Strategies for data analysis: I. Observational studies

Gilda Piaggio

UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction
World Health Organization

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What strategy of analysis?

The choice of a strategy of analysis depends on:

- Objectives of the study
- Type of study
- The study design
- Outcome

Objectives of the study

- Descriptive
- Comparative: estimation and test of hypothesis about an effect
- Model building

Types of studies

- Censuses and surveys
- Cross-sectional study
- Cohort studies
- Case-control studies
- Experimental studies

Observational

Study design

For observational studies:

- Completely randomized sampling
- Stratified sampling
- Non-paired or paired (case-control studies)

Analysis of a comparative multicentre cross-sectional study

- Define analysis population according to protocol
- Describe prognostic variables by exposure group
- Provide crude effect of risk factor on outcome measure
- Provide effect of risk factor on outcome measure adjusting for possible confounders
- Look for effect modifiers and conduct stratified analysis

Define analysis population

- Count recruited subjects, decide on exclusions according to protocol and on numbers of eligible subjects by exposure group and by centre
- Look for missing data on the main outcome among eligible subjects and compute numbers of subjects to be included in the analysis by exposure group and by centre

Describe prognostic variables by exposure group

- Compute, by exposure group:
  - means and standard deviations (continuous variables)
  - medians and quartiles (discrete variables)
  - percentages (categorical variables)
- Compare prognostic variables between exposure groups to discover possible confounders

Comparison of prognostic variables between exposure groups

Comparison is made by assessing the prognostic relevance of the difference observed, **not using tests of hypothesis**:

'Confounding of the treatment effect by extraneous factors is a distortion within a body of data; statistical tests of significance are directed at the question of inference beyond the data in hand...(and) is clearly inmaterial'

Rothman, 1977

Comparison of prognostic variables between exposure groups

'The extent to which an extraneous factor can distort the assessment of the treatment effects depends on two relationships:

- the extent of the imbalance of the extraneous factor among the groups
- the degree to which the extraneous factor is associated with the outcome under study'

Rothman, 1977

Estimate crude effect of risk factor

- Estimate the magnitude of the effect adjusting for centre
- Give confidence intervals for the effect, not just p-values:

'The p-value...incorporates information on the magnitude of the effect and the precision with which the effect is measured, and thus inevitably fails to provide distinct information about each of these...Confidence intervals convey information about both magnitude of effect and precision...'

Rothman, 1986

Adjust the effect of the risk factor for possible confounders

- Determine possible confounders:
  - Variables with imbalance between groups
  - Variables related to outcome: perform analyses to examine association between different variables and the outcome
- Adjust for confounders:
  - Include confounders in a multivariate model
  - Account for collinearity between variables in the model

Look for effect modifiers: stratified analysis

- Look for effect modifiers in stratified analyses (for example, centre)
- Test interactions
- If there are important effect modifiers, present a stratified analysis

Strategies for data analysis: II. Randomized controlled trials

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Study design

For experimental studies:

- Completely randomized
- Paired-matched
- Stratified
- Cluster randomized
- Cross-over

Protocol deviations in the analysis

- Ineligible patients
  - inclusion of all randomized subjects guards against any bias incurred by subjective choice of ineligible subjects
  - inclusion better if the trial's findings are to be extrapolated to future clinical practice in which eligibility for a given treatment is less-strictly defined
  - can be excluded when eligibility criteria are clear and objective and when the trial is double-blind

Protocol deviations in the analysis

- Non-compliance and withdrawals: analysis should be done by '**intention to treat**' principle (pragmatic approach)

'...all eligible patients, regardless of compliance with protocol should be included in the analysis of results whenever possible'

'The alternative 'explanatory approach' or 'analysis of compliers only' can distort treatment comparisons'

Pocock, 1983

Protocol deviations in the analysis

Intention to treat is not possible or can be relaxed:

- when outcome is not known (for example, in withdrawals)
- when a subject withdraws before treatment starts (caution: check if numbers and reasons are similar between groups)
- in Phase I and Phase II clinical trials, which explore properties of treatment in idealized conditions

Analysis of a multicentre randomized controlled trial

- Provide a trial profile
- Describe prognostic variables by treatment group
- Provide crude effect of treatment on outcome measure
- Provide effect of treatment on outcome measure adjusting for possible confounders
- Look for effect modifiers and conduct stratified analyses

Trial profile

Construct a flow chart providing numbers of:

- registered or eligible subjects
- randomized subjects
- subjects assigned to each group

and for each group,

- subjects withdrawn (lost to follow-up and other reasons)
- subjects who completed the trial (with outcome known)
- subjects who did not receive or comply with the treatment as allocated

Comparison of baseline characteristics between treatment groups

Comparison is made by assessing the prognostic relevance of the difference observed, **not using tests of hypothesis**:

- Compute sample statistics (means and standard deviations or medians and quartiles or percentages) by treatment group
- Compare baseline characteristics between treatment groups to discover possible confounders: randomization will produce very similar baseline statistics if the sample size is large

Estimate crude effect of treatment

- Estimate the **magnitude** of the effect and compute a confidence interval
- A p-value can also be provided

Look for effect modifiers: stratified analysis

- Stratify by centre
- Test homogeneity of effect across centres (and/or test interaction of treatment by centre)
- If there is homogeneity between centres, pool the effect over centres (adjust effect for centres)
- Consider other effect modifiers

Adjust the effect of the treatment for possible confounders

- Use same procedure described for observational studies to determine possible confounders
- Confounding is not as important as in observational studies because randomization will produce balance between treatment groups

Presentation

- Describe protocol deviations from the study as planned, together with the reasons (for ineligibility, non-compliance, withdrawal)
- Percentages: state results in absolute numbers (10/20, not only 50%)
- Present statistics in sufficient detail to permit alternative analyses and replication

Interpretation

- State findings clearly
- Discuss internal validity: sources of bias and imprecision
- Discuss external validity

Steroid hormone contraception and bone mineral density: a cross-sectional study in a diverse international population

Objective: to assess peak bone mass according to steroid hormonal contraceptive use.

Methods: cross-sectional study done at 7 centres in three geographic regions of the developing world. Women of 30-34 years of age attending family planning clinics who had at least 24 months of lifetime use of combined oral contraceptives (COC), depot-medroxyprogesterone (DMPA) or Norplant were recruited along with a comparison group of never users. Bone mineral density was measured at two sites.