

Study designs used in clinical research

**Introduction to Research Methods,
Experimental Design and Ethics for Research
Students at the Dental School, University of
Adelaide**

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Hierarchy of study designs

Researcher's
role in study
Observation

Study design

Case report/
case series

Cross-sectional
survey

Case-control study

Cohort study

Intervention

Non-experimental

Experimental
(randomized controlled
trial = RCT)

...provides
evidence about

New/unusual
conditions
Disease frequency

Etiology


Etiology and risk

Prognosis

Efficacy of therapy/
prevention

Strength of evidence for making
treatment recommendations
↓

Uniform framework for clinical study designs*

Population	Who is eligible for this study? To what population can results be generalized?
Assignment	Who is selected from the population and how? How are comparison groups created? What treatment (if any) is provided?
Assessment	What is measured?
Analysis	How are outcomes analyzed? How are groups compared?
Interpretation	What conclusions are appropriate?  What time frame is needed for the study?

* Based on Riegelman and Hirsch, 1996

Overview of case reports

Aim: Describe occurrence of new or unusual conditions in one (or a few) selected patient who has the condition

Key methodological requirements

- “Luck” in being the first to encounter an interesting case
- Rigor in diagnosis, testing and documentation of clinical findings

Strengths

- over one million case reports indexed on Medline
- uses language that is familiar to clinicians and easy to interpret
- useful reminder about conditions, diagnoses etc. that are rarely seen in most practices
- for researchers, case reports generate hypotheses that can be tested using other study designs

Limitations

- tendency to publish "gee whiz" reports of strange conditions that have little relevance to daily practice
- some authors erroneously try to imply causation, therapeutic benefits, etc

Case report from Medline

Authors: Smart ER. Macleod RI. Lawrence CM.

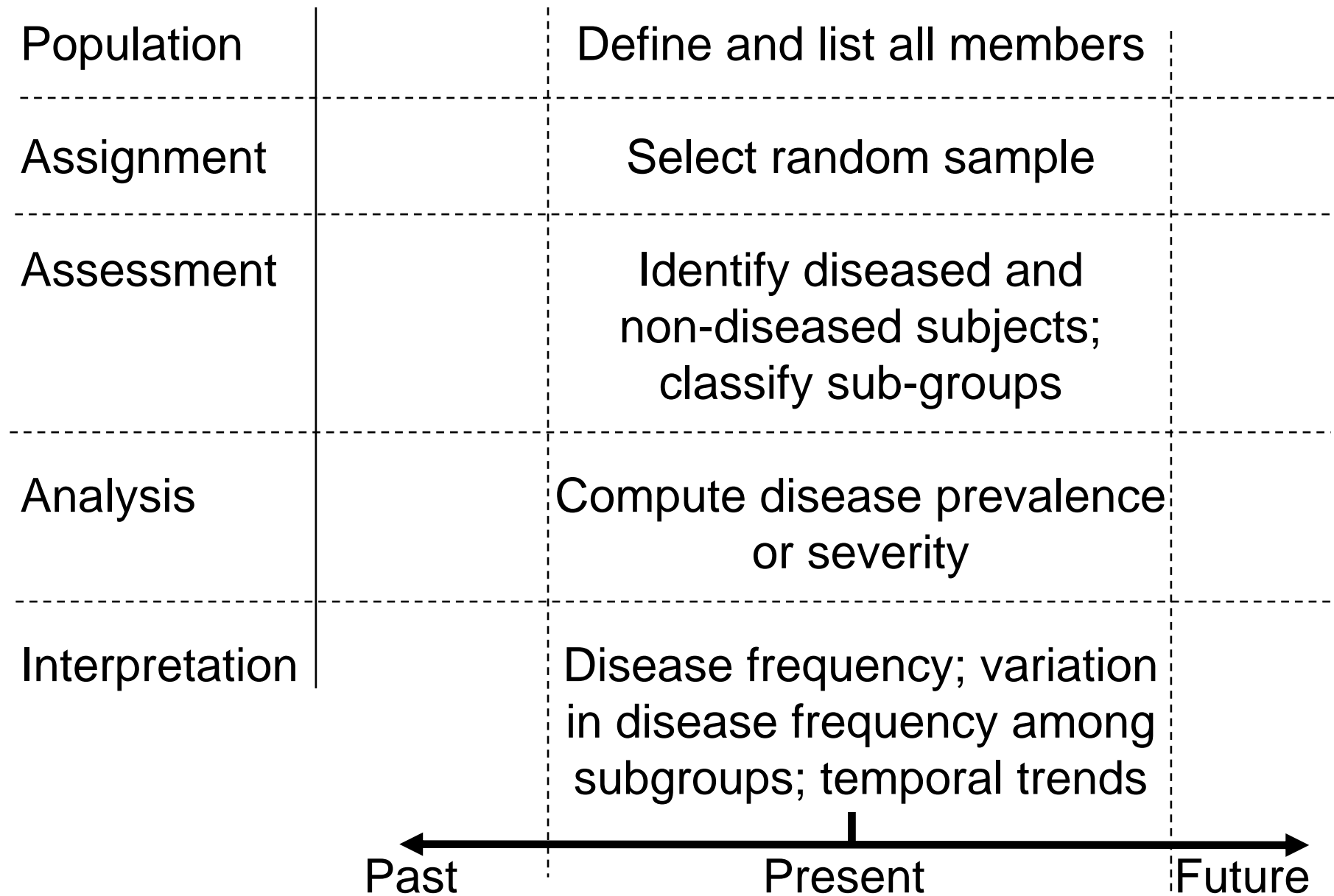
Title: Allergic reactions to rubber gloves in dental patients: report of three cases.

