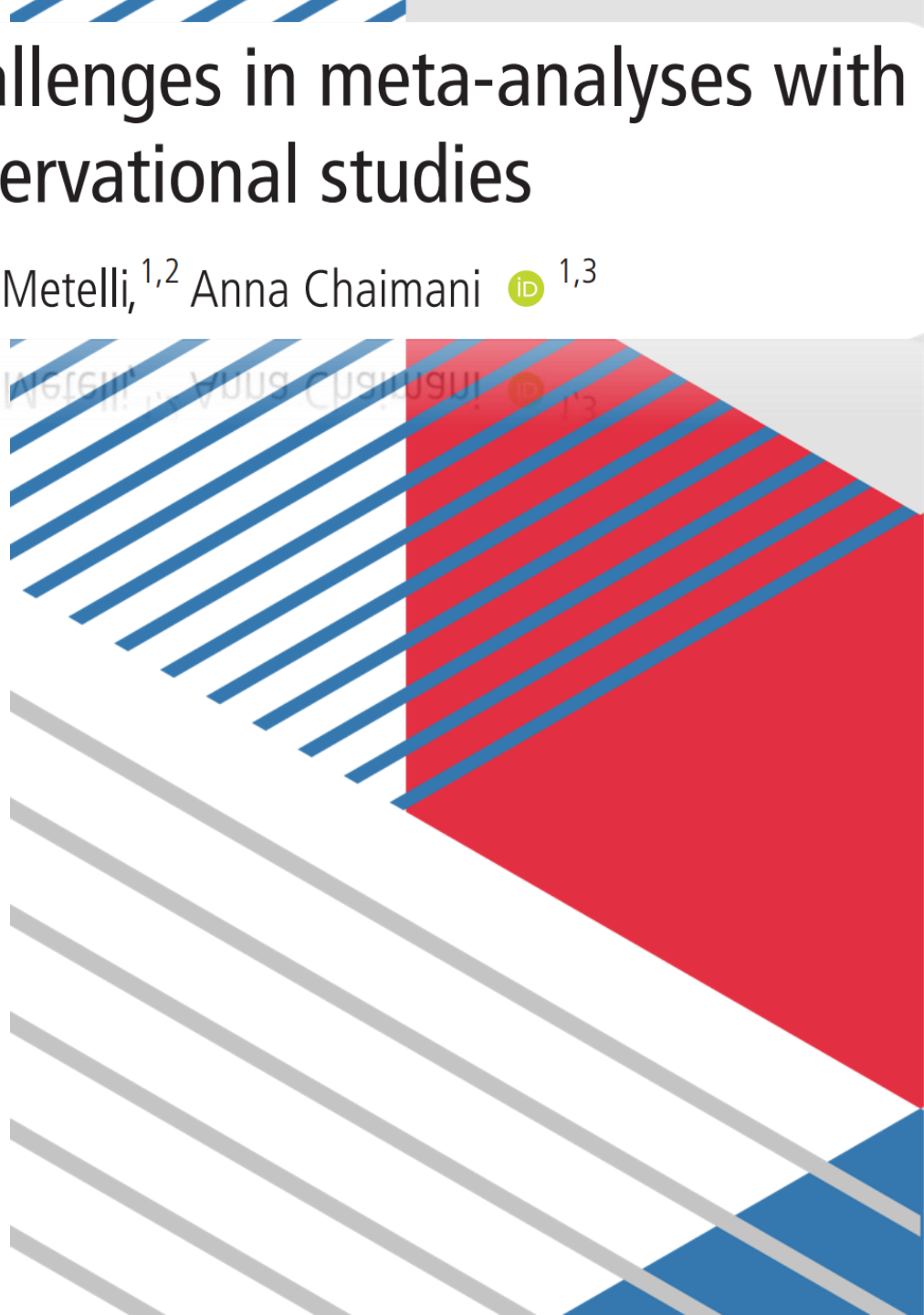
Evid Based Ment Health 2020



The effect estimates from all the randomized and non-randomized evidence should not directly be combined in a meta-analysis without any type of statistical adjustment

Sarri G et al., BMJ Evidence-Based Medicine 2020

1. Searching for relevant studies

- **Restricting the search in common large databases such as MEDLINE may achieve a sensitivity on average between 65% and 80%, depending on the medical field.**

