Issues in popular designs for observational studies

Doug Altman

University of Oxford

on behalf of STRATOS TG5: “Study Design”

TG5 Members

Chairs:

Mitchell Gail, Suzanne Cadarette

Members:

Doug Altman, Gary Collins, Luc Duchateau, Stephen Evans, Neil Pearce, Peggy Sekula, Elizabeth Williamson, Mark Woodward

TG5 overview

- Good study design is the foundation of a convincing observational study
- Poor design can introduce threats to both internal validity and generalizability in ways that cannot always be compensated for during the analysis
- Topic Group 5 (TG5) of the STRengthening Analytical Thinking for Observational Studies (STRATOS) Initiative focuses on these issues

Observational studies

- Observational studies – most of the published literature!
  - Objectives may be therapeutic, prognostic, diagnostic, aetiological, descriptive

- Several guidelines exist for reporting the findings of observational research, notably the STROBE Statement and various extensions
- STRATOS group is developing corresponding guidance for designing/planning such studies
  - Not saying how research *should* be done
  - Issues to consider

Design

- What do we mean by design?
  a. Cohort, case-control, cross-sectional, etc
  b. All aspects of the **planning** of a study, i.e. everything that goes in a protocol

- Planning is fundamentally important – errors cannot be rectified later

Protocol

- **Objectives**
- **Study design** (a) which type (cohort, case-control, etc)
  (b) Matching?
- **Setting**
- **Participants** – eligibility criteria, how selected; matching criteria and numbers of matches if relevant; diagnostic criteria, if applicable
- **Variables** – outcomes, exposures, predictors, potential confounders, and effect modifiers
- **Data sources** & **methods of measurement**
- **Bias** – any efforts to address potential sources of bias (e.g. blinding)
- **Study size**
- **Quantitative variables**

  Is handling of continuous variables (whether and how to categorise) an issue in design or analysis, or both?
- **Statistical analysis strategy**

  whether will adjust for confounding (and how?)

  whether will impute missing data, etc. (and how?)

  etc

Guidance?

- Do we need guidance on these issues?
- Some designs are very common and familiar – cohort, case-control, cross-sectional

  Others are rarer and may not be widely understood, e.g. ecological studies, self-controlled case series, ...
- Most observational studies are not done by epidemiologists (and are published in clinical journals)!
- Errors in study design are common, from very simple to advanced issues
- Some studies are very large – yielding a very precise but wrong answer
- Ignorance about statistics afflicts all types of research

Surg Endosc (2016) 30:1172–1182
DOI 10.1007/s00464-015-4325-4

SURGICAL ENDOSCOPY and Other Interventional Techniques

Early laparoscopic cholecystectomy is superior to delayed acute cholecystitis: a meta-analysis of case–control studies

Amy M. Cao[1] · Guy D. Eslick[1] · Michael R. Cox[1]

"The very large number of patients in these studies outweighs any potential for selection bias."

- This was a meta-analysis of studies of prognosis – can't be addressed by a case-control design
- That is bad enough, but ...

Disinformation

World Journal of Methodology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5662/wjm.v6.i1.101