Source: British Dental Journal. 172(12):445-7, 1992 Jun 20.

Abstract:

Three cases of allergy to rubber are described, in which the patients exhibited peri-oral rashes following dental treatment by personnel wearing latex rubber gloves. Two of the patients were aware of possible allergy to domestic rubber products but did not reveal this as part of their medical history. With the increase in numbers of dentists wearing rubber gloves it is probable that there will be many more such cases reported in the future. Rubber products must then be added to the list of potential allergens which may be of some import to the practice of dentistry.

Design for cross-sectional surveys



Overview of cross-sectional surveys

Aim: Describe frequency of disease(s) of interest in a nominated population

- frequency=prevalence (eg. % with disease) or severity (eg. mean DMFT)

Key methodological requirements

- Access to population and sampling frame (list of all people in population)
- Method of random sampling from sampling frame
- Consistent use of standardized criteria for clinical examination of all subjects

Strengths

- best way to document burden of disease in population at one point in time
- readily-interpretable results, particularly for comparing with previous studies to identify trends in disease

Limitations

- potential non-participation bias when <100% of sampled subjects are examined (which is virtually inevitable)
- diligence is required to minimize other sources of bias (eg. examiner inconsistency) within a given survey
- but it is very difficult to assess the extent of biases between studies
- tendency to over-interpret results (eg. making inferences about ageing despite the fact that surveys are conducted at one point in time)

Cross-sectional survey from Medline

Authors: Paul T. Brandt RS .

Title: Oral and dental health status of children with cleft lip and/or palate.

Source: Cleft Palate-Craniofacial Journal. 35(4):329-32, 1998 Jul.

