# Epidemiology:
## Study Design and Data Analysis

Thomas R. Vetter, M.D., M.P.H.
Maurice S. Albin Professor of Anesthesiology
Vice Chair and Director, Division of Pain Medicine
Department of Anesthesiology
University of Alabama School of Medicine
Birmingham, Alabama



## Two Introductory Observations

"A little knowledge is a dangerous thing, but a little want of knowledge is also a dangerous thing."

Samuel Butler (1835-1902)

"For some, epidemiology is too simple to warrant serious consideration, and for others it is too convoluted to understand. I hope to demonstrate to the reader that neither view is correct."

Kenneth J. Rothman
*Epidemiology: An Introduction*, 2002

## My Presentation Objectives

❶ Practical basics of **biostatistics**, including **sample size, power analysis, and confidence interval**s

❷ Practical basics of **clinical epidemiology**

❸ Sources of **bias** in study design

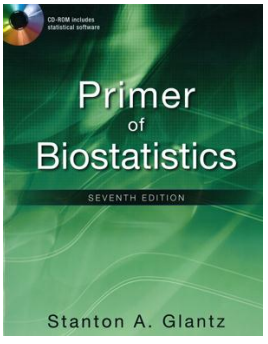
❹ Concept of **confounding** in study design

❺ Methods to identify and to control for bias and confounding, including **regression modeling** and **propensity scores**

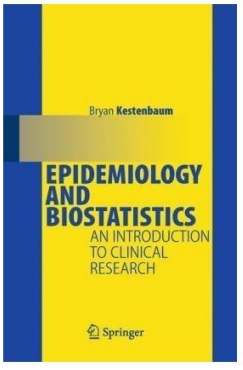
❻ Readily available, user-friendly **biostatistics and epidemiology software** options for the clinical researcher

## Excellent Introductory Resources

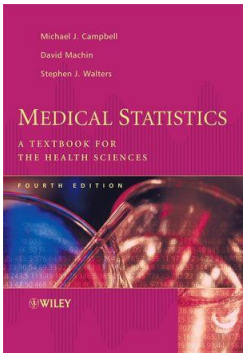
**Primer of Biostatistics**
7th Edition, 2011
Glantz




**Epidemiology and Biostatistics**
1st Edition, 2009
Kestenbaum

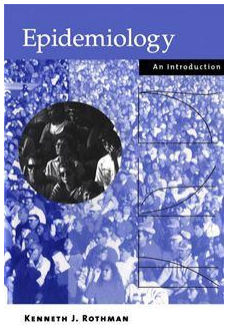



**Medical Statistics**
4th Edition, 2007
Campbell, Machin & Walters

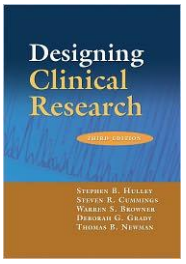


## More Excellent Introductory Resources

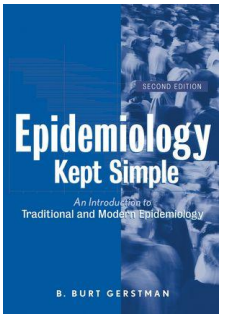
**Epidemiology: An Introduction**
1st Edition, 2002
Rothman




**Designing Clinical Research**
3rd Edition, 2006
Hulley, Cummings, Browner, Grady & Newman



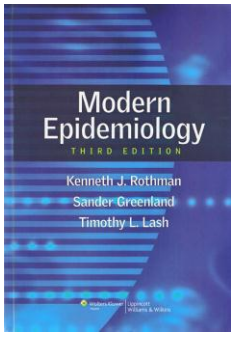

**Epidemiology Kept Simple**
2nd Edition, 2003
Gerstman




**U Penn Center for Clinical Epidemiology and Biostatistics (CCEB): Volume 1**
**www.cceb.upenn.edu/pages/localio/EPI521**

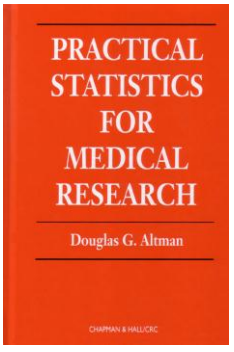
## Excellent Intermediate Resources

**Modern Epidemiology**
3rd Edition, 2008
Rothman, Greenland, & Lash




**Epidemiology: Study Design and Data Analysis**
2nd Edition, 2004
Woodward


**Practical Statistics for Medical Research**
1991, Altman

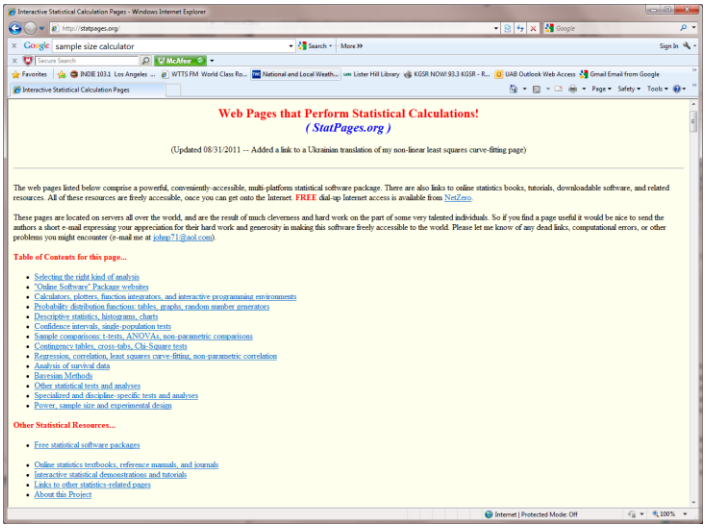



**U Penn Center for Clinical Epidemiology and Biostatistics (CCEB): Volume 2**
**www.cceb.upenn.edu/pages/localio/EPI521**

# **StatSoft**: www.statsoft.com/textbook

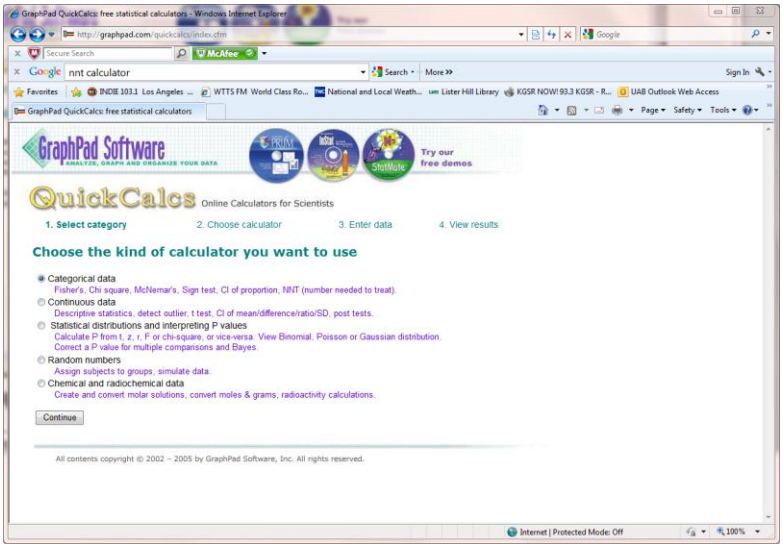

**"StatSoft has freely provided the Electronic Statistics Textbook as a public service for more than 12 years now."**

# **StatPages**: http://statpages.org/




**"**The web pages listed below comprise a powerful, conveniently-accessible, multi-platform statistical software package. There are also links to online statistics books, tutorials, downloadable software, and related resources. All of these resources are freely accessible, once you can get onto the Internet**."**