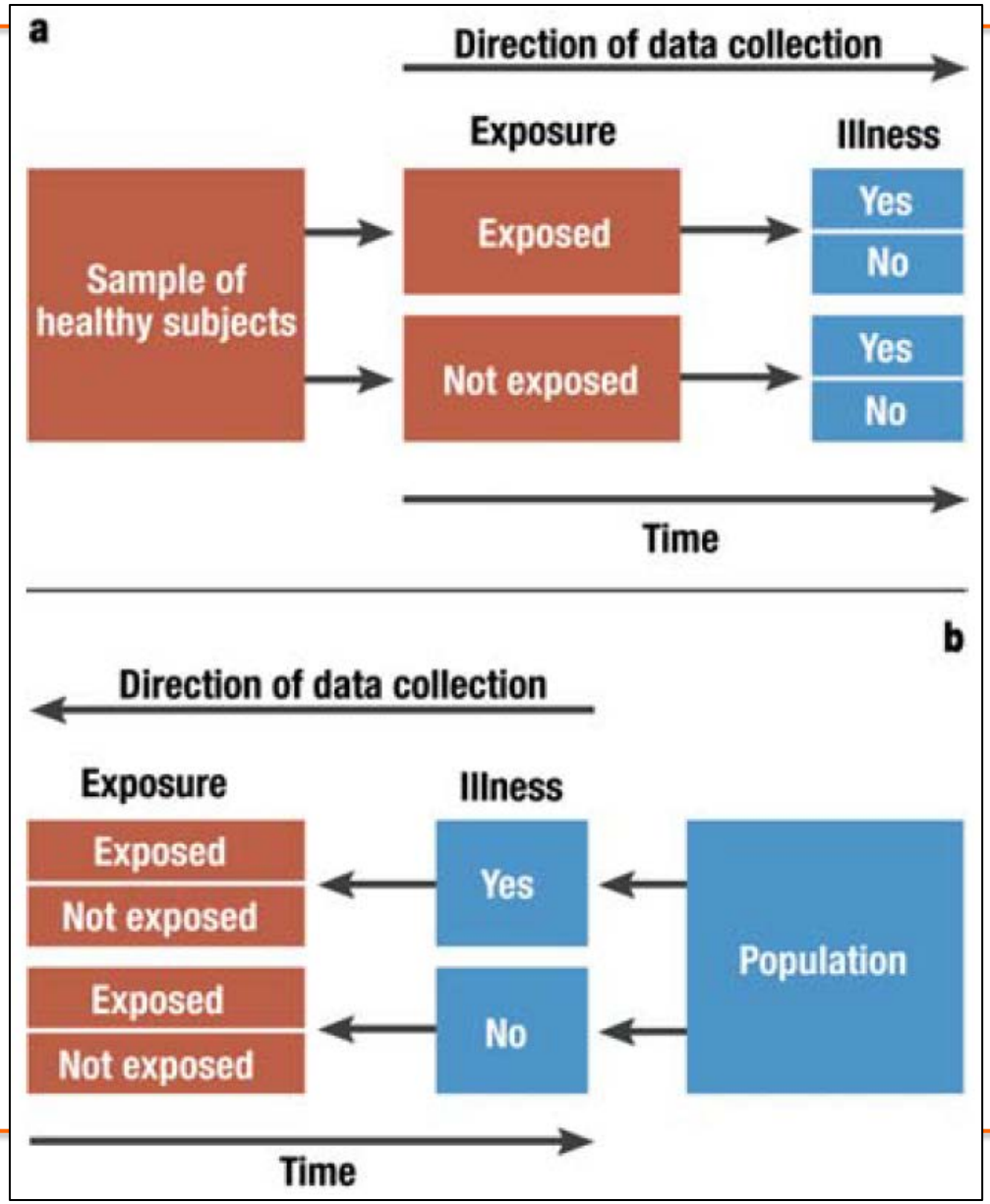
World J Methodol 2016 March 26; 6(1): 101-104
ISSN 2222-0682 (online)

MINIREVIEWS

Study design in evidence-based surgery: What is the role of case-control studies?

Amy M Cao, Michael R Cox, Guy D Eslick

So what is a case-control study?



Perhaps confusion arises from prospective or retrospective cohort studies

- same key idea: look forward from exposure

Cannot have a "prospective case-control study"

- 28000 hits on Google Scholar!

Rohrig et al,
Dtsch Arztebl Int 2009

Bias

- A key aspect of planning is avoidance of bias (as far as possible)

RESEARCH METHODS AND REPORTING

ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions

Jonathan AC Sterne,[1] Miguel A Hernán,[2] Barnaby C Reeves,[3] Jelena Savović,[1,4] Nancy D Berkman,[5] Meera Viswanathan,[6] David Henry,[7] Douglas G Altman,[8] Mohammed T Ansari,[9] Isabelle Boutron,[10] James R Carpenter,[11] An-Wen Chan,[12] Rachel Churchill,[13] Jonathan J Deeks,[14] Asbjørn Hróbjartsson,[15] Jamie Kirkham,[16] Peter Jüni,[17] Yoon K Loke,[18] Theresa D Pigott,[19] Craig R Ramsay,[20] Deborah Regidor,[21] Hannah R Rothstein,[22] Lakhbir Sandhu,[23] Pasqualina L Santaguida,[24] Holger J Schünemann,[25] Beverly Shea,[26] Ian Shrier,[27] Peter Tugwell,[28] Lucy Turner,[29] Jeffrey C Valentine,[30] Hugh Waddington,[31] Elizabeth Waters,[32] George A Wells,[33] Penny F Whiting,[34] Julian PT Higgins[35]

BMJ 2016;355:i4919

- The same issues are mostly relevant also to studies of aetiology – replace “intervention” by “exposure”

ROBINS-I – bias domains

- “The tool views each study as an attempt to emulate (mimic) a hypothetical pragmatic randomised trial, and covers seven distinct domains through which bias might be introduced”