Abstract

OBJECTIVE: To ascertain the oral and dental health status of children with cleft lip and/or palate. **DESIGN:** Oral and dental examinations were carried out on 114 selected children with cleft lip and/or palate, using standard criteria and indices. **SETTING:** These children were examined at two cleft palate clinics in the United Kingdom. **PATIENTS:** All children examined were between the ages of 3 and 18 years. **RESULTS:** Sixty one (53.5%) of the subjects exhibited no evidence of previous caries experience, but as many as 20% exhibited active decay. The mean caries experience in the deciduous dentition (dmfs) was 2.3, and that in the permanent dentition (DMFS) was 0.9. Caries experience of the Caucasian children of the sample was lower (mean dmfs 1.9) than that of the Asian children (mean dmfs 5.5). The mean simplified debris index of the sample was 0.9, and the mean gingival bleeding index was 0.4. Children with cleft lip and palate had generally poorer oral and gingival health than those with isolated clefts of the lip or palate. **CONCLUSION:** Twenty percent of the sample had active decay. These children had poor oral health in the surgically repaired anterior segment.

Overview of case-control studies

Aim: First step in identification of risk factors

- risk factor=exposure or personal characteristic associated with increased frequency of disease

Key methodological requirements

- Access to population in which cases and controls can be sampled readily
- Method to measure exposure (or other personal characteristic) consistently both for cases and controls
- Cases and controls must have equal and non-zero potential to be exposed

Strengths

- capacity to study multiple putative risk factors for a single disease
- very efficient, requiring relatively few subjects, little time, and low cost

Limitations

- potential biases if cases and controls are sampled from different sampling frames (typically a problem in hospital-based case-control studies)
- often impossible to guarantee that exposure preceded disease onset
- statistical association between exposure and disease is not sufficient to demonstrate causation, hence reliance on additional causal criteria (eg. biological plausibility, based on in-vitro or animal experimental studies)

Case-control study from Medline

Authors: Schildt EB. Eriksson M. Hardell L. Magnuson A .

Title: Oral infections and dental factors in relation to oral cancer: a Swedish case-control study.

Source: European Journal of Cancer Prevention. 7(3):201-6, 1998 Jun.

Abstract

We investigated the role of oral infections, dentition and dental X-rays for oral cancer in a north Swedish population. This case-control study consisted of 410 cases with oral cancer for the period 1980-89 and 410 matched controls. All subjects received a mailed questionnaire. The response rates were 96% and 91% for cases and controls, respectively. The univariate analysis showed a statistically significant increased risk for oral cancer among individuals reporting problems with recurrent clinical oral infection (odds ratio (OR) 3.8). Separate analyses were made for groups with a clearly stated HSV-1 infection (OR 1.9) and highly suspected HSV-1 infection (OR 3.3) as reported by the subjects. Odds ratios were also calculated for infections in relation to tobacco and alcohol habits. For individuals reporting recurrent infection problems an increased risk was observed in every combination category. Dental factors such as different fillings, dentures and fixed prostheses showed no increased risks. Dental X-ray did not produce an increased OR either. A multivariate analysis suggested that the most important risk factors were oral infections followed by liquor consumption and active smoking

Overview of cohort studies

Aim: Describe disease frequency and confirm risk factors

- frequency = incidence (% of people developing new disease)

Key methodological requirements

- Access to population that is disease free but at risk of developing disease
- Method to classify people's level of exposure to putative causes at time of recruitment
- Method to follow and account for all people, often for many years
- Method to measure new events of disease among all people

Strengths

- capacity to study multiple diseases
- establishes clear temporal sequence between exposure and disease onset

Limitations

- time consuming and therefore costly
- potential non-participation bias when <100% of sampled subjects are followed up (which is virtually inevitable)
- diligence is required to minimize other sources of bias (eg. examiner inconsistency)
- evidence that confirmed risk factor is causal relies on additional criteria (eg. biological plausibility)

Cohort study from Medline

Authors: Garcia RI. Krall EA. Vokonas PS .

