Study designs in medical research

Study design is the procedure under which a study is carried out

Two main categories

- Observation:
  - Identify subjects, then
  - Observe and record characteristics
- Experiment
  - Identify subjects,
  - Place in common context,
  - Intervene, then
  - Observe effects of intervention

Observation vs Experiment

- Observations are readily obtained, but subject to bias, that is systematic errors
- Some observational designs are less subject to bias than others
- Experiments are hard to do well
- Experiments can answer narrow questions definitively
- Generalizability of results from experiments may be at issue, eg new drug testing that excludes women subjects

Observational studies

- Case Series
- Case-control studies
- Cohort Studies
- (Meta-Analyses)

Your patients are going to ask if they should eat more oatmeal, and here's why:

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FDA approves first food specific health claim for oatmeal.

OATS MAY INDEPENDENTLY LOWER CHOLESTEROL BY 5%.

Oat consumption has been found to lower cholesterol in adult men and women aged 20 to 70 years old whether or not they had elevated cholesterol levels to start. The benefits are greatest for those individuals with initial high cholesterol levels.
A 1992 meta-analysis published in JAMA (1992: Vol. 267; pp 3317-3325) pooled data from over a dozen clinical trials and clearly documented the ability of oat soluble fiber to lower total cholesterol, independent of and incremental to a low fat diet.

NORMAL PLASMA CHOLESTEROL IN AN 88-YEAR-OLD MAN WHO EATS 25 EGGS A DAY

Mechanisms of Adaptation

FRED KERN, JR., M.D.

Case Report

An 88-year-old man who lived in a retirement community complained only of loneliness since his wife's death. He was an articulate, well-educated elderly man, healthy except for an extremely poor memory without other specific neurologic deficits. He had been given a diagnosis of Alzheimer's disease and was intermittently depressed. His general health had been excellent, without notable symptoms. He had mild constipation. His weight had been constant at 82 to 86 kg (height, 1.87 m). He had no history (according to the patient and his personal physician of 15 years) of heart disease, stroke, or kidney disease except for an episode of mild chest pain three years earlier. The only objective change at that time was transient depression of the ST segments and T waves in the lateral leads on his electrocardiogram. The patient had been treated for angina and had had no recurrence. There was no history of gallstones or of symptoms of biliary tract disease, but no cholecystography or ultrasound examination had been done recently. His physician's records showed numerous serum cholesterol measurements that ranged from 3.88 to 5.18 mmol per liter (150 to 200 mg per deciliter).

The patient had never smoked and never drank excessively. His father died of unknown causes at the age of 40, and his mother died at 76. One sister died at the age of 82, and another was alive at 86; their plasma lipid values were not available.

The patient's poor memory impaired the accuracy of the dietary history, but his consumption of 20 to 30 eggs a day was verified. Although he could not remember the duration of this eating pattern, his physician attested to its presence for 15 years; a friend, for even longer. He always soft-boiled the eggs and ate them throughout the day. He kept a careful record, egg by egg, of the number ingested each day. The nurse at the retirement home confirmed the daily delivery to him of approximately two dozen eggs. A psychiatrist and a clinical psychologist had characterized this unusual eating habit as compulsive behavior, based on complex psychological factors. Efforts to modify the behavior had been unsuccessful. The patient stated, "Eating these eggs ruins my life, but I can't help it."

Case series

- Example: “Normal plasma cholesterol in an 88-year-old man who eats 25 eggs a day” [Kern J, NEJM 1991; 324:896–899]
- Advantages
  - Excellent at identifying unusual situation
  - Good for generating hypotheses amenable to rigorous test
- Disadvantages
  - Generally short-term
  - Investigators self-select (bias!)
  - Generally no controls

Controls

- A control is a standard of comparison for
  - Effects
  - Variability

Case-control studies

- Controlled studies
- Retrospective

A Coccidioidomycosis Outbreak Following the Northridge, Calif, Earthquake

Eileen Schneider, MD; Rana A. Hajjeh, MD; Richard A. Spiegel, DVM; Randall W. Jibson, PhD; Edwin L. Harp, PhD; Grant A. Marshall, MS; Robert A. Gunn, MD; Michael M. McNeil, MBBS; Robert W. Pinner, MD; Roy C. Baron, MD; Ronald C. Burger; Lori C. Hutwagner, MS; Casey Crump; Leo Kaufman, PhD; Susan E. Reef, MD; Gary M. Feldman, MD; Demosthenes Pappagianis, MD; S. Benson Werner, MD

How are Case-Control Studies Done?

- Identify cases (with condition of interest, here, coccidioidomycosis)
- Match to disease-free controls who are similar with respect to known risk factors for condition
- Compare degree of exposure to possible risk factor (here, being in dust cloud).

