Subgroup Analysis in Clinical Trials

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Definition

- Subgroup effect: true value of covariable-treatment interaction effect (treatment effect modifiers) is not zero

The promise:

- Subgroup analyses can potentially improve population and individual health by identifying, through subgroup analysis, treatments with favourable risk-benefit or cost-effectiveness ratios for individual patients.

Key challenge: multiplicity

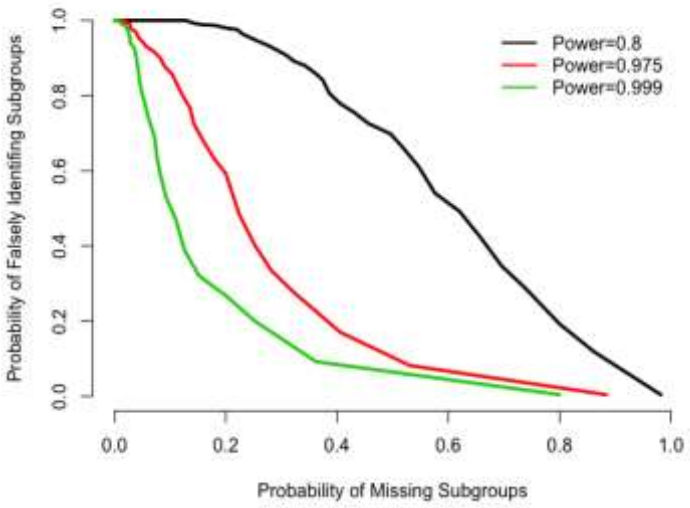
Same data used to both identify subgroups and to estimate subgroup effects

- Unreliable inference/poor discrimination due to multiple testing
- Identified subgroup effects will be over-estimated
- Uncertainty identified subgroup effects under-estimated

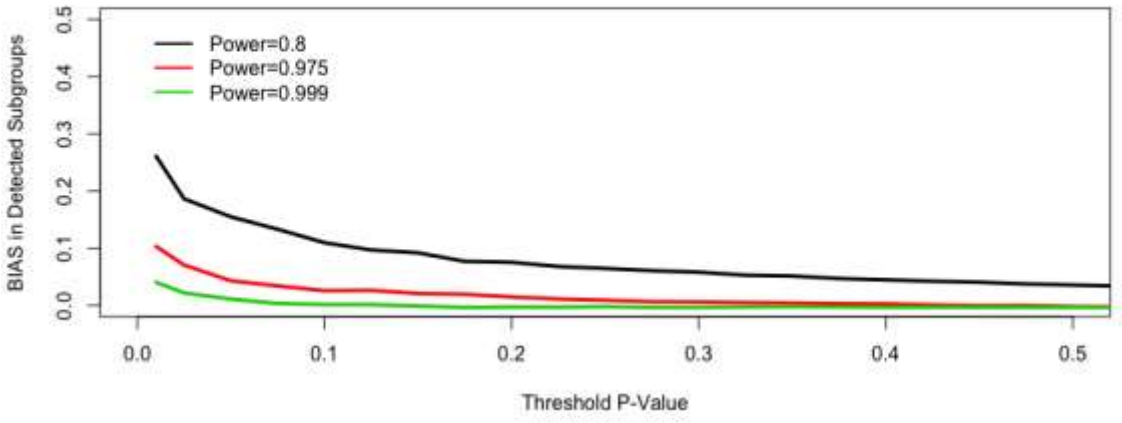
Poor discrimination

Simulation:

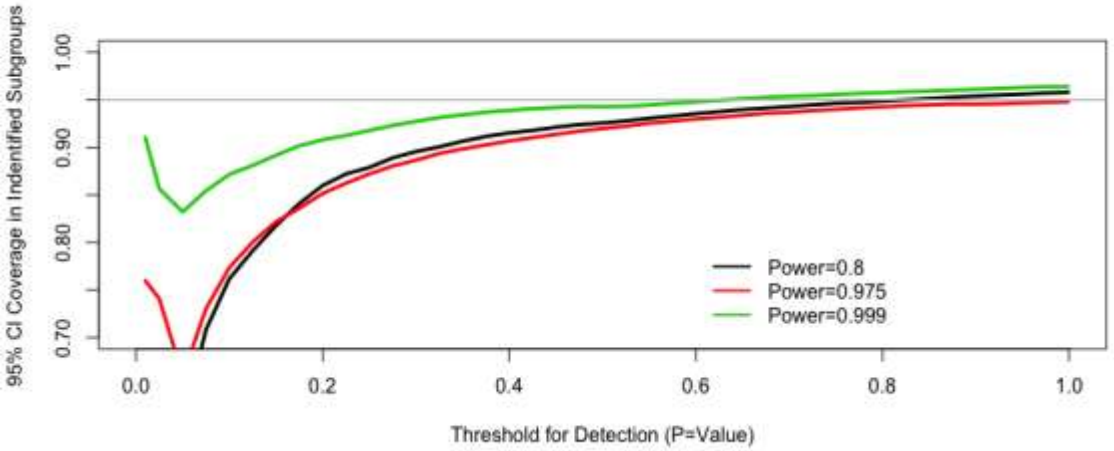
- 5 Candidate variables tested
- 4 candidate variables treatment effect not modified, no subgroup effect
- 1 “true” subgroup where treatment has no effect (substantial subgroup effect)