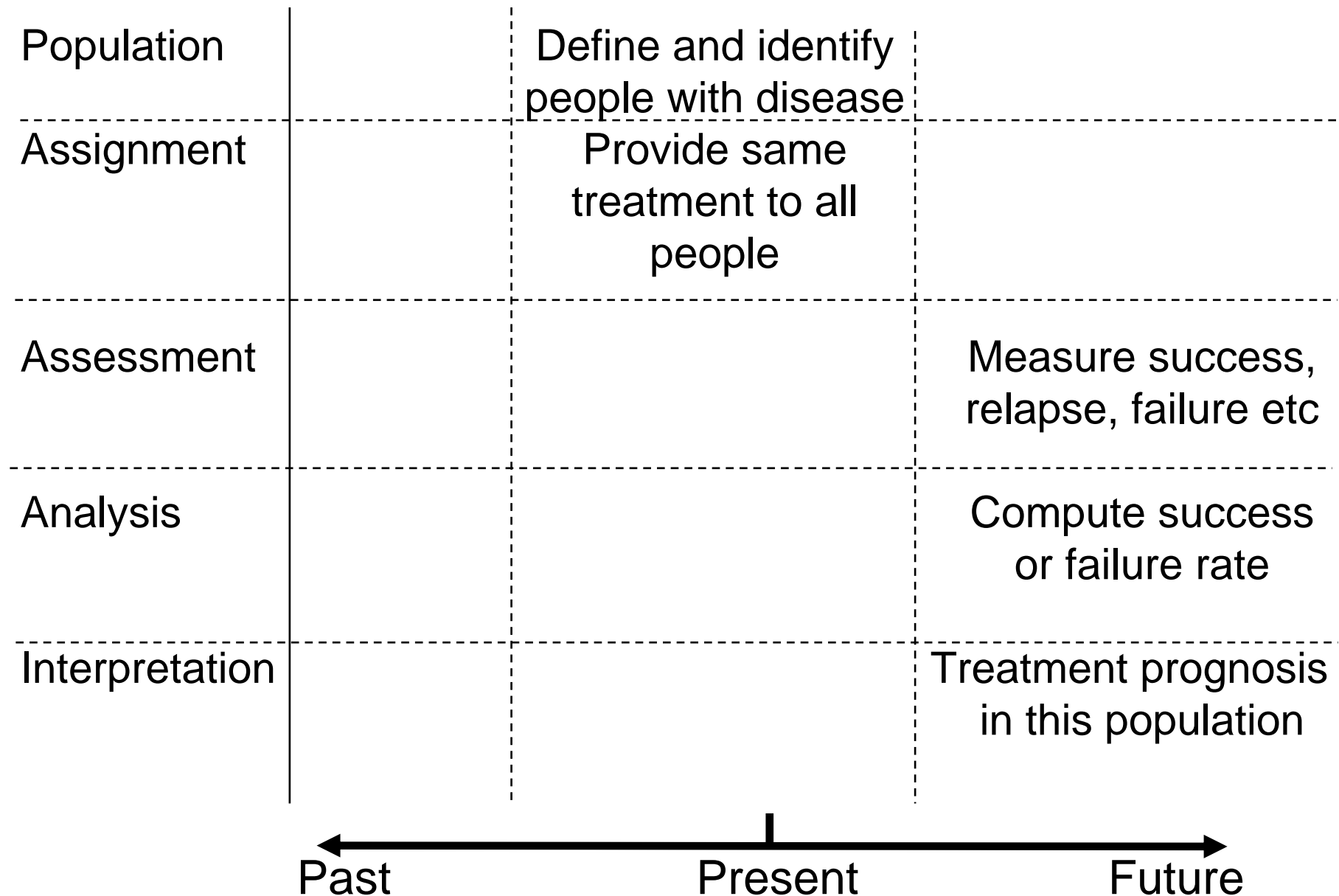
Title: Periodontal disease and mortality from all causes in the VA Dental Longitudinal Study.

Source : Annals of Periodontology. 3(1):339-49, 1998 Jul.