## **GraphPad**: http://graphpad.com




**Great set of pretty easy to use calculators – not SA, Stata, SPSS, or Minitab – but it's free!**

## **OpenEpi 2.3.1**: www.openepi.com


**"A Collaborative, Open-Source Project in Epidemiologic Computing"**

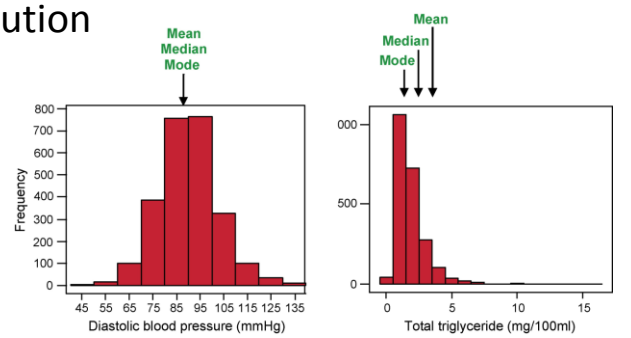
## Fundamentals of Inferential Statistics

- **Central Limit Theorem**
  - The distribution of means (averages) of many trials is always normal, even if the distribution of each trial is not normal.
- **Law of Large Numbers**
  - Provided the sample size is large enough, the sample mean ($\overline{X}$) will be "close" to the population mean (μ) with a specified level of probability.
  - The larger the sample size, the closer the sample will represent the entire population.
  - In practical terms, the **sample N must be ≥ about 30**.
- Allow us to make an **inference** – based upon the **sample variable** – about the **population parameter**

## Types of Data

- Various measurement scales
- **Nominal** or categorical
  - e.g., gender, race, blood type
- **Dichotomous** or binary (+/- or yes/no)
  - e.g., death, pregnancy, postoperative MI, PONV
- **Continuous** or interval
  - e.g., mean BP, serum glucose, 100 mm VAS pain score
- **Ordinal** or rank-ordered
  - e.g., 5 point sedation score, 11 point NRS pain score
- We often collapse continuous data into dichotomous data using a "cut-point value" (< x and > x).

# Measures of Central Tendency and Normal Distribution




- **Mean, median, and mode** are measures of central tendency.
- **Mean** is most sensitive to outliers.
- Examine the histograms to assess the data distribution for **normality**: Diastolic blood pressure are **normally distributed** *whereas* triglycerides are **skewed** (to the left)
- **Parametric data** are normally distributed *versus* **non-parametric data** are not.
- **Ordinal data** are *always* non-parametric and should be described with a **median** (IQR).

McCrum-Gardner, E. Which is the correct statistical test to use? Br J Oral Maxillofac Surg, 2008;46(1), 38-41.

# What Test Statistic to Used?

| | Two Groups | Two Groups | Two Groups | Three or More Groups |
|---|---|---|---|---|
| **Data** | **Unpaired** | **Paired** | **> 2 Measurements per study subject** | **Unpaired** |
| Continuous (interval) | Independent t-test | Paired t-test | ANOVA with repeated measures | ANOVA |
| Ordinal or non-normally distributed continuous | Mann-Whitney U-test | Wilcoxon signed rank test | Friedman's test | Kruskal-Wallis test |
| Nominal or categorical | Chi-squared ($\chi 2$) test with 2 X 2 contingency table (Fisher's exact if any cell size is < 5) | McNemar's test | Cochran's *Q* test | Chi-squared ($\chi 2$) test with 2 X N contingency table (Fisher's exact if any cell size is < 5) |

Glantz SA: Primer of Biostatistics, 7th Edition, 2011.

## Hypothesis Testing I

- $H_0$: the **null hypothesis**: $\mu_1 = \mu_2$
- $H_a$: the **alternative hypothesis**: $\mu_1 \neq \mu_2$
- $\mu$ is population mean but could be $\rho$ (proportion)
- Is the difference observed between study sample 1 and study sample 2 significant enough to reject the $H_0$ and accept the $H_a$?
- "We hypothesized that _____ was more effective than _____ in treating _____ in _____."
- "This study was undertaken to assess the efficacy of ____ in reducing the incidence of _____ in _____."
- **Both** statements are the alternative hypothesis.

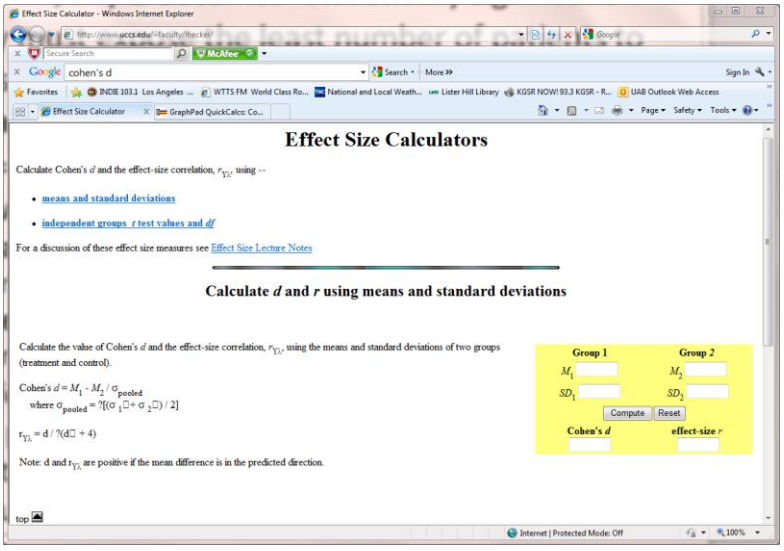
## Hypothesis Testing II

- **Type I error**
  - Rejecting $H_0$ when it is in fact true
  - False positive study
  - Probability of Type I error = $\alpha$, usually set at 0.05
  - Increased risk with repeated measurements
- **Type II error**
  - Accepting $H_a$ when it is in fact false
  - False negative study
  - Probability of Type II error = $\beta$, usually set at 0.20
- **P-value** = chance of a committing a **Type I error** or that the observed sample difference is due **simply** to **chance** and not the intervention/factor being studied
- Really no such thing as "very significant" ($p < 0.01$) or "highly significant" ($p < 0.001$): instead it's **all-or-none**

# So You Reject the Null Hypothesis

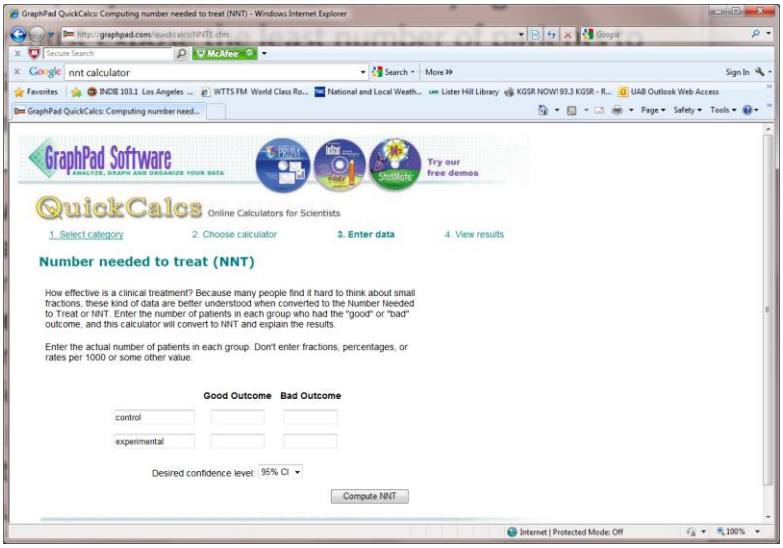
- **But** is the observed difference **clinically significant**?
- **Effect size** for continuous data:
  - **Cohen's d** = [mean group 1] – [mean group 2] / Pooled standard deviation
  - 0 to 0.3 → "small" effect
  - 0.3 to 0.6 →"medium" effect
  - > 0.6 to theoretically ∞ → "large" effect
- **Number needed to treat (NNT)** for dichotomous data:
  - NNT = 100 ÷ ARR (absolute risk reduction)
- Many online calculators for both Cohen's d and NNT
  - http://www.uccs.edu/~faculty/lbecker/
  - http://graphpad.com/quickcalcs/NNT1.cfm

# http://www.uccs.edu/~faculty/lbecker/




**Simple interface to determine effect size (Cohen's d)**

## http://graphpad.com/quickcalcs/NNT1.cfm




**Simple interface to determine number needed to treat (NNT)**

## Sample Size and Power Analysis I

- As N → ∞, any Δ becomes "statistically significant"
- Ethically must expose the least number of patients to the risks of the study or not being optimally treated
- **Power analysis** done to determine sample size (N)
- **Power** = **1 – β**: e.g., 1 – 0.20 = 0.8 or 80%
- Need two things to determine needed sample size:
  - **Minimal clinically significant difference** in most important (primary) clinical outcome variable
  - **Expected sample variance** (standard deviation) – can be derived from previous studies – but is often unknown
- Also need to know what test statistic is indicated!
  - Student's t-test, Chi-square, etc.

