Disclosure

The presenter has advised that the following presentation is subject to no conflicts of interest and has nothing to disclose.

“Anchoring effect” in Random Effects Meta Analysis: a cautionary tale

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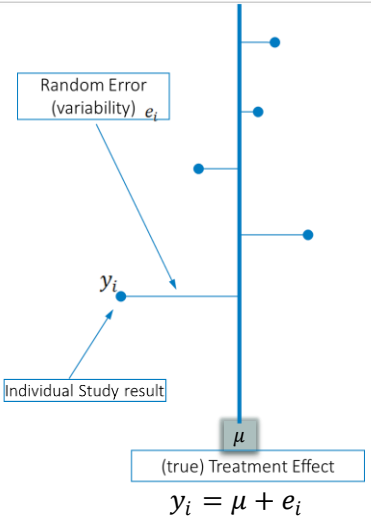
Introduction

- Meta Analysis refers to the statistical synthesis of results from a series of systematically reviewed studies addressing similar clinical questions
- I will refer in this talk to head-to-head Meta Analysis of randomised controlled trials
- With the massive growth in number of Meta Analysis, increasing importance in updated results: "***how does this new trial change the overall result?***"
- This talk introduces the concept of ***anchoring*** – an undesirable situation in which, with certain methods, a previous pooled effect is impervious to change with the advent of new trial evidence

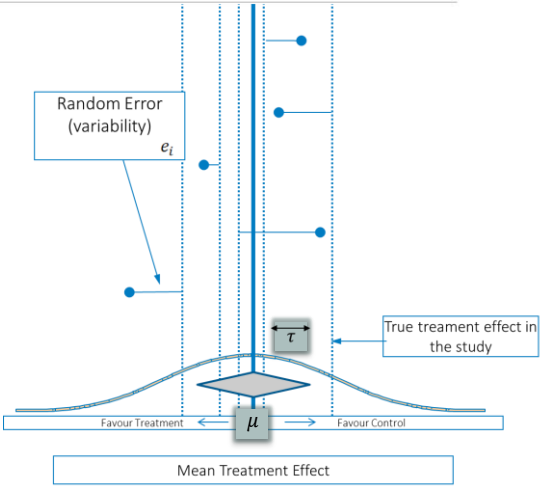
Models available (and their assumptions): the Fixed Effect Model (FEM)

- We rely on the pooled ("weighted") effect, based on the assumption that each study is a near replication of a single experiment
- ***Differences among study results are due only to chance***
- A FEM would be appropriate if the objective is to determine whether the treatment had an effect in the observed studies (i.e., a ***conditional inference***) or when it is believed that the true treatment effects in each study are the same



Models available (and their assumptions): the Random Effects Model (REM)

- REM assumes that the observed treatment effect for a study is a combination of a treatment effect common to all studies plus a component specific to that study alone
- REM also assumes that ***all studies are randomly drawn from a pool*** of all possible evidence
- Common error to adopt REM in presence of statistical heterogeneity (SH):
  - Lack of SH does not preclude heterogeneity
  - Presence of SH does not confirm it is quantitatively important



$$y_i = \mu + \delta_i + e_i$$
$$e_i \sim N(0, v_i)$$
$$\delta_i \sim N(0, \tau^2)$$

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FEM vs REM

- Both models have strong assumptions
- The model choice depends on the objective of the analysis and knowledge of the included studies
- FEM are commonly used when there are too few studies with which to estimate the τ from the data alone
- REM most commonly used because:
  - Correctly, it reflects an extra source of potential variability
  - **Incorrectly, it is assumed to 'take care' of heterogeneity**
- The most widely used REM is based on an estimator developed by DerSimonian and Laird (DL) in mid-1980s. It is the standard (or only) method available in any software

Which REM? Which τ?

- DL confidence intervals too narrow (high false positive rates) when few studies and/or large between-study differences
- Hartung-Knapp and Sidik-Jonkman method (HKSJ) makes small sample size adjustments to the variance estimates
  - consistently better error rates than DL method
  - many suggest it should be the standard for REM

- **There are >15 methods to estimate τ and >5 methods to estimate its uncertainty with variability across difference software packages**
- The imprecision in the estimates of τ are not acknowledged in both FEM and REM
- Authors have advocated the routine use of prediction intervals to represent the heterogeneity in the same metric of the intervention effect size measure, and to give a range of values that can be expected in future settings

Why not go Bayesian?

