Design of observational studies: a fresh look at classical designs

TG5: STUDY DESIGN

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TG5 overview

- Design forms a key aspect of any observational study.
- Poor design can introduce threats to both internal validity and generalizability in ways that cannot always be compensated for during the analysis of the collected data.
- Topic Group 5 (TG5) of the STRengthening Analytical Thinking for Observational Studies (STRATOS) Initiative focuses on these issues.

Hasn’t design already been solved?

- There are established principles for good study design
- However, practitioners designing new observational studies have to take into account a number of relatively recent developments:
  - new ways of accessing and recruiting study participants.
  - access to new types of data,
  - new ways of measuring exposures and outcomes of interest
  - the increasing tendency to recruit very large multi-purpose cohorts with the aim of subsequently addressing a wide range of specific research questions, often through sub-studies

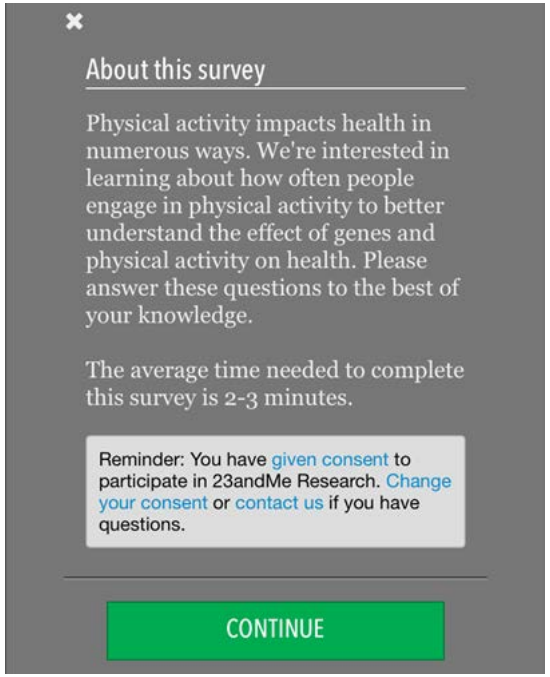
(1) New ways of accessing participants

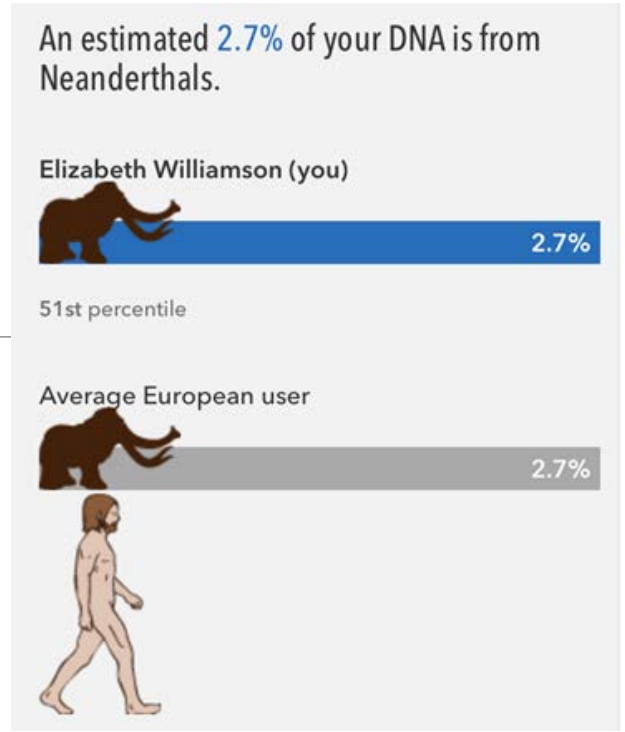
- Facebook, social media, internet based sampling, convenience samples
- Cost-effective
  - Example: Carter-Harris et al, Journal Medical Internet Research, 2016
  - Comparison of social media recruitment campaign (Facebook) vs 3-day newspaper ad campaign
  - Outcome – completed web-based lung cancer health belief survey
  - Cost per completed survey:
    - $1.51 recruiting via Facebook
    - $40.80 by newspaper advertisement
- Useful if hard to identify study base
  - Example: Snart-Gravid – Danish Web-based pregnancy planning study (Mikkelsen, 2009)

Example: 23andMe

- Genomics and biotechnology company
  - Personalised genetic risk factors, traits, inherited conditions, ancestry
- Genetic research
  - Consent when you sign up
  - Surveys every time you log on.
  - Answer as many questions as you want

Key idea: giving participant something they want





NAME	CONFIDENCE	OUTCOME
Alcohol Flush Reaction	★★★★	Does Not Flush
Bitter Taste Perception	★★★★	Unlikely to Taste
Red Hair	★★★★	<1% Chance
Earwax Type	★★★★	Wet
Eye Color	★★★★	Likely Blue
Hair Curl	★★★★	Straighter Hair on Average
Lactose Intolerance	★★★★	Likely Tolerant

Questions

Who are the participants?

How do they relate to a “target” population?

To whom can we generalise the study results?

Can the selection of participants lead to bias in study conclusions?

When do we need to exercise caution in interpreting and generalising results?

Particularly where the study participation is a side-effect…

Validation of participant-reported data – participants never meet researchers

More scope for differential measurement error / missingness?