- **Achieving a sensitivity of about 90% required searching for observational studies in At least Four Databases**

Lemeshow AR et al., J Clin Epidemiol 2005

2. Extracting data

Researchers should consider the most important potential confounders in advance (when preparing the protocol) and opt for extracting results adjusted at least for these or most of these characteristics

Metelli S & Chaimani A;
Evid Based Ment Health 2020

3. Synthesizing data and controlling for bias (1)

At the stage of data synthesis, the main issues in the presence of observational studies are

(1) How to accommodate the possibly large heterogeneity that may be present especially when different types of observational studies, or also RCTs, are combined in the same analysis

(2) How to account for different biases

Metelli S & Chaimani A;
Evid Based Ment Health 2020

3. Synthesizing data and controlling for bias (2)

- ❑ **The random effects model accounts better for this apparent heterogeneity.**
- ❑ **Subgroup analysis or meta-regression by**
  - ✓ Study design
  - ✓ Type of analysis (eg, different adjustment factors)
- ❑ **The risk of bias of the studies should also be considered as a potential source of variability; performing a sensitivity analysis excluding studies of lower credibility can reveal whether such studies have an impact on the summary effect**

Metelli S & Chaimani A;
Evid Based Ment Health 2020

Issues of confounding adjustment in meta-analysis

- **Propensity scores are now also being used frequently in the analysis of observational studies as they likely allow reduction of confounding and selection bias**

- **Despite the fact that these methods have the potential to produce less biased results, at the meta-analysis level they increase the methodological heterogeneity as often different studies use different analysis methods or different adjustment factors and the comparability of their results is questionable**