- Bayesian random-effects models provide a better accounting of the uncertainty at a cost of being slightly more computationally intensive
- We can incorporate external evidence on the treatment effects, τ and their relative uncertainty
- Usually the base-case scenarios are around the use of non-informative priors. *But vague priors can be informative in any case*
- **It's generally agreed to use a non-informative prior** on the treatment effect (although we may like to employ historical priors as we accumulate further evidence)
- **It is desirable to use informative prior distributions on τ**: there are various "off-the-shelf" priors (see Turner et al., 2014) to better capture between-study heterogeneity expected in various research settings

Motivating example

- Meta Analysis on antihypertensive drugs in those aged >80 years (Gueyffier et al, Lancet 1999)
- Comprising 7 (subgroup analysis) trials and 2,856 patients
- It showed statistically significant reduction of non-fatal events
- …but borderline statistically significant adverse mortality results

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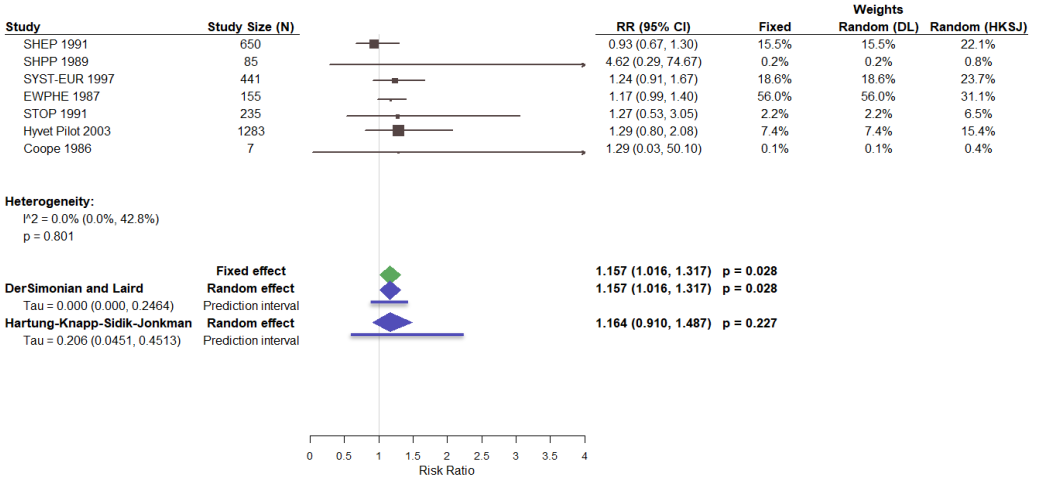
Meta Analysis



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The follow-up story

- Meta Analysis on antihypertensive drugs in those aged >80 years (Gueyffier et al, Lancet 1999)
- Comprising 7 (subgroup analysis) trials and 2,856 patients
- It showed statistically significant reduction of non-fatal events
- …but borderline statistically significant adverse mortality results
- Then came HYVET trial with 3,845 patients aged >80 years (NEJM, 2008)
- Statistically significant reduction in nonfatal events and mortality associated with hypertensive treatment

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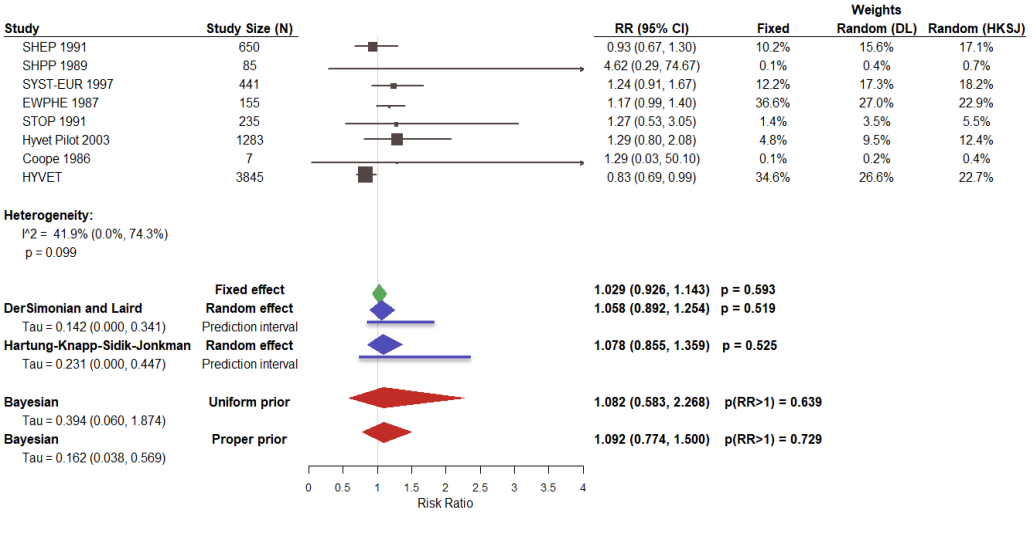
Meta Analysis with HYVET