The logic of Case-Control Studies

- Cases differ from controls only in having the disease
- If exposure does not predispose to having the disease, then exposure should be equally distributed between the cases and controls.
- The extent of greater previous exposure among the cases reflects the increased risk that exposure confers

Measures of effect

- Relative risk (ratio of probabilities of contracting disease given exposure), or
- Odds ratio (ratio of the odds of contracting disease given exposure)
- RR or OR of 1 indicate no effect of exposure (equal odds)
  - "Physically being in a dust cloud (OR 3.0; CI, 1.6-5.4; P<.001) significantly increased the risk for being diagnosed with coccidioidomycosis"

Objective.—To describe a coccidioidomycosis outbreak in Ventura County following the January 1994 earthquake, centered in Northridge, Calif, and to identify factors that increased the risk for acquiring acute coccidioidomycosis infection.

Design.—Epidemic investigation, population-based skin test survey, and case-control study.

Setting.—Ventura County, California.

Results.—In Ventura County, between January 24 and March 15, 1994, 203 outbreak-associated coccidioidomycosis cases, including 3 fatalities, were identified (attack rate [AR], 30 cases per 100 000 population). The majority of cases (56%) and the highest AR (114 per 100 000 population) occurred in the town of Simi Valley, a community located at the base of a mountain range that experienced numerous landslides associated with the earthquake. Disease onset for cases peaked 2 weeks after the earthquake. The AR was 2.8 times greater for persons 40 years of age and older than for younger persons (relative risk, 2.8; 95% confidence interval [CI], 2.1-3.7; $P<.001$). Environmental data indicated that large dust clouds, generated by landslides following the earthquake and strong aftershocks in the Santa Susana Mountains north of Simi Valley, were dispersed into nearby valleys by northeast winds. Simi Valley case-control study data indicated that physically being in a dust cloud (odds ratio, 3.0; 95% CI, 1.6-5.4; $P<.001$) and time spent in a dust cloud ($P<.001$) significantly increased the risk for being diagnosed with acute coccidioidomycosis.

Conclusions.—Both the location and timing of cases strongly suggest that the coccidioidomycosis outbreak in Ventura County was caused when arthrospores were spread in dust clouds generated by the earthquake. This is the first report of a coccidioidomycosis outbreak following an earthquake. Public and physician awareness, especially in endemic areas following similar dust cloud–generating events, may result in prevention and early recognition of acute coccidioidomycosis.

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Original Contributions

Inhaled Steroids and the Risk of Hospitalization for Asthma

James G. Donahue, DVM, PhD; Scott T. Weiss, MD, MS; James M. Livingston, MBA; Marcia A. Goetsch; Dirk K. Greineder, MD, PhD; Richard Platt, MD, MS

Objective.—To determine if anti-inflammatory treatment for asthma reduces the risk of asthma hospitalization.

Design.—Retrospective cohort study.

Setting.—A health maintenance organization (HMO) in eastern Massachusetts.

Participants.—Members of the HMO who were identified during the period October 1991 through September 1994 as having a diagnosis of asthma using a computerized medical record system.

Main Outcome.—Hospitalization for asthma.

Results.—Of the 16 941 eligible persons, 742 (4.4%) were hospitalized for asthma. The overall relative risk (RR) of hospitalization among those who received inhaled steroids was 0.5 (95% confidence interval [CI], 0.4-0.6) after adjustment for β-agonist dispensing. Additional adjustment for age, race, other asthma medications, and amount and type of ambulatory care for asthma did not substantially affect the inverse relationship between use of inhaled steroids and hospitalization. Cromolyn was similarly associated with reduced risk, especially among children (RR,0.8; 95% CI, 0.7-0.9). In contrast, increasing β-agonist use was associated with increasing hospitalization risk even after adjustment for other factors and medications. The steroid-associated protection was most marked among individuals who received the largest amount of β-agonist.

Conclusions.—Inhaled steroids and, to a lesser extent, cromolyn confer significant protection against exacerbations of asthma leading to hospitalization. These results support the use of inhaled steroids by individuals who require more than occasional β-agonist use to control asthma symptoms.

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Cohort studies

- Prospective
- Controlled
- Can determine causes and incidence of diseases as well as identify risk factors
- Generally expensive and difficult to carry out
- Procedure for cohort study
- Logic of the cohort study

Procedure for cohort study

- Identify groups of exposed subjects and control subjects
- Match for other risk factors
- Follow over time
- Record the fraction in each group who develop the condition of interest
- Compare these fractions using RR or OR

Logic of the cohort study

Differences in the rate at which exposed and control subjects contract a disease is due to the differences in exposure, since other known risk factors are equally present in the two groups

Coronary Angioplasty Volume-Outcome Relationships for Hospitals and Cardiologists

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Objective.—To assess the relationship between each of 2 provider volume measures (annual hospital volume and annual cardiologist volume) for percutaneous transluminal coronary angioplasty (PTCA) and 2 outcomes of PTCA (in-hospital mortality and same-stay coronary artery bypass graft [CABG] surgery).

Design.—Cohort study, using data from January 1, 1991, through December 31, 1994, from the Coronary Angioplasty Reporting System of the New York State Department of Health.

Setting.—Thirty-one hospitals in New York State in which PTCA was performed during 1991-1994.

Patients.—All 62 670 patients discharged after undergoing PTCA in these hospitals during 1991-1994.