# Sample Size and Power Analysis II

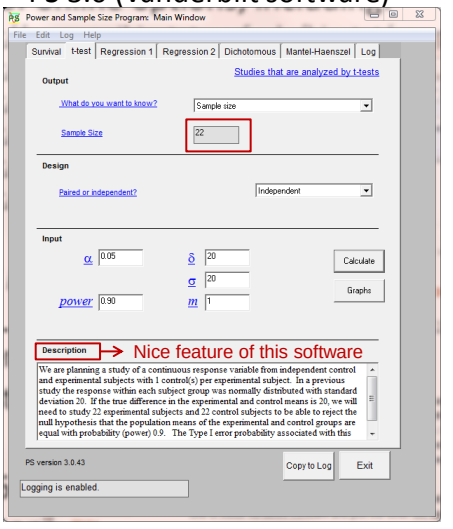
- Slew of online options, including:
  - http://www.epibiostat.ucsf.edu/biostat/sampsize.html#proportions
  - http://hedwig.mgh.harvard.edu/sample_size/size.html
  - http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize
  - http://statpages.org/#Power
  - http://www.stat.ubc.ca/~rollin/stats/ssize/
  - http://department.obg.cuhk.edu.hk/researchsupport/statstesthome.asp

- "An *a priori* sample size determination indicated that _____ patients per group would be needed to have 90% power of detecting a pain score difference of 20 ± 20 (SD) at rest at 24 hours postoperatively with an α = 0.05."

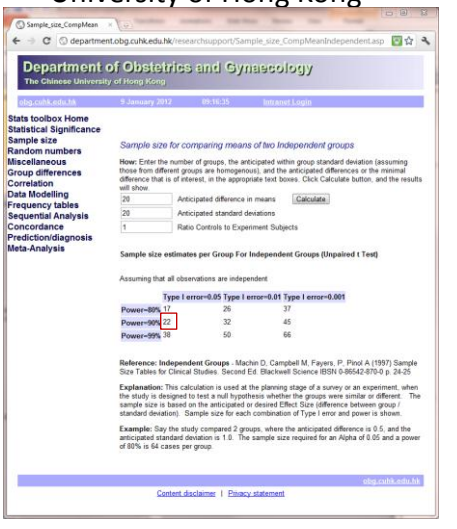
- $\overline{X}_1$ = 60 on 100 mm VAS and $\overline{X}_2 = 80$ on 100 mm VAS
- The standard deviation (SD) for both groups = 20

# Sample Size and Power Analysis III

PS 3.0 (Vanderbilt software)



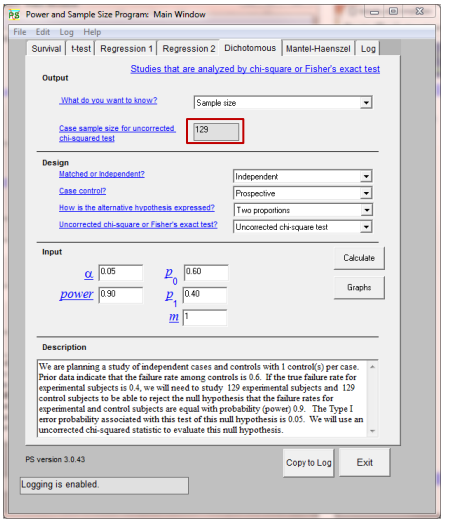

University of Hong Kong



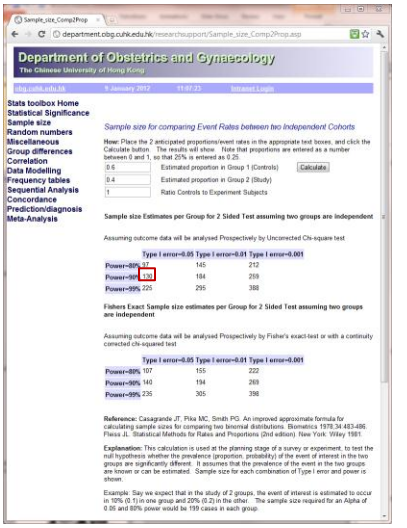

**But** despite power analysis of N = 22, remember Law of Large Numbers (N ≥ 30).

# Sample Size and Power Analysis IV

PS 3.0 (Vanderbilt software)




University of Hong Kong




**But** with a Chi-square with expected 60% versus 40% incidence: N must be 130 (!)

# Confidence Intervals

- **Sample value** is only a single, variable **estimate** of the **true value** or parameter in the population.
- Confidence interval is the range of values within which we can be ___% confident that this true value lies.
- Can be determined for a mean, proportion, or risk ratio
- 95% CI = $\overline{X}$ ± 1.96[SD/√n]: where $\overline{X}$ is the mean and *n* is the sample size, 1.96 is 95% *z-score*
- 90% *z-score* = 1.65 and 99% *z-score* = 2.58 so the **90% CI is narrower and the 99% CI is wider than the 95% CI for the <u>same</u> random sample**
- **Larger the sample N → narrower the CI**

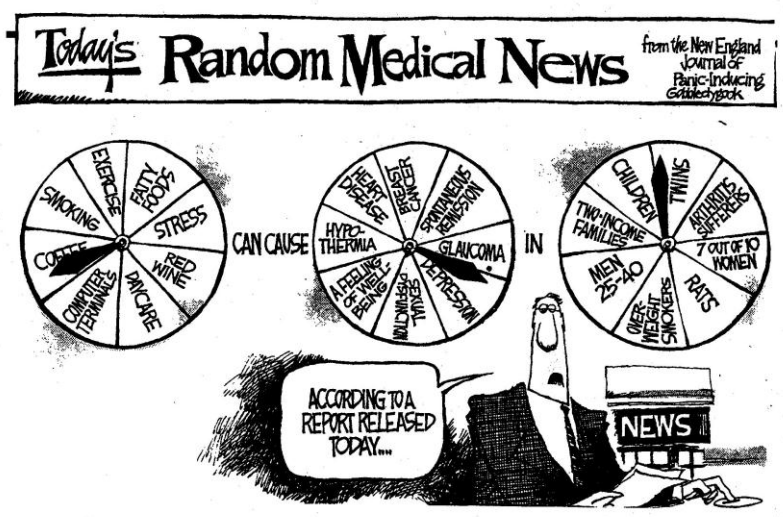
# RRR, ARR, CIs and P-Values All-In-One

| Control Group | Treatment Group | Relative Risk Reduction (RRR) or Efficacy | 95% CI for the RRR | P-Value |
|---|---|---|---|---|
| 2/4 | 1/4 | 50% | –174 to 92 | 0.53 |
| 10/20 | 5/20 | 50% | –14 to 79.5 | 0.19 |
| 20/40 | 10/40 | 50% | 9.5 to 73.4 | 0.04 |
| 50/100 | 25/100 | 50% | 26.8 to 66.4 | 0.0004 |
| 500/1000 | 250/1000 | 50% | 43.5 to 55.9 | < 0.0001 |

- In all five examples, the **ARR = 25%** and the **NNT** = 100/25 = **4**
- Note that as N increases, the P-value becomes smaller.
- Note that as N increases, the 95% CI becomes narrower.
- But what are we to make of the lower and upper limits of 95% CI?
- If **positive** study, look at **lower limit** and see if still clinically significant.
- If **negative** study, look at **upper limit** and see if still clinically significant.