Bias



Estimation of uncertainty



Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses

BMJ 2010; 340 doi: http://dx.doi.org/10.1136/bmj.c117 (Published 30 March 2010) Cite this as: BMJ 2010;340:c117

Xin Sun, research fellow[12], Matthias Briel, senior researcher[13], Stephen D Walter, professor[1], Gordon H Guyatt, professor[14]

1. Reduce number of subgrouping variables tested
   - **A priori specification**
   - **Limit to a small number**
2. Consider the size or statistical significance of observed subgroup effects
   - **Is there a low likelihood that chance explains the effects?**
   - **Is the effect large?**
3. Synthesise supportive evidence
   - **Biological plausibility**
   - **Data from other endpoints / studies**

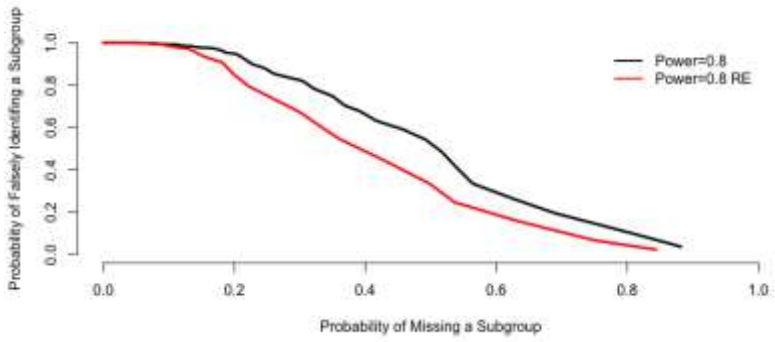
Proposed criteria are neither necessary or sufficient…

Sun et al: “It is unlikely that a subgroup claim will meet either all or none of our criteria—in almost all instances, a subgroup claim will meet some but not all the criteria... Judgment about its credibility will depend on how strongly clinicians and policy makers believe the subgroup effect is real.”

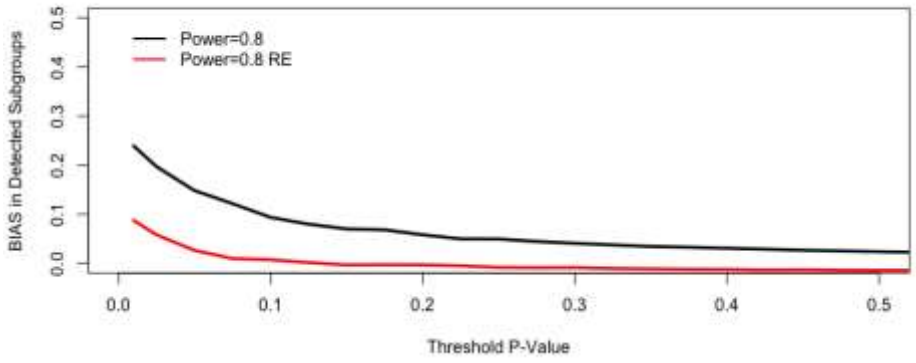
Ongoing MRC Funded Project: Development of a fully Bayesian framework for the Identification and estimation of Subgroup effects in Randomised Controlled Trials (BISECT)

- To develop, and test through simulation and case studies, a fully Bayesian statistical model for the identification and estimation of subgroup effects
  - Fixed interactions effects
  - Random Interaction Effects: Provides “shrunken” estimates of interaction effects
  - Mixture Models: Interaction effects come from either a null of non-null distribution
  - Split sample designs
  - …
- To develop and pilot web-based methods for the **formal elicitation of *a priori* judgement** from “experts” regarding potential subgroup effects
- To provide guidance regarding the application of these Bayesian approaches to subgroup analysis throughout the development life cycle

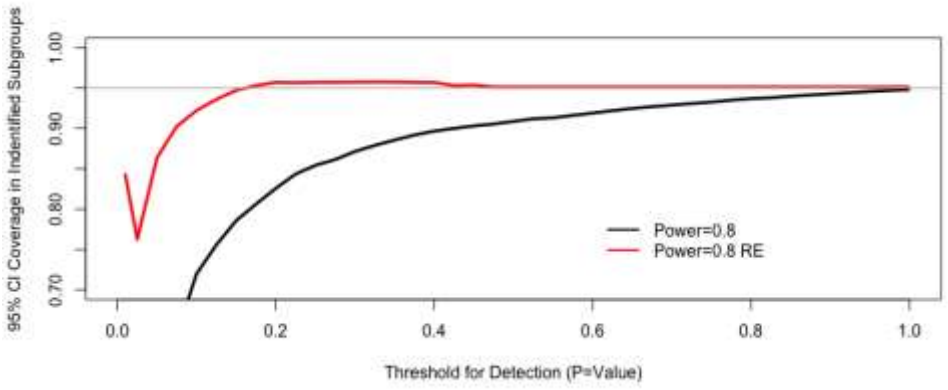
Random vs Fixed Effects Model: Discrimination