Effects of confounder adjustment

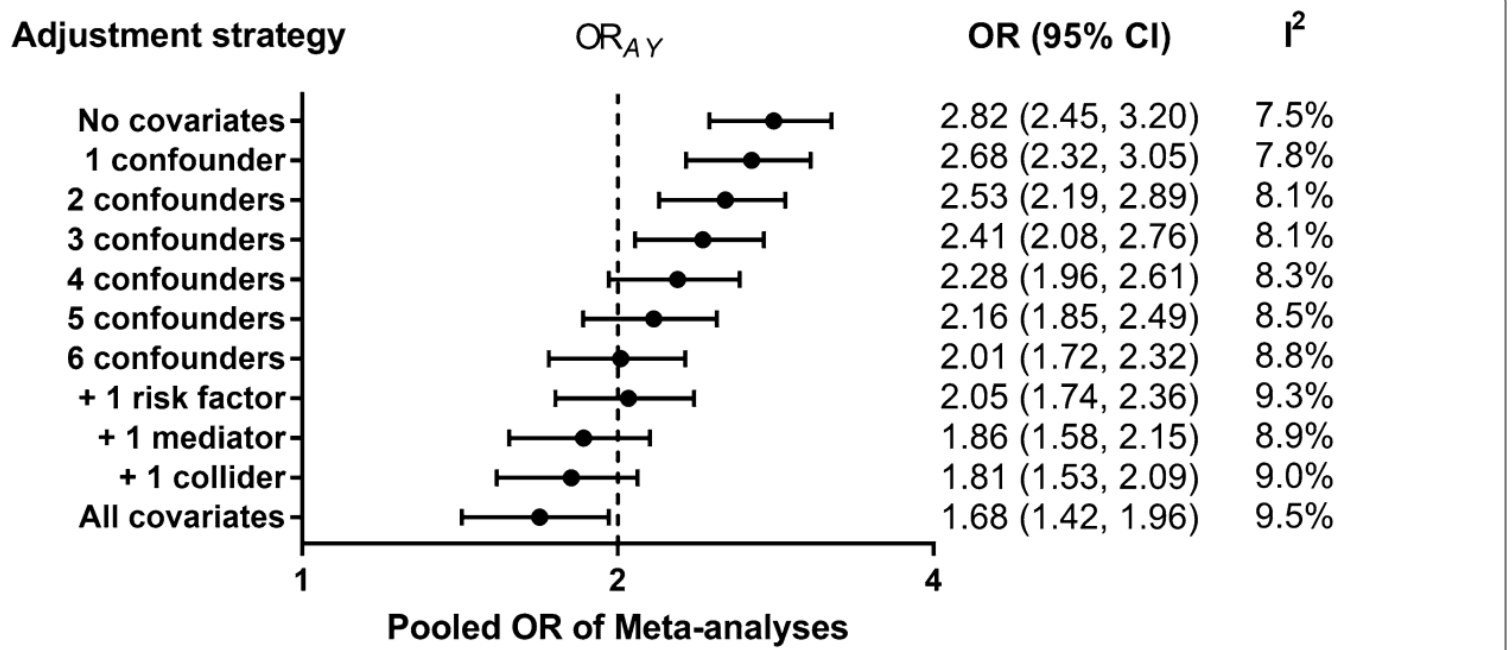


Fig. 2 Pooled ORs of meta-analyses in scenario Ref ($OR_{AY}=2$). OR, odds ratio; CI, confidence interval; *A*, exposure; *Y*, outcome. Pooled crude OR (no covariates) overestimated the true effect. The overestimation gradually decreased with the adjustment of more confounders. Pooled full-adjusted OR (6 confounders) had the closest effect estimation. Further adjustment of risk factor, mediator or collider slightly affected the estimation accuracy. Pooled all-adjusted OR (all covariates) underestimated the true effect

- **Pooled crude OR (no covariates) overestimated the true effect.**
- **The overestimation gradually decreased with the adjustment of more confounders**
- **Pooled full-adjusted OR (6 confounders) had the closest effect estimation**

Yan et al., BMC Med Inform Decis Mak 2020

3. Synthesizing data and controlling for bias (2)

"Bayesian hierarchical models"

The incorporation of observational evidence as prior information in a Bayesian meta-analysis of RCTs or employing a 'design-adjusted' analysis that allows studies of lower credibility to get less weight in the synthesis was originally suggested in the context of network meta-analysis but can be also applied for the case of pairwise meta-analysis

Combining evidence from different sources fits naturally in the "Bayesian framework" where the inclusion of all available evidence is anticipated

I: Unadjusted for potential imbalances (model I)

II: Adjustment using study arm differences (model II)

III: Adjustment using aggregate study values (model III)

IV: Downweighing using an informative prior (model IV)

✓ The more the variance from the non-randomized studies is inflated, the more their evidence is downweighed.

McCarron C et al., Medical Research Methodology 2010
McCarron C et al., PLOS One 2011

Research Article

Statistics in Medicine

Received 8 May 2012, Accepted 28 January 2013 Published online 25 February 2013 in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/sim.5764

Incorporating data from various trial designs into a mixed treatment comparison model

Susanne Schmitz,[a*†] Roisin Adams[b] and Cathal Walsh[a,b]

Three alternative methods of combining data from different trial designs in a mixed treatment comparison model

1. **Naive pooling is the simplest approach and does not differentiate between-trial designs**
2. **Utilizing observational data as prior information allows adjusting for bias due to trial design**
3. **Three-level hierarchical model**

Allows for bias adjustment while also accounting for heterogeneity between-trial designs

Bayesian hierarchical methods for meta-analysis combining randomized-controlled and single-arm studies

Statistical Methods in Medical Research
2019, Vol. 28(5) 1293–1310

DOI: 10.1177/0962280218754928
journals.sagepub.com/home/smm
SAGE

Jing Zhang,[1] Chia-Wen Ko,[2] Lei Nie,[2] Yong Chen[3] and Ram Tiwari[2]

Three methods are proposed:

1. **Bivariate generalized linear mixed effects models**
2. **Hierarchical power prior model**
3. **Hierarchical commensurate prior model**

Adjust for design difference and potential biases

Method # 2 and 3: provide strategies to downweight the single-arm studies

Hierarchical commensurate prior model is recommended as the primary method for evidence synthesis because of its accuracy and robustness.