Barratt, A., et al. Tips for learners of evidence-based medicine: 1. Relative risk reduction, absolute risk reduction and number needed to treat. CMAJ, 2004;171(4):353-358.

# Sometimes it seems like…




**Exposure to general anesthetics early in life can cause learning disabilities later in childhood…MAYBE.**

**Jim Borgman**
**The Cincinnati Enquirer**
King Features Syndicate

# Thoughts on Clinical Trials to Address the Effects of Anesthesia on the Developing Brain

◆ EDITORIAL VIEWS

Anesthesiology 2008; 109:757–61 

***Anesthesia and Neurodevelopment in Children***

*Time for an Answer?*

Lena S. Sun, M.D., Guohua Li, M.D., Dr.P.H., Charles DiMaggio, Ph.D., M.P.H., Mary Byrne, Ph.D., M.P.H., Virginia Rauh, Sc.D.,M.S.W., Jeanne Brooks-Gunn, Ph.D., Ed.M.,Athina Kakavouli, M.D., Alastair Wood, M.D., Coinvestigators of the Pediatric Anesthesia Neurodevelopment Assessment (PANDA) Research Network

◆ EDITORIAL VIEWS

Anesthesiology 2008; 109:941–4 

***Anesthesia and Outcome after Neonatal Surgery***

*The Role for Randomized Trials*

Andrew J. Davidson, M.B., B.S., M.D., Mary Ellen McCann, M.D., M.P.H., Neil S. Morton, M.B., Ch.B., Paul S. Myles, M.D., M.P.H.

◆ EDITORIAL VIEWS

Anesthesiology 2009; 110:1–3 

***Anesthetic Effects on the Developing Brain***

*Insights from Epidemiology*

Tom G. Hansen, M.D., Ph.D., for the Danish Registry Study Group, Randall Flick, M.D., M.P.H.

# Three Current Clinical Trials to Address the Effect of Anesthesia on the Developing Brain

- **Retrospective cohort study of children who had anesthetic exposure before age 3 yrs, the period of synaptogenesis in humans, with prospective follow-up and direct assessment**
  - Sun LS, Li G, DiMaggio C, Byrne M, Rauh V, Brooks-Gun J, Kakavouli A, Wood A, Coinvestigators of the Pediatric Anesthesia Neurodevelopment Assessment (PANDA) Research Network: Anesthesia and neurodevelopment in children: Time for an answer. Anesthesiology 2008; 109:757–61
- **Prospective randomized controlled trial of healthy infants undergoing inguinal herniorraphy receiving either spinal or general anesthesia, with an N of 598 and IQ at age 5 yrs**
  - Davidson AJ, McCann ME, Morton NS, Myles PS: Anesthesia and outcome after neonatal surgery: The role for randomized trials. Anesthesiology 2008; 109:941–4
- **Case-control study using very large Denmark national and Rochester (Olmstead County), MN population databases, with identification and control for a number of confounders**
  - Hansen TG, for the Danish Registry Study Group, Flick R: Anesthetic effects on the developing brain: Insights from epidemiology. Anesthesiology 2009; 110:1–3

## Public Health Epidemiology

- The study of the distribution of diseases in **populations** and the factors that influence the occurrence of disease
- Epidemiology attempts to determine **who** is most prone to a particular disease or outcome; **where** the risk of the disease or outcome is highest; **when** the disease or outcome is most likely to occur; **how much** the risk is increased through exposure; and **how many** cases of the disease could be avoided by eliminating the exposure
- Target Population → Study Population → Study Sample
- A **"web of causation"** is almost always present.

BMJ: "Epidemiology for the Uninitiated"
http://www.bmj.com/epidem/epid.html

## Bradford Hill's Attributes of Causation

- **Strength**: stronger the association, less likely due to bias
- **Consistency**: persons, places, circumstances and times
- **Specificity**: one disease and one exposure relationship
- **Temporality**: which is the cart and which is the horse?
- **Biological gradient**: presence of a dose-response curve
- **Biological plausibility**: makes sense given what we know
- **Coherence**: congruent with the natural history of disease
- **Experimentation**: evidence derived from clinical trials
- **Analogy**: similar relationships shown with other E → D

A.B. Hill, "The Environment and Disease: Association or Causation?"
*Proceedings of the Royal Society of Medicine*, 58 (1965), 295-300.

## Clinical Epidemiology

- Application of epidemiological principles and methods to questions regarding diagnosis, prognosis, and therapy
- Randomized clinical trial is the prime example
- **Pharmacoepidemiology**
  - Drug benefits versus adverse effects → innately very applicable to anesthesiology & pain medicine
  - Often conducted **after** the drug has been marketed
- **Clinical Outcomes and Comparative Effectiveness Research**
  - Epidemiologic methods plus clinical decision analysis and an economic evaluation → to determine optimal treatment
  - Patient-reported outcome of health-related quality of life
  - Phase 2 Translational or Implementation Research (NIH/AHRQ)

## Efficacy, Effectiveness *versus* Efficiency

- The evaluation of a new or existing healthcare intervention or treatment involves one or more of three steps:

**❶ Efficacy**

- Achieving its stated clinical goal
- Demonstrated under **optimal** circumstances in a prospective randomized controlled trial (RCT) – **but** the results are limited to the study subjects

**❷ Effectiveness**

- Producing greater benefit than harm
- Assessed under **ordinary** circumstances in the more **general population** often by way of an observational yet analytic longitudinal cohort study

**❸ Efficiency**

- Health status improvement for a given amount of resources ($) expended
- Determined via a cost-effectiveness analysis or cost-utility analysis

Robinson & Vetter (2009): *Healthcare Economic Evaluation of Chronic Pain*

## Prevalence versus Incidence

- **Incidence** = # of *new* outcomes or cases of the disease
- **Prevalence** = # of *existing* outcomes or cases of the disease
  - **Proportion** – ranges from 0% to 100%
  - **Point prevalence** – at a specific **point** in time
  - **Period prevalence** – over a more sustained time **period**
- The longer the **duration** of a condition or disease, intuitively, the greater the prevalence of the disease
- Prevalence ≅ Incidence X Average Duration of Disease
- Common cold has a **high incidence** but a short duration → **low point prevalence**
- Type II DM has a **lower incidence** but a long duration → **higher point prevalence**

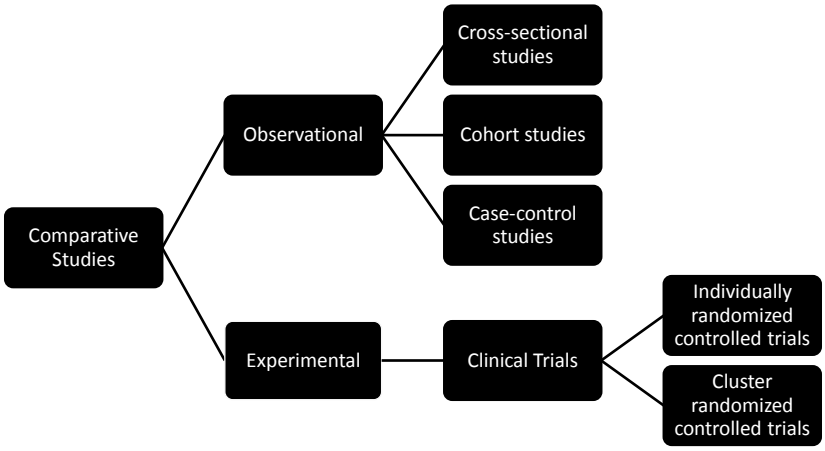
## Cumulative Incidence

- Cumulative incidence is the most common way to estimate **risk** in the source population of interest
- **Cumulative incidence (CI)** = quotient of

$$\frac{\text{\# of } \textbf{new} \text{ cases observed during the follow-up period}}{\text{\# of } \textbf{disease-free} \text{ subjects at start of follow-up period}}$$