Abstract

We have examined the relationship of periodontal disease to mortality from all causes in the VA Dental Longitudinal Study and Normative Aging Study, a prospective cohort study of the determinants of disease in aging men. Subjects were screened for entry into the closed-panel cohort in the mid-1960s, based on good medical health. They are not VA patients. We have used proportional hazards regression models to assess the relationship of periodontal health status at baseline to all-cause mortality over a 25+-year follow-up period. A total of 804 dentate subjects who were alive and medically healthy through their first follow-up exam were used in the analysis; of these, 166 died during subsequent follow-up through December 1996. Survival was calculated in years from baseline exam to death or censoring (most recent study examination date). To define periodontal health status at baseline, we separately used radiographic alveolar bone loss (ABL) (person-level scores of mean whole-mouth % ABL, measured with a Schei ruler using full-mouth series of periapical films) and periodontal clinical probing depths. Covariates included age at baseline, and assessments at baseline of smoking and alcohol use, education, body mass index, serum cholesterol, white blood cell count, blood pressure, family history of heart disease, and number of teeth present. We found that periodontal status at baseline was a significant and independent predictor of mortality in this cohort, while controlling for other recognized predictors in multivariate models. For each 20% increment in mean whole-mouth ABL, the subject's risk of death increased by 51% (RR = 1.51; 95% CI = 1.11-2.04). The increase in risk attributable to periodontal status was found to be similar in magnitude to, and independent of that attributable to cigarette smoking in this cohort. While the increased risk due to smoking was 1.52-fold (95% CI = 1.06-2.19), being in the population quintile with highest ABL scores (i.e., worst periodontal status) was associated with a 1.85 fold increase in risk (95% CI = 1.25-2.74) using multivariate analyses. The hypothesis that chronic oral infections, as in periodontitis, may have important systemic sequelae merits further investigation in prospective controlled studies

Design for non-experimental intervention studies



Overview of non-experimental intervention studies

Aim: Describe rate of treatment success or failure

Key methodological requirements

- access to patient population that has consistently received the same treatment
- other requirements similar to cohort studies

Strengths

- similar to cohort studies

Limitations

- similar to cohort studies
- potential for spontaneous improvements in health due to well-characterized biases (Hawthorne effect, placebo effect, regression to mean)
- tendency to over-interpret results as evidence of efficacy which is not possible in the absence of a randomly-assigned, placebo controlled comparison group that is followed concurrently

Non-experimental intervention study from Medline

Authors: Arvidson K. Bystedt H. Frykholm A. von Konow L. Lothigius E .

Title: Five-year prospective follow-up report of the Astra Tech Dental Implant System in the treatment of edentulous mandibles.

Source: Clinical Oral Implants Research. 9(4):225-34, 1998 Aug.

Abstract

This report of the 1st 2 prospective studies using the Astra Tech Implant System and fixed detachable bridges for rehabilitation of mandibular edentulism, presents clinical and radiographic data at the 5-year follow-up. The original material comprised 109 subjects, 56 of whom had been included in the original study, using the 1st generation Astra Tech Implant. Two subjects were excluded and the 3-year follow-up report was based on the remaining 54 subjects and 310 fixtures. In all 16 subjects were lost to follow-up and the 5-year results are based on the remaining 91 subjects with 517 fixtures in function: 5 fixtures were lost due to mobility at abutment installation and during the 1st year, 2 fixtures were removed due to pain, and after 4 years in situ 1 fixture failed. The cumulative fixture survival rate at 5 years was 98.7% and the bridge survival rate was 100%.

Conclusions: clinical study designs

- **Different study designs answer different clinical questions**
 - **If abstracts (and published papers!) do not state study design, readers need to be able to determine which design has been used and determine if it is appropriate to answer the question posed by the researchers**
- **Avoid the temptation to over-interpret results that call for a more rigorous study design**
 - **eg. case-studies do not provide evidence about causes of disease, prognosis or efficacy of treatment**
- **Each study design has its own methodological requirements, strengths and weaknesses**
- **No single study is perfect**
 - **Clinical decisions should be based on consistent findings from several studies that use similar design and methodology**