4. Results

Performing subgroup analysis by study designs

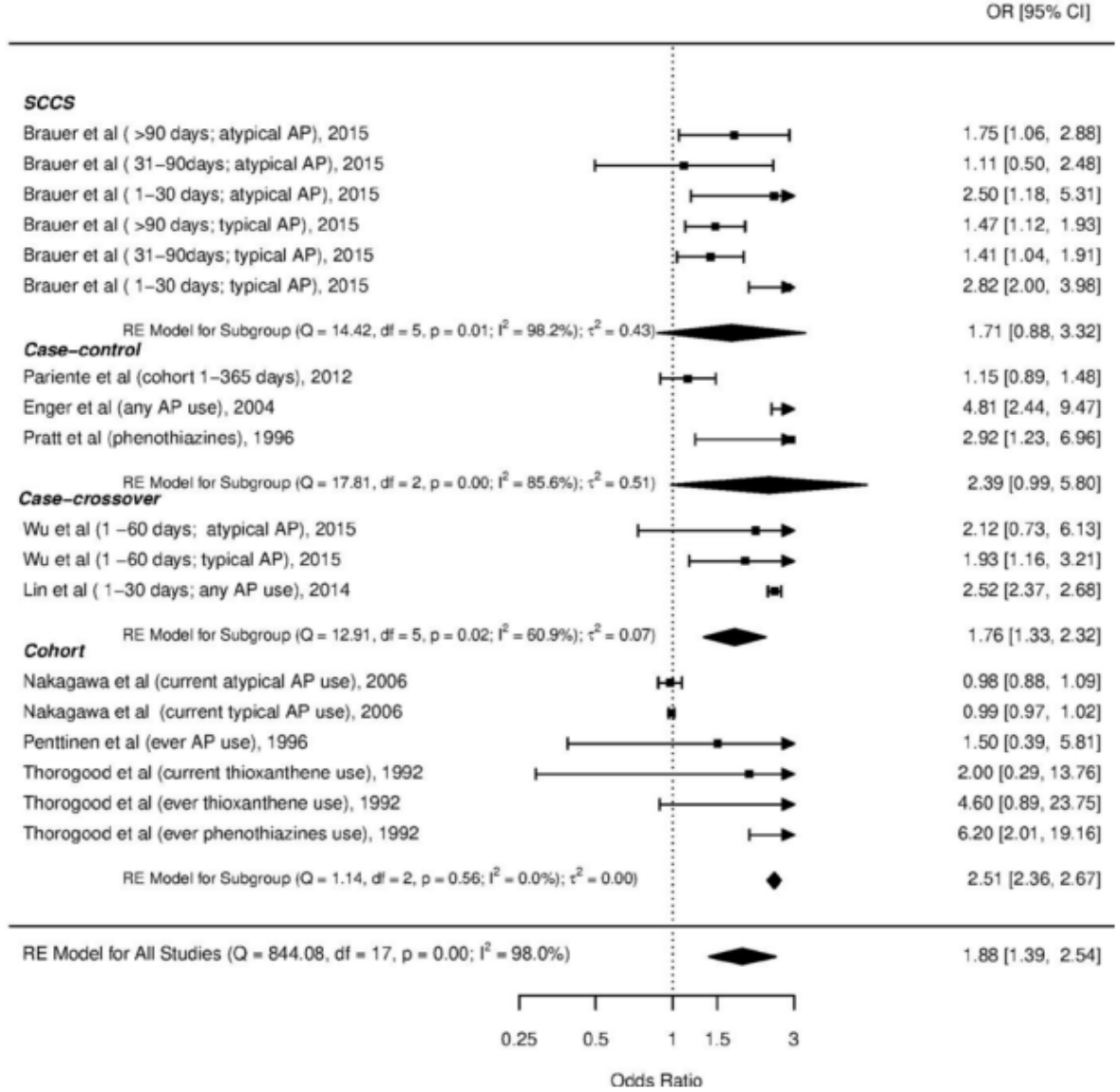


Figure 2 Subgroup analysis by study design (AP=antipsycotics, RE=random effects).

Conclusions

- **Synthesis** should be guided through examination of the amount of clinical and methodological heterogeneity, and possible biases
- The effect estimates from all the randomized and non-randomized evidence **should not** directly be combined in a meta-analysis without any type of statistical adjustment
- **Bayesian hierarchical models** can be used to adjust confounding and bias
- Reporting **subgroup analysis** by study designs and type of analysis (i.e., adjustment methods)

Questions & answers

Invite questions from the audience.