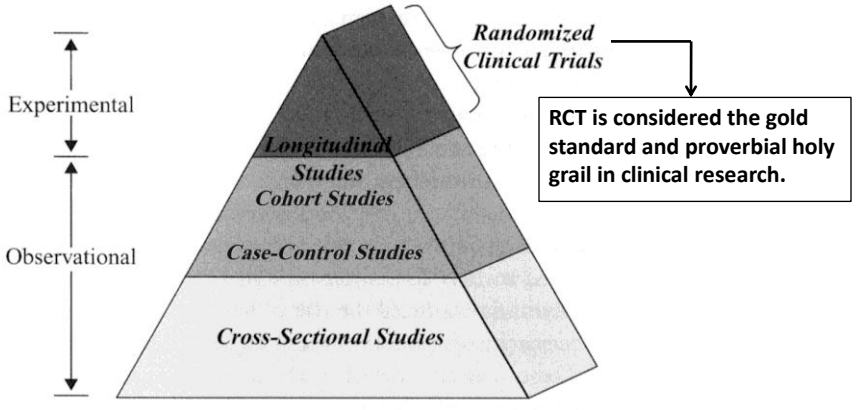
- A few examples:
  - Postoperative emergence delirium with sevoflurane
  - Persistent incisional pain 3 months after thoracotomy
  - 3-year IQ deficit after receiving a neonatal anesthestic
  - 5-year mortality after aprotinin versus tranexamic acid use
  - 10-year myocardial infarction with HDL < 40 mg/dL

# Basic Study Design Schematic




www.gfmer.ch/PGC_RH_2005/pdf/Cluster_Randomized_Trials.pdf

# Hierarchy of Risk Estimation Studies




Modified from Kraemer, Lowe & Kupfer, *To Your Health: How to Understand What Research Tells Us About Risk* (2005), pg. 107

# What's Wrong with an RCT?

**Table 1** Comparison of cohort studies and randomised controlled trials

| Item | Cohort studies | Randomised controlled trials |
|---|---|---|
| Populations studied | Diverse populations of patients who are observed in a range of settings | Highly selected populations recruited on the basis of detailed criteria and treated at selected sites |
| Allocation to the intervention | Based on decisions made by providers or patients | Based on chance and controlled by investigators |
| Outcomes | Can be defined after the intervention and can include rare or unexpected events | Primary outcomes are determined before patients are entered into study and are focused on predicted benefits and risks |
| Follow-up | Many cohort studies rely on existing experience (retrospective studies) and can provide an opportunity for long follow-up | Prospective studies; often have short follow-up because of costs and pressure to produce timely evidence |
| Analysis | Sophisticated multivariate techniques may be required to deal with confounding | Analysis is straightforward |

- Highly restricted study subject eligibility based upon well-defined inclusion and exclusion criteria – can make study enrollment protracted
- Ethical and logistical constraints preclude using an RCT design to answer certain questions – often more complex, "real-world" challenges.
- Minorities and both age extremes – pediatric and geriatric patients – are conventionally excluded despite equal or greater clinical need.
- The results of an RCT often lack external validity and cannot be generalized to the more diverse population – with co-existing diseases.
- Simple randomization may not sufficiently control for confounding variables.

Rochon et al., *BMJ* 2005;330:895-897

# 1. Cross-Sectional Study

- Examines the relationship between potential risk factors and outcomes during a short period of time ("snapshot")
- Potential risk factors or outcomes are not likely to change during the duration or time frame of the study.
- Cross-sectional study estimates the **point prevalence.**
- Valuable as pilot study to establish tentative association
- Generate hypotheses for more rigorous studies
- Examples: Co-existing depression among patients presenting to a chronic pain medicine clinic; positive pregnancy test among pediatric surgical outpatients

## 2. Cohort Study

- Longitudinal study of E → D **risk** relationship (forward)
- **Single exposure with multiple subsequent outcomes**
- At the outset of study all participants are outcome-free
- Natural or self-selection into risk categories
- During follow-up period participants are reassessed as to whether the outcome has occurred.
- Time-consuming and costly to perform if prospective
- Loss to follow-up and differential attrition can lead to bias (systematic error) and thus validity issues.
- An **RCT** represents an **experimental** form of cohort study.

## What is Risk?

- Risk: The **probability** of an outcome within a population
- Likelihood a person in a population will have the outcome
- Risk is a number between 0% and 100% or 0 and 1.0
- The specified health outcome is binary (+/− or yes/no).
- The study population must be clearly defined.
- While well-defined, this population cannot be known: thus a representative study sample is selected and an estimated risk in this study sample is determined.
- Risk estimate is for a specific and logical risk time period, e.g., 24 hours postoperatively, 5 year follow-up.
- **Efficacy = $(risk_{control} - risk_{intervention})/(risk_{control})$ = RRR**

## What is a Risk Ratio?

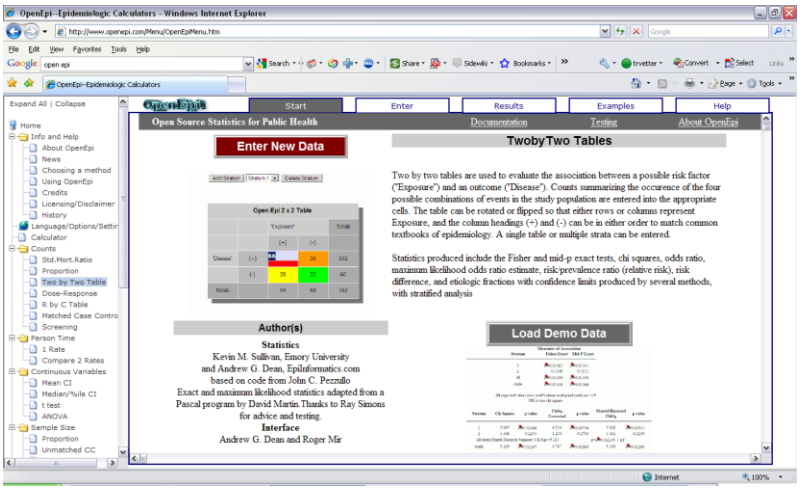
- A ratio is the quotient of two numbers
- Risk ratio = Risk in group A ÷ Risk in Group B
- Risk ratio ranges from 0 to infinity (∞) with 1 = null value
- In most epidemiological studies Group A and Group B differ by way of a self-selected or natural series of events
- Whereas in a randomized controlled trial (RCT) Group A and Group B differ in a randomized yet very controlled manner with each group receiving a specific treatment
- Risk ratio allows for a **comparison** of the risk of the disease or outcome in Group A versus Group B.
- **More appropriate for high incidence conditions**

## 2 X 2 Table

| | **Drug X** | **Drug Y** | **Total** |
|---|---|---|---|
| **Outcome (+)** | **A** | **B** | **A+B** |
| **Outcome (−)** | **C** | **D** | **C+D** |
| **Total** | **A + C** | **B + D** | **A + B + C+ D** |

Frequency or Proportion for Drug X = A/(A+C) and
Frequency or Proportion for Drug Y = B/(B+D)
**Risk for Drug X** = A/(A+C) and **Risk for Drug Y** = B/(B+D)
**Risk Ratio** = [A/(A+C)] ÷ [B/(B+D)]

# OpenEpi 2.3.1: www.openepi.com




**Menu → Counts Folder → Two by Two Table: 2X2 Contingency Table**

# Nurse-Controlled Analgesia

| | Neonate | Older 1 Month | Total |
|---|---|---|---|
| Serious Adverse Event (+) | 13 | 26 | 39 |
| Serious Adverse Event (−) | 497 | 9543 | 10049 |
| Total | 510 | 9569 | 10079 |

**Risk for Neonate** = 13/510 = 0.025 or 2.5%

**Risk for Older 1 Month** = 26/9569 = 0.0027 or 0.27%

**Risk Ratio or Relative Risk** = 0.025/0.0027 = **9.4** (4.8,18.2)

Howard et al., Nurse-Controlled Analgesia (NCA) Following Major Surgery in 10000 Patients in a Children's Hospital, *Pediatric Anesthesia* 2010;20:126-134