Pre-exposure

- Bias due to confounding
- Bias in selection of participants into the study

At exposure

- Bias in classification of exposures

Bias due to confounding

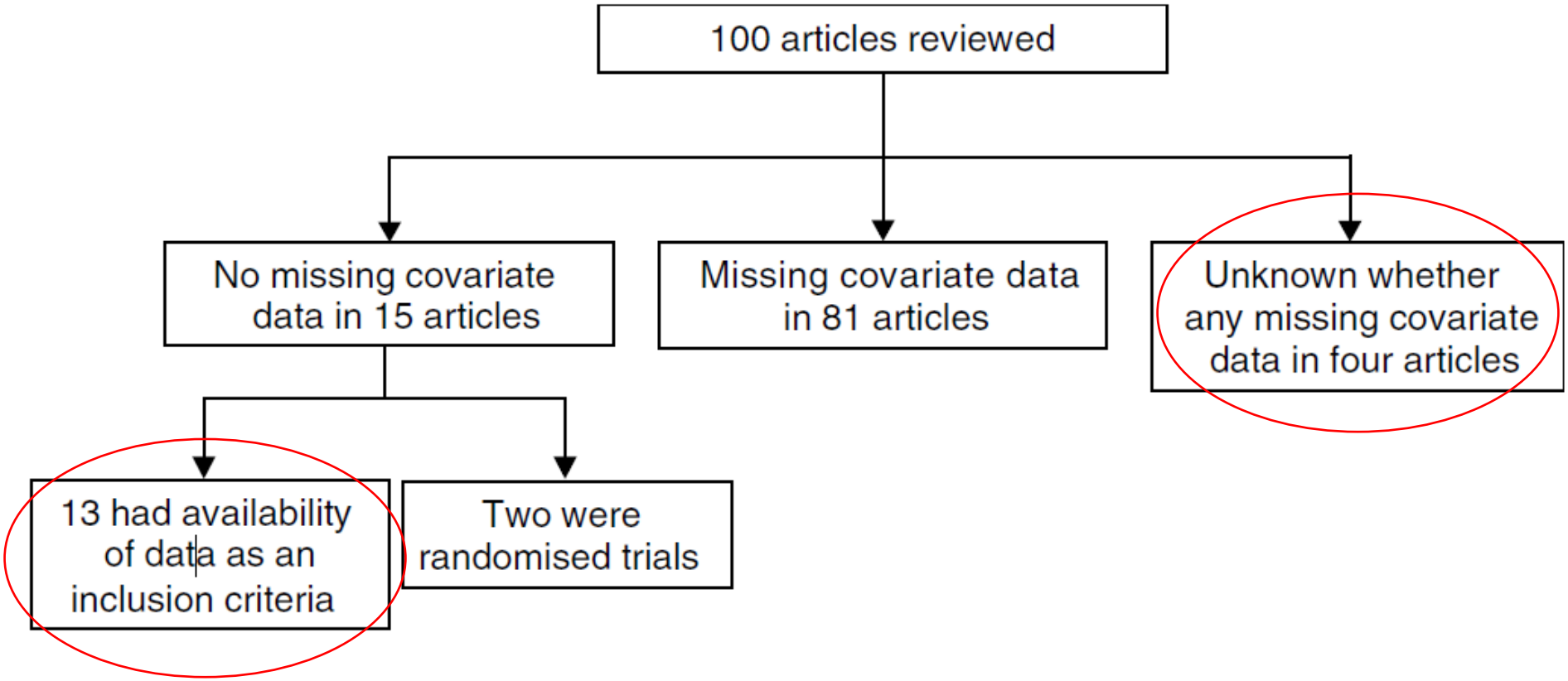
- Method to control for measured confounders needs to be considered as part of planning a study
- Which variables to consider? (NB baseline data only)

- Appropriate methods include stratification, regression, matching, standardization, g-estimation, and inverse probability weighting.

  Whether and how to use matching is a design issue

  Can control for individual variables or for the estimated propensity score (Sterne, ROBINS-I)

Bias from inclusion criteria



Burton & Altman, *Br J Cancer* 2004

ROBINS-I – bias domains

- “The tool views each study as an attempt to emulate (mimic) a hypothetical pragmatic randomised trial, and covers seven distinct domains through which bias might be introduced”

Pre-intervention

- Bias due to confounding
- Bias in selection of participants into the study

At intervention

- Bias in classification of exposures

ROBINS-I – bias domains

- "The tool views each study as an attempt to emulate (mimic) a hypothetical pragmatic randomised trial, and covers seven distinct domains through which bias might be introduced"

