INVESTIGATING HETEROGENEITY IN SYSTEMATIC REVIEWS WITH A FOCUS ON GENDER

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Systematic Reviews

- Combining data from existing research using strong methods (question, search, data extraction, data pooling)
- Systematic reviews are frequently considered one of the highest levels of evidence
  - Cause wide-sweeping changes in health-care, public policy, etc
  - But are infrequently used by decision makers
- Major drawback
  - There is frequent heterogeneity between RCTs included
  - Undermines applicability

Heterogeneity

- Sources of heterogeneity in systematic reviews:
  - statistical heterogeneity (variation in point estimates between trials)
  - methodological heterogeneity (variation in study methods: e.g. blinding)
  - clinical heterogeneity (variation in intervention, participants, outcome measurement, setting)
  - heterogeneity due to unknown or unrecorded trial characteristics
- Results in incompatibility in the quantitative results
- Undermines applicability of meta-analyses
- Should examine possible reasons for heterogeneity

Clinical Heterogeneity

- Variations in the treatment effect that are due to difference in clinical characteristics
  - Patient/participant level (e.g., age, sex, gender, baseline severity)
  - Treatment/intervention level (e.g., dose, timing, route, personnel, comparator)
  - Outcome / measurement level (e.g., type of event, measure, timing)
  - Study setting (e.g., time of year, geographic setting, where data collected)
- P.I.C.O.T.

When choosing clinical covariates, consider

- Those covariates with a clear rationale for their role as a treatment effect modifier
  - Pathophysiologic / pharmacologic evidence
  - Evidence from a previous research (e.g., large clinical trial)
  - Clinical grounds
- Include clinical experts
  - Part of the team
  - Poll clinicians during review (might plan for this too)

Clinical Covariates to Consider

Patient level

- Age
- Baseline disease severity
- Sex/gender
- Ethnicity
- Comorbidities
- Other important features of the disease (e.g., prognostic markers)

Clinical Covariates to Consider

Intervention level

- Dose/strength/Intensity of treatment
- Duration of treatment
- Brand
- Co-interventions
- Timing
- Route of administration
- Compliance
- Other..

Clinical Covariates to Consider

Outcome level

- Event type
- Length of follow-up
- Outcome measure type
- Outcome definition
- Timing of outcome

Clinical Covariates to Consider

Other

- Research setting
- Early stopping
- Population attributable risk
- Control event rate / baseline risk
  - Controversial since is a conglomerate measure of covariates
  - Does not help with clinical decision making

Exploring Heterogeneity

- Subgroup analyses
  - Do separate meta-analyses on subgroups of studies (e.g., different intervention characteristics)
  - Compare means with analogue to the ANOVA
- Meta-regression
  - Same as standard regression
  - Outcome variable (pooled effect estimate) is predicted by one or more explanatory variables (covariates; e.g. dose or duration of intervention)

Other investigations of heterogeneity

- May go beyond pre-planned analyses where this is reasonable
- There are several methods of doing this
  - Looking at summary data sheets
  - Looking at forest plots from meta-analyses
  - Other useful plots
    - L'Abbe
    - Funnel plots
    - Galbraith plots
    - Radial plots
    - Influence plots
    - Dose/response curves

Interpretation of results of investigations

- Use caution
  - Observational only (unless stratified in trials on similar variables)
  - Thus, hypothesis generating only**
- Consider
  - Confounding between covariates
  - Biases (e.g., misclassification, dilution, selection)
  - Magnitude and direction of effect and CI ; not just p-value
  - Think through causal relationships
  - Parabolic relationships (beyond linearity)
- Do not state consistency of effect if no subgroup effects are found

Relatively Comprehensive Resources

- Cochrane Handbook
- Centre for Reviews & Dissemination handbook
- Our publications
  - Gagnier JJ, Beyene J, Moher D, Boon H, Bombardier C. Methods of assessing clinical heterogeneity in systematic reviews: A methodologic review. BMC Medical Res Methodology. 2012. PMID: 22846171.
  - Gagnier JJ, Morgenstern H, Moher D. Recommendations for investigating clinical heterogeneity in systematic reviews and meta-analyses. 2013. BMC Med Res Method. (Under Review).

Thank-you

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