## Risk and Risk Reduction: Definitions

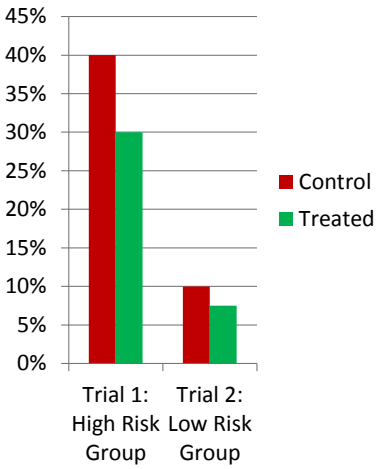
- **Event rate**
  - Number of people experiencing an event as a proportion of the number of people in the sample or population
- **Relative risk reduction**
  - Difference in event rates between 2 groups, expressed as a proportion of the event rate in the untreated group; usually constant across populations with different risks
- **Absolute risk reduction**
  - Arithmetic difference between 2 event rates; varies with the underlying risk of an event in the individual patient

Barratt, A., et al. Tips for learners of evidence-based medicine: 1. Relative risk reduction, absolute risk reduction and number needed to treat. CMAJ, 2004;171(4):353-358

## Risk Difference and the Number Needed to Treat

- **Risk Difference** or Cumulative Incidence Difference (CID) = $CI_1 - CI_0$ → with 1 = those exposed and 0 = unexposed
- **Absolute Risk Reduction (ARR)** in clinical epidemiology
- **Number Needed to Treat** (NNT) = $1/(CI_1 - CI_0) = 1/ARR$
- **Number Needed to Harm** (NNH) in the case of an untoward event (stroke, MI, death) or an adverse side effect (respiratory depression, persistent paresthesia)
- **Far more germane than a simple p-value**

# Basic Example of RRR, ARR, NNT




Barratt, A., et al. Tips for learners of evidence-based medicine: 1. Relative risk reduction, absolute risk reduction and number needed to treat. CMAJ, 2004;171(4):353-358.

- High risk group
  **RRR** = [40% – 30%] /40% = **25%**
  **ARR** = 40% – 30% = **10%**
  **NNT** = 100/10 = **10**
- Low risk group
  **RRR** = [10% – 7.5%] /10% = **25%**
  **ARR** = 10% – 7.5% = **2.5%**
  **NNT** = 100/2.5 = **40**
- Lower the event rate control group, larger the difference between RRR and ARR
- RRR → efficacy

# Hypothesis Testing

- In an RCT *versus* in a prospective cohort study
- **RCT** Ho: $P_1 - P_0 = 0$ or $P_1 = P_0$ and Ha: $P_1 - P_0 \neq 0$ or $P_1 \neq P_0$
  - **P** = proportion of the study group with the outcome
- **Cohort Study** Ho: $RR = CI_1/CI_0 = 1$ and Ha: $RR = CI_1/CI_0 \neq 1$
  - **RR** = risk ratio
  - **CI** = cumulative incidence of the disease or outcome in cohort
- **A cohort study and an RCT are essentially asking the same questions: what is the effect of the exposure (treatment) on the disease (outcome) and is it significant?**

## Postoperative Nausea & Vomiting

| | Clonidine Caudal (2 mcg/kg) | Hydromorphone Caudal (10 mcg/kg) |
|---|---|---|
| **(+) PONV** | **10 (50% incidence)** | **18 (90% incidence)** |
| **(−) PONV** | **10** | **2** |
| **Total** | **20** | **20** |
| **PONV Risk** | **10 ÷ 20 = 0.5** | **18 ÷ 20 = 0.9** |

**Fisher's exact test P** = **0.014** (because a cell size ≤ 5)
**Risk ratio (RR)** = 0.9 ÷ 0.5 = **1.8** → PONV 1.8 times as likely
**Absolute risk reduction (ARR)** = 0.9 − 0.5 = **0.4 or 40%**
**Number needed to treat (NNT)** = 1 ÷ 0.4 = **2.5 patients**

## Ketamine and Hallucinations

- Incidence and risk of hallucinations in awake or sedated patients not receiving a benzodiazepine was high:
  - Risk of 10.43% versus risk of 5.70% → 4.73% risk difference
  - **Risk ratio of 2.32** (95% CI, 1.09 – 4.92)
  - **Number needed to harm** = 1 ÷ (0.1043 − 0.057) = **21**
- In anesthetized patients the incidence of hallucinations was low and independent of benzodiazepine administration:
  - Risk of 0.76% versus risk of 0.41% → 0.35% risk difference
  - **Risk ratio of 1.49** but not significant (95% CI, 0.18 – 12.6)
  - **Number needed to harm** = 1 ÷ (0.0035) = **286**

Elia & Tramer, *Pain* 2005;113:61-70

## 3. Case-Control Study

- Is the observed outcome related to the exposure?
- Outcome or disease is observed first: E ← D (backward)
- **Single outcome with multiple previous exposures**
- Cases are subjects with the outcome of interest
- Controls are subjects without the outcome of interest
- Controls sampled from the same source population but must be sampled independently of their exposure status
- Less costly and less time-consuming than cohort study
- Efficient for **rare** outcomes
- **Cannot** generate an overall risk or rate estimate but instead an **odds ratio** is determined and not a risk ratio

## Probability versus Odds

- **Probability (P)**
  - Number of times an outcome occurs out of the total # of attempts
  - Ranges from 0 to 1
  - "Epi Beauty" won 30 of 50 races
  - P of winning is 30/50 = 0.60
- **Odds**
  - P ÷ (1 − P) = probability of winning ÷ probability of losing
  - Ranges from 0 to infinity (∞)
  - Horse race: Odds of winning = 0.6/(1 − 0.6) = 0.6/0.4 = 1.5 to 1
- **Odds Ratio**
  - Ratio of the odds of the disease or clinical outcome **with the exposure** versus **without the exposure**

## 2 X 2 Table Revisited

| | Outcome (+)<br>Cases with Disease | Outcome (−)<br>Controls<br>w/o Disease |
|---|---|---|
| **Exposure (+)** | **A** | **B** |
| **Exposure (−)** | **C** | **D** |

- A and C are selected based on disease (outcome) status
- We cannot calculate the rate or risk of getting the disease (outcome) because we do not know the denominator (size of study population)
- Odds = number of cases with disease ÷ number of non-cases of disease
- **Odds with exposure** = (A/B) and **odds without exposure** = (C/D)
- **Odds ratio with *versus* without exposure** = (A/B) ÷ (C/D) = AD/BC

## Perioperative Questions That Could Be Addressed by a Case-Control Study

- **Rare outcomes with several possible exposure risk factors**
- What are the risk factors for malignant hyperthermia?
- Is epidural catheter placement under general anesthesia a risk factor for postoperative paraplegia?
- Does pulse oximetry and/or end-tidal capnography decrease the risk of perioperative brain anoxia?
- Does neonatal anesthesia cause later cognitive deficits?
- **Is nurse or parent proxy-patient controlled analgesia (PCA) a risk factor for respiratory depression or arrest?**
- Examples of fertile ground for case-control studies:
  - ASA Closed Claims Project
  - Pediatric Perioperative Cardiac Arrest (POCA) Registry
  - Multicenter Perioperative Outcomes Group (MPOG)

# Patient-Controlled Analgesia by Proxy

**Threshold Event (TE) =** ↓O2 saturation, bradypnea, & oversedation

| | TE (+) | TE (–) | Total |
|---|---|---|---|
| PCA-Proxy | 21 | 124 | 145 |
| PCA w/o Proxy | 37 | 120 | 157 |

**Exposure odds ratio =** (21 X 120) ÷ (124 X 37) = 0.54 (0.30 − 0.99)

$X^2$ test P ≤ 0.015 *versus* $X^2$ test P = 0.045 actual

**Rescue Event (RE) =** naloxone, airway intervention, & escalation of care (to ICU)

| | RE (+) | RE (–) | Total |
|---|---|---|---|
| PCA-Proxy | 11 | 134 | 145 |
| PCA w/o Proxy | 1 | 156 | 157 |