Pre-exposure

- Bias due to confounding
- Bias in selection of participants into the study

At exposure

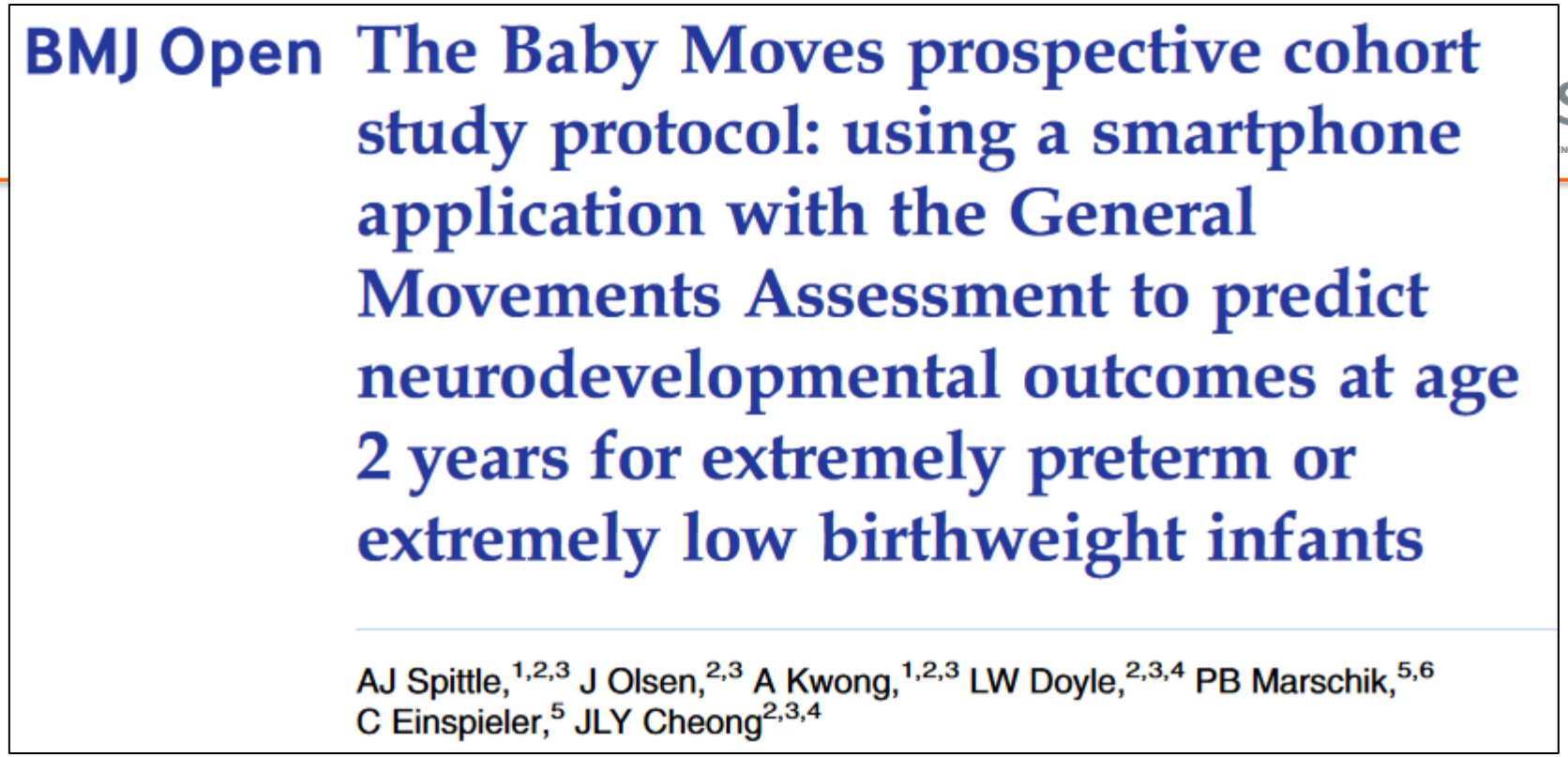
- Bias in classification of exposures

Post-exposure

- Bias due to deviations from intended interventions
- Bias due to missing data
- Bias in measurement of outcomes
- Bias in selection of the reported result

What's new?

- New ways of accessing participants
  - Social media, internet
    - bias from self-selection: Keiding & Louis, *JRSSA* 2016
- New types of data
  - Routinely collected data, electronic health records, social media
- New ways of measuring variables
  - Wearables, omics, images, apps



"Parents will video their infant's general movements at two time points between 3 and 4 months' corrected age using the Baby Moves app.

Videos will be scored by certified GMA assessors and classified as normal or abnormal."

Tonne et al. Integrated assessment of exposure to PM2.5 in South India and its relation with cardiovascular risk: Design of the CHAI observational cohort study. *Int J Hygiene Environ Health* 2017

Fig. 5. Personal monitoring equipment used in panel study including (from left to right) MicroPEM, wearable camera, and gravimetric sampler.

- Much research is done by those with little training in research methods or even good research practices

"I am the president and organizer of this meeting and would like you to consider the possibility of giving us a brief course (the format would be for you to decide … your suggestions would be welcome; our ignorance is rampant).

TG5 outputs

- Overview paper

  Setting out key principles for study design

- Subsequently applying these key design principles to a number of specific settings
  - Design for prognostic studies
  - Design for studies using routinely collected data
  - ...

STRATOS guidance

- Will help researchers to choose the design
- Will offer guidance on *issues to consider* specific to that design
- Will not prevent errors

  but we hope to contribute to improvement in the methodological quality of observational research