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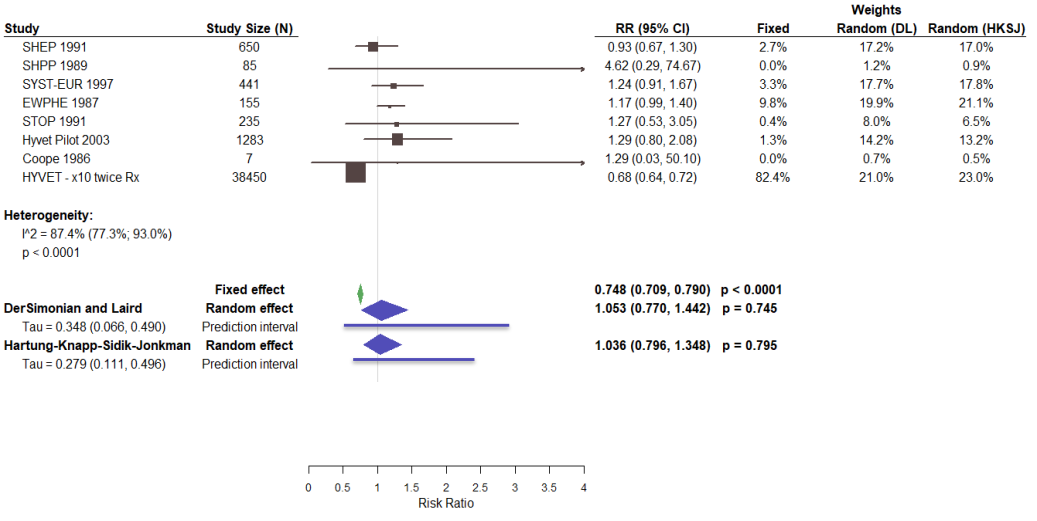
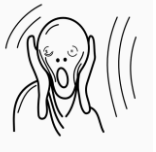
What if HYVET was 10x bigger with 2x treatment effect?



Summary table

Scenario	FEM RR (95%CI)	Weight given to HYVET trial	DL-REM RR (95%CI)	Weight given to HYVET trial	HKSJ-REM RR (95%CI)	Weight given to HYVET trial	Bayesian Meta Analysis RR (95% CrI)
Prior to HYVET	1.16 (1.02; 1.32)	-	1.16 (1.02; 1.32)	-	1.16 (0.91; 1.49)	-	1
With HYVET	1.03 (0.93; 1.14)	35%	1.06 (0.89; 1.25)	27%	1.08 (0.86; 1.36)	23%	1
With HYVET (10x sample size)	0.87 (0.83; 0.92)	84%	1.06 (0.86; 1.32)	26%	1.07 (0.85; 1.34)	25%	1
With HYVET (100x sample size)	0.83 (0.82; 0.85)	98%	1.07 (0.86; 1.33)	26%	1.07 (0.85; 1.34)	25%	0



Final remarks

- Every model comes with assumptions
- Be careful with the standard approaches - FEM tends to over-react, **REM tends to remain anchored**
- **Do not rely on a single model**, challenge the findings
- Do not neglect the between-study variance and its uncertainty
- **Bayesian Meta Analysis** is a flexible option but do not miss the opportunity to employ adequate/informative priors (at least for τ) to overcome the weaknesses of FEM and REM (taken in isolation)

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Thank you!

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