**Exposure odds ratio =** (11 X 156) ÷ (134 X 1) = 12.8 (1.6 − 100.0)

$X^2$ test P ≤ 0.015
$X^2$ test P = 0.005 actual

Voepel-Lewis et al., The Prevalence of Risk Factors for Adverse Events in Children Receiving Patient-Controlled Analgesia by Proxy or Patient-Controlled Analgesia after Surgery *Anesthesia & Analgesia* 2008;107:7-75

# Two Other Types of Study Design

- **Nested case-control study**
  - A case-control study that is set or nested within an existing cohort study or even an intervention study like an RCT
  - Greatest advantage of nested study is that cases and controls come from the same population, which avoids selection bias.
- **Cluster randomized trial**
  - Study subjects in an intervention study naturally occur in separate groups or clusters (e.g., geographic location)
  - Rather than randomize individuals to treatment, randomize based upon the clusters (e.g., hospital, surgical service)
  - Often applied for convenience or out of necessity
  - Deceptively simple to construct and data analysis is complex

# Sources of Error in Study Design

- **Random Error**: simple variability in the sample data
- **Systematic Error** or **Bias**: 3 basic types

**❶ Selection Bias**

- Individuals have different probabilities of being in the study sample based upon relevant characteristics (E and D)
- Differential loss to follow-up – including in an RCT

**❷ Information Bias**

- Misclassification of exposure and/or disease (outcome) status, validity of diagnosis as measured by sensitivity and specificity
- Observer bias is mitigated via blinding (masking) in an RCT

**❸ Confounding**

- Effect of the exposure of interest is mixed together with and confused by the effect of one or more other variables

# Random Error *versus* Systematic Error

Estimate (variable) = parameter + random error + systematic error

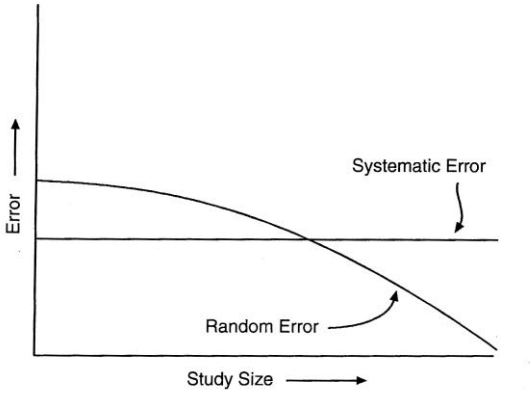



**Figure 5–1.** Relation of systematic error and random error to study size.

As N increases, the SEM decreases and thus 95% CI becomes narrower

Rothman, *Epidemiology: An Introduction* (2002), pg. 95

# Example of Confounding

| | CAD Present | CAD Absent |
|---|---|---|
| **Vitamin E Supplement (+)** | **50** | **500** |
| **Vitamin E Supplement (–)** | **66** | **384** |

1000 subjects, age 50-55 years, followed for 15 years:

Risk with vitamin E supplement use = 50/550 = **0.09 (9%)**

Risk w/o vitamin E supplement use = 66/450 = **0.15 (15%)**

Risk ratio = 0.09/0.15 = 0.62; **P = 0.008**

**Risk odds ratio (crude)** = (50 X 384) ÷ (500 X 66) = **0.58**

Vitamin E appears cardio-protective…but is it really?

Fitzmaurice, Confused by Confounding? *Nutrition* 2003; 19:189-191

# Example of Confounding (Cont'd)

## Smokers

| | CAD Present | CAD Absent |
|---|---|---|
| **Vitamin E Supplement (+)** | **10** | **40** |
| **Vitamin E Supplement (–)** | **50** | **200** |

→ **Stratum risk odds ratio = (10 X 200) ÷ (40 X 50) = 1.0**

**P = 0.85**

**There is no association between vitamin E supplement and CAD after controlling for the effects of smoking.**

## Non-Smokers

| | CAD Present | CAD Absent |
|---|---|---|
| **Vitamin E Supplement (+)** | **40** | **460** |
| **Vitamin E Supplement (–)** | **16** | **184** |

→ **Stratum risk odds ratio = (40 X 184) ÷ (460 X 16) = 1.0**

**P = 0.88**

Fitzmaurice, Confused by Confounding? *Nutrition* 2003;19:189-191

**Stratum-specific odds ratios are similar in magnitude**

## Interaction *versus* Confounding

- **Confounding** (from the Latin *confundere* meaning "to mix together"): an **undesirable distortion** of the association between an exposure (E) and disease (D) brought about by **extraneous factors** (C1, C2, etc).
- **Interaction**: "**effect modification"** whereby the effect on the response (y) of one explanatory variable (x) **depends** on the level of one or more other explanatory variables
- Two-way or two factor model: $y = b_0 + b_1x_1 + b_2x_2 + \mathbf{b_3x_1x_2}$
  - The joint effect of two or more explanatory variables is larger or smaller than the sum of the parts.
  - $\mathbf{b_3x_1x_2}$ = **interaction term** tested with $H_0$: $b_3 = 0$
- **Synergism** (from the Greek *sunergos* meaning "working together") is a type of **biological interaction**.

## Interaction *versus* Confounding

### Interaction

- Smoking (C) **amplifies** the risk of thromboembolic disease (D) with oral contraceptive use (E).
- Interaction exists between the **interdependent risk factors** of smoking (C) and oral contraceptive use (E).
- This **effect modification** is biological synergism.

### Confounding

- Smoking (C) **confuses** the relationship between alcohol consumption (E) and lung cancer (D).
- Since alcohol and smoking are related, and smoking (C) is an **independent risk factor** for lung cancer (D).
- This **extraneous factor** results in confounding.

Woodward, *Epidemiology: Study Design and Data Analysis* (2005)
Rothman, Greenland, & Lash, *Modern Epidemiology* (2008)

## Potential Confounder

- For a variable to be considered a confounder of an association, it must satisfy three basic conditions:

1. The potential confounder must be associated with the disease or outcome of interest.
2. The potential confounder must be associated with the exposure of interest.
3. The potential confounder must **not** be an "intermediate" variable in the casual relation between the exposure and disease or outcome (i.e., it is not part of the "web of causation").

Fitzmaurice, Confused by Confounding? *Nutrition* 2003;19:189-191

## Basic Ways to Reduce Confounding

- Randomization
- Restriction
- Matching
- Weighting
- Stratification
- Regression
- Propensity scores
- Instrumental variables
- Analysis of covariance (ANCOVA)

Wunsch, Linde-Zwirble & Angus, *Journal of Critical Care* 2006;21:1-7

# Techniques to Adjust for Confounding in Observational Studies

**Table 1** Techniques to adjust for confounding in observational studies

| Technique | Strengths | Weaknesses |
|---|---|---|
| Matching | Simple<br>Balances confounding factors | Difficulty finding matches<br>Possibility of overmatching<br>Requires strong understanding of confounders involved<br>Inability to examine effect of confounders used for matching |
| Stratification | Simple<br>Ability to see effect modification | Difficult to interpret with many subgroups<br>Requires strong understanding of confounders involved |
| Multivariable adjustment | Can include many confounders<br>Can examine effects of individual confounders<br>Ability to examine multilevel effects | More complicated analysis<br>Potentially poor fit of model<br>Possibility of missing effect modification |
| Propensity scores | Single number generated for simpler matching<br>Ability to assess for bias between groups | Potentially matching very different patients with similar scores |
| Instrumental variables | Only single variable needed<br>Ability to look at questions where other types of adjustment can not be easily accomplished | Difficult to ensure variable is not at all associated with the outcome |

Wunsch, Linde-Zwirble & Angus, *Journal of Critical Care* 2006;21:1-7

# Randomization

- Randomization is only applicable in an experimental study in which exposure is assigned or controlled.
- With a large enough sample size (N), randomization produces two or more study groups with nearly the same distribution of the study subject (patient) characteristics that are plausible confounding variables.
- **Randomization also reduces confounding by any other <u>unidentified</u> factors or variables.**
- But randomization is not always feasible or ethical, especially in retrospective studies or longitudinal observational studies.