Random vs Fixed Effects Model: Bias



Random vs Fixed Effects Model: Uncertainty

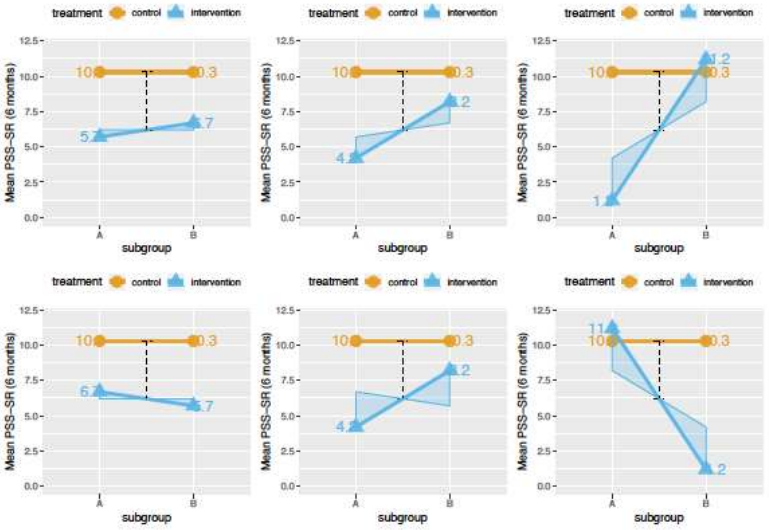


Three step elicitation process

1. Likelihood that candidate variables are treatment effect modifiers
   Likely / speculative / implausible
2. Likely direction of effect
   Treatment Effect greater/smaller in given subgroup
3 Magnitude of effects

- We will only progress to steps 2 and 3 where respondents express that they possess relevant knowledge
- At each step we record the bases for the belief:
  - Empirical observation
  - Subject area knowledge

Step 3: Beliefs regarding magnitude of subgroup effects captured using Graphical Tool



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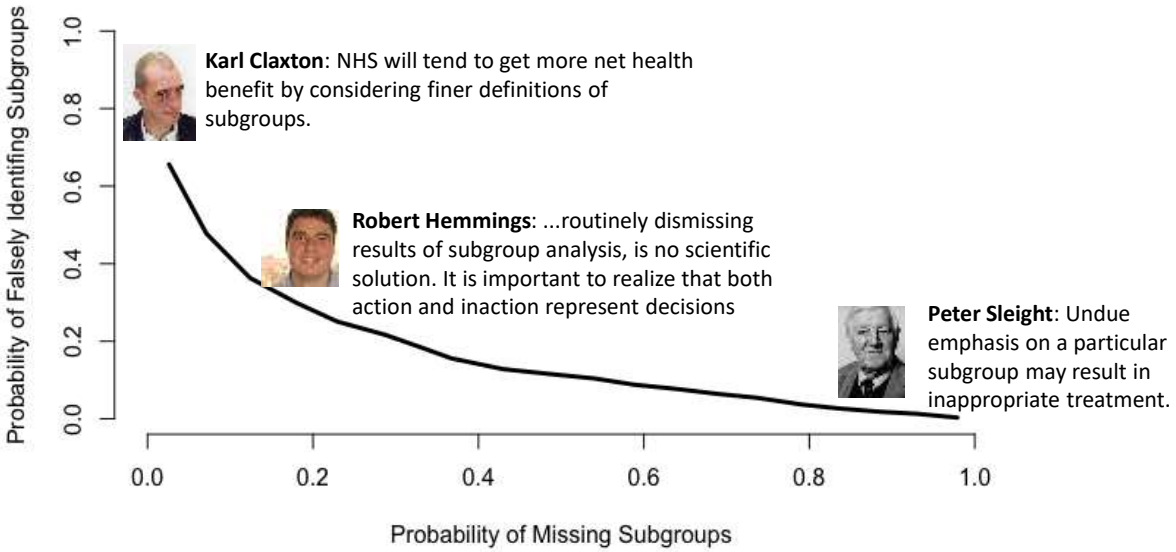
Are you a Karl, a Robert, or a Peter



Karl Claxton: NHS will tend to get more net health benefit by considering finer definitions of subgroups.

Robert Hemmings: ...routinely dismissing results of subgroup analysis, is no scientific solution. It is important to realize that both action and inaction represent decisions

Peter Sleight: Undue emphasis on a particular subgroup may result in inappropriate treatment.

Conclusions

- Capacity to identify subgroups effects often limited based on trial data alone
- Statistical approaches that account for the joint process of identification and estimation may help (a bit)
- Thoughtful inclusion of external evidence is critical