(2) New types of data

- Routinely collected data (found data) are increasingly used for health research
- Electronic health records are an important example
- Increasing interest in linking routinely collected health, social care, educational data etc.
- Tweets, coffee purchases, etc.

Example: mPower: Mobile Parkinson Disease Study

Apple ResearchKit

- Open source framework for building apps,
- Promoted as useful for enrolling participants and conduct studies

mPower: Mobile Parkinson Disease Study

- (n>10,000)
- Inclusion criteria: have an iPhone, 18+ yrs old, (have PD)
- Aims: Establish natural course, look at predictors of worse symptoms, etc.
- App to monitor health in Parkinson's Disease
- Mix of surveys and tasks that activate phone sensors (dexterity, balance, gait)
- Completed whenever participant wants
- Self-tracking, sharing with doctor, engaging, fun

Example: TB in migrants to the UK

Aldridge et al, Lancet, forthcoming

Data sources

- Migrants screened pre-entry
  - International Organisation for Migration (IOM), Jan 2006 – Dec 2012
  - Part of a pilot pre-entry screening programme in 15 countries
- UK TB cases
  - Enhanced Tuberculosis Surveillance system, Jan 2006 – Dec 2013
  - All clinical cases notified in England, Wales and Northern Ireland (EWNI)
  - Includes strain typing data
- Study aim: risk factors for TB diagnosis after entry to UK

Questions

Follow-up occasions do not follow a pre-planned schedule:

- Measurement process likely correlated with things we're interested in
- E.g. people go to their GP because they are ill

Data not collected for research purposes:

- Unmeasured confounding more of a concern
- Measurement error/misclassification more of a concern?

Impact of linkage

(3) New ways of measuring variables

Omics (metabolomics, proteomics, etc.)

Images

Wearables

Apps

Example: Cloudy with a Chance of Pain

Funded by Arthritis Research UK, PI Will Dixon

Inclusion criteria: Arthritis, chronic pain, 17+ years

Aims: Study the association between weather and pain

Exposure and outcome measured using smartphone:

- Custom-designed app to measure pain
- Use GPS to get location, link with localised weather data

Initial problems in piloting:

- apps drained battery life…
- … so participants left phones at home

CLOUDY WITH A CHANCE OF PAIN

Questions

Lab data:

- Dealing with batch effects

Technical problems with apps:

- What to anticipate, designing pilot studies
- Validating the app?

Constant stream (velocity) of some measurements:

- Technical (e.g. storage), interpretation
- E.g. PA – single question vs daily step counts

(4) Multi-purpose cohorts

- Large cohort studies may have a large number of research questions in mind (some may be not yet in mind)
- Specific research questions often intended to be addressed through sub-studies
- Some resources, e.g. biospecimens, may be scarce

Questions

Much classical study design pertains to scenarios with a specific research question (or small number thereof) in mind

What do we need to do differently when we aim to address a number of questions, but don't necessarily know specifically what they are upfront?

Reducing participant burden - measure different things on different people? How?

Allocation of limited resources:

How to design sub-studies so e,g, remaining biospecimens are not a biased sample (conditioning on having plasma left for next sub-study won't produce misleading results)

Developments in analytic methods – build into design?

Missing data:

- E.g. plan to collect auxiliary variables if anticipating MAR + MI
- (Subset of) Linkage to assess, and correct for, MNAR

Confounding:

- Causal graphs have had important role in helping us to understand how to approach confounding and identify selection bias
  - Role at the design stage?
- Linkage to reduce confounding bias via calibration approaches

Dealing with measurement error

- Can we help deal with, or quantify, measurement error at design stage?

Messier, routinely collected data:

- Scope for building in an element of randomisation? (TWICS)

TG5 aims

Classical design principles remain important

These issues may lead to modifications and extensions of best practice in study design.

The aim of TG5 is to

Provide guidelines about the application and extensions of established principles of study design to a range of new (observational) applications;

Illustrate key principles of good design using a range of existing observational studies in order to highlight potential pitfalls in design for practitioners, particularly those within disciplines where these are sometimes poorly applied.

TG5 activities

- Overview paper
  - Setting out key principles for study design
- Subsequently applying these key design principles to a number of specific settings, in collaboration with other topic group members
  - Design for prognostic studies
  - Design for studies using routinely collected data
- Design forms an important aspect of topics of other TGs, e.g.
  - Design for studies addressing complex causal questions
  - Design for studies where measurement error will be an issue

References

Carter-Harris L, Bartlett Ellis R, Warrick A, Rawl S. Beyond traditional newspaper advertisement: leveraging facebook-targeted advertisement to recruitlong-term smokers for research. *Journal Medical Internet Research*, 2016, 18(6):e117

Mikkelsen EM, Hatch EE, Wise LA, Rothman KJ, Riis A, Sorensen HT.Cohort profile The Danish Web-based pregnancy planning study – 'Snart-Gravid' *IJE*. 2009, 38(4):938-943.

Aldridge RW, Zenner D, White PJ, Williamson EJ, Muzyamba MC, Dhavan P, Mosca D, Thomas HL, Lalor MK, Abubakar I, Hayward AC. Tuberculosis in migrants moving from high to low incidence countries: a population-based cohort study of 519,955 migrants to the England, Wales and Northern Ireland screened pre-entry. Lancet, 2016, forthcoming