Main Outcome Measures.—Rates of in-hospital mortality and CABG surgery during the same stay as the PTCA.

Results.—The overall in-hospital mortality rate for patients undergoing PTCA in New York during 1991-1994 was 0.90%, and the same-stay CABG surgery rate was 3.43%. Patients undergoing PTCA in hospitals with annual PTCA volumes less than 600 experienced a significantly higher risk-adjusted in-hospital mortality rate of 0.96% (95% confidence interval [CI], 0.91%-1.01%) and risk-adjusted same-stay CABG surgery rate of 3.92% (95% CI, 3.76%-4.08%). Patients undergoing PTCA by cardiologists with annual PTCA volumes less than 75 had mortality rates of 1.03% (95% CI, 0.91%-1.17%) and same-stay CABG surgery rates of 3.93% (95% CI, 3.65%-4.24%); both of these rates were also significantly higher than the rates for all patients. Also, same-stay CABG surgery rates for patients undergoing PTCA in hospitals with annual volumes of 600 to 999 performed by cardiologists with annual volumes of 75 to 174 (2.99%; 95% CI, 2.69%-3.31%) and 175 or more (2.84%; 95% CI, 2.57%-3.14%) were significantly lower than the overall statewide rate (3.43%).

Conclusions.—In New York State, both hospital PTCA volume and cardiologist PTCA volume are significantly inversely related to in-hospital mortality rate and same-stay CABG surgery rate for patients undergoing PTCA.

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Experimental studies

Clinical trials

A clinical trial is a comparative, prospective experiment conducted in human subjects. (4 requirements)

Controlled vs Uncontrolled studies

Historical controls

Controlled vs Uncontrolled studies

- Controlled → comparison made relative to a simultaneous reference condition
- Uncontrolled → comparison implicit
  - Previous experience
  - Historical evidence
  - Anecdote
- Controlled trials…

Controlled trials…

- …make it possible to ascribe differences in outcome to differences in treatment
- Differences from expectation in uncontrolled studies could also be due to many other factors
  - Different kinds of patients
  - Change in standard of care
  - Improving technique, etc

Historical controls

- Are better than no controls
- Example: ddI vs AZT for AIDS
- But not by much
- Example: gastric freezing for peptic ulcer

The New England Journal of Medicine

THE EFFECTS OF IBUPROFEN ON THE PHYSIOLOGY AND SURVIVAL OF PATIENTS WITH SEPSIS

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Randomization & Concurrent Controls

- Randomized vs nonrandomized assignment to Rx
- "The randomized clinical trial is the epitome of all research designs because it provides the strongest evidence for concluding causation."
- Conclusions from nonrandomized studies subject to many sources of bias

ABSTRACT

Background In patients with sepsis the production of arachidonic acid metabolites by cyclooxygenase increases, but the pathophysiologic role of these prostaglandins is unclear. In animal models, inhibition of cyclooxygenase by treatment with ibuprofen before the onset of sepsis reduces physiologic abnormalities and improves survival. In pilot studies of patients with sepsis, treatment with ibuprofen led to improvements in gas exchange and airway mechanics.

Methods From October 1989 to March 1995, we conducted a randomized, double-blind, placebo-controlled trial of intravenous ibuprofen (10 mg per kilogram of body weight [maximal dose, 800 mg], given every six hours for eight doses) in 455 patients who had sepsis, defined as fever, tachycardia, tachypnea, and acute failure of at least one organ system.

Results In the ibuprofen group, but not the placebo group, there were significant declines in urinary levels of prostacyclin and thromboxane, temperature, heart rate, oxygen consumption, and lactic acidosis. With ibuprofen therapy there was no increased incidence of renal dysfunction, gastrointestinal bleeding, or other adverse events. However, treatment with ibuprofen did not reduce the incidence or duration of shock or the acute respiratory distress syndrome and did not significantly improve the rate of survival at 30 days (mortality, 37 percent with ibuprofen vs. 40 percent with placebo).

Conclusions In patients with sepsis, treatment with ibuprofen reduces levels of prostacyclin and thromboxane and decreases fever, tachycardia, oxygen consumption, and lactic acidosis, but it does not prevent the development of shock or the acute respiratory distress syndrome and does not improve survival. (N Engl J Med 1997;336:912-8.)

Patients can serve as own controls

- This is usually beneficial
- The comparison removes patient differences.

Example: Vasocon-A

- Subjects received placebo eye drops in one eye, Vasocon-A drops in the other eye
  - Randomization determined which eye gets placebo for each pt
  - Cat-dander extract applied to both eyes
  - Response between eyes compared.

Paired designs

- Work best when outcome can be observed shortly after treatment, and
- Disease and treatment are both short-lived

Blinding

- Good practice: factors that can affect the evaluation of outcome should not be permitted to influence the evaluation process
- Double-blind design
  - Neither patient nor outcome evaluator knows Rx to which patient was assigned
- Single-blind
  - Patient or evaluator is blinded as to Rx, but not both
- Triple-blind
  - Patient, Physician, and Data analyst are blinded as to Rx identity