## Restriction

- Often applied in addition to randomization
- Study inclusion and even more so study exclusion criteria control for the ***identified*** confounders.
- Trade-off is that study findings are assuredly valid only for the restricted study population from which the study sample is drawn.
- This external validity issue must be considered in generalizing findings to a more diverse population.
- One of the challenges of applying evidence-based medicine in one's daily practice: Are these study findings applicable to my given patient?

## Matching

- Individuals from the two study groups are paired based upon the presumed confounding variables.
- Allows for even distribution of potential confounders
- Most often applied in case-control studies
- Age, sex, race are common matching variables.
- Expensive and time consuming
- Reduces the power of the study because not all study subjects can be matched
- Does not assuredly control for other confounders and in fact can introduce hidden confounding
- **Restriction in an RCT is a "loose" form of matching.**

## Assessing for Confounding in RCT I

- In almost all clinical trials, the study groups are compared using parametric or non-parametric statistics for any differences in baseline characteristics:
  - Demographics
  - Anthropometrics
  - Other pertinent clinical variables
- Absence of "statistically significant" difference is often taken to indicate study group comparability and a lack of confounding by these covariates.
  - **More conservative p-value of 0.20 may be better**
  - **Residual cofounding may be present despite p > 0.05**
- The results of a statistical test for significant difference – "the almighty p-value" – depend on the sample size (N):
  - As N → ∞, any observed difference achieves a $p < 0.05$
  - With a larger N, there is a greater likelihood of baseline difference

## Assessing for Confounding in RCT II

- Ho: $\rho_1 = \rho_2$ with ρ = population proportion (parameter) or
  $\mu_1 = \mu_2$ with μ = population mean (parameter)
  Ho rejected if $p < 0.05$
- **But in assessing for confounding in an RCT our required assumption or the Ho:** Any imbalance between the study groups in a baseline clinical feature or risk factor is **simply due to chance and not randomization**
- But *successful* randomized allocation requires that any observed imbalance **must be due to chance**
- **The Ho thus cannot be rejected (!) even with a $p < 0.05$**
- A statistically significant imbalance in a baseline risk factor in and of itself does <u>not</u> reflect the amount of confounding → instead we need to determine **<u>how much of an effect</u>** does the risk factor have on the outcome?

Rothman, *Epidemiology: An Introduction* (2002), page 209

## Stratification

- One of the most effective techniques for adjusting for the effects of confounding in an analysis
- Association is evaluated within distinct groups, or ***strata***, comprised of individuals who are relatively homogenous in terms of the confounding variable.
- A crude overall estimate of association is ***adjusted*** for the confounding variables.
- Generated by taking a **weighted average** of the stratum-specific estimates of association.
- Requires stratum-specific estimates of association to be uniform across the levels of the potential confounder. Otherwise stratum-specific estimates should be reported.

## Assessing for Confounding in RCT III

- Better approach for **dichotomous** (binary) outcomes:

1. Control for the confounder using conventional study design with study subject randomization and restriction
2. Determine the *potentially* confounded **crude** results
3. Stratify the results on the potential confounding variables (e.g., age and gender) and then determine pooled **Mantel-Haenszel adjusted** results
4. Compare the crude results with the adjusted results
5. If the two estimates are comparable → conclude that confounding is not present
6. If two estimates are "**meaningfully different"** (> 10%) → conclude that confounding is present

# Cochran-Mantel-Haenszel Method

- One of the most widely used methods for combining or pooling stratum-specific estimates of association
- Generates an adjusted estimate of association (odds ratio)
- Can also generate an adjusted estimate of risk ratio

| | Disease or Outcome (+) | Disease or Outcome (–) |
|---|---|---|
| **Exposure (+)** | $a_j$ | $b_j$ |
| **Exposure (–)** | $c_j$ | $d_j$ |

$$\hat{OR}_{MH} = \sum_{j=1}^{K} \frac{a_j d_j}{n_j} \Big/ \sum_{j=1}^{K} \frac{b_j c_j}{n_j}$$

$n_j$ = total number of observations in the $j^{th}$ table = ($a_j + b_j + c_j + d_j$)

j levels of the stratification variable (e.g., two strata for male and female)

Create a series of stratum-specific 2X2 contingency tables

j total number of 2x2 contingency tables

# Example of Mantel-Haenszel Method I

**Entire Cohort**

| | CAD (+) | CAD (–) |
|---|---|---|
| Vitamin E Supplement (+) | 50 | 501 |
| Vitamin E Supplement (–) | 65 | 384 |

**Smokers**

| | CAD (+) | CAD (–) |
|---|---|---|
| Vitamin E Supplement (+) | 11 | 40 |
| Vitamin E Supplement (–) | 49 | 200 |

**Non-Smokers**

| | CAD (+) | CAD (–) |
|---|---|---|
| Vitamin E Supplement (+) | 39 | 461 |
| Vitamin E Supplement (–) | 16 | 184 |

→ **Crude odds ratio = 0.59**
**(95% CI, 0.40 − 0.87)**

**CONFOUNDING**

**MH adjusted odds ratio = 1.03**
**(95% CI, 0.64 − 1.65)**

→ **Stratum odds ratio = 1.12**
**(95% CI, 0.54 − 2.34)**

**INTERACTION is not present between vitamin E supplement and smoking because the stratum-specific odds ratios are not significantly different.**

→ **Stratum odds ratio = 0.97**
**(95% CI, 0.53 − 1.78)**

Fitzmaurice, Adjusting for Confounding, *Nutrition* 2004; 20:594-596

# Example of Mantel-Haenszel Method II

**Smoking and Pregnancy Outcome among African-American and White Women: The Risk for a Small for Gestational Age (SGA) Newborn**

**Entire Cohort**

| | SGA (+) | SGA (−) |
|---|---|---|
| Smoked during pregnancy (+) | 105 | 517 |
| Smoked during pregnancy (−) | 105 | 1317 |

**African-Americans**

| | SGA (+) | SGA (−) |
|---|---|---|
| Smoked during pregnancy (+) | 21 | 180 |
| Smoked during pregnancy (−) | 64 | 702 |

**Whites**

| | SGA (+) | SGA (−) |
|---|---|---|
| Smoked during pregnancy (+) | 84 | 337 |
| Smoked during pregnancy (−) | 41 | 615 |

**Modified** from Savitz et al., *Epidemiology* 2001;12:636-642

→ **Crude odds ratio = 2.55**
**(95% CI, 1.91 − 3.40)**

**NO CONFOUNDING**

**MH adjusted odds ratio = 2.56**
**(95% CI, 1.89 − 3.45)**

→ **Stratum odds ratio = 1.28**
**(95% CI, 0.76 − 2.15)**

**INTERACTION may be present between race and smoking b/c the stratum-specific odds ratios are significantly different**

→ **Stratum odds ratio = 3.74**
**(95% CI, 2.52 − 5.56)**

# Regression

- When there are many potential confounding variables, **(k)**, the resulting strata **($2^k$)** have too few individuals to generate a precise estimate of association.
- Alternatively, estimate the exposure effect of interest using a regression model for the dependence of the disease (outcome) on the primary exposure and any potential confounding variables.
  - Assess the effect of the use of vitamin E supplements on CAD, while **controlling for or adjusting for** not only smoking history but also other potential confounders (e.g., age, BMI, physical activity, LDL, HgbA1C)
- Requires assumptions be met and a larger sample size and does not ensure confounder distributions are comparable

Fitzmaurice, Confounding: Regression adjustment, *Nutrition* 2006;22:581-583

# Methods of Regression I

- **Simple linear regression**: single continuous outcome variable (y) and a single predictor variable (x)
  - $y = b_1x_1 + b_0 + \varepsilon$
  - $b_1$ = slope and $b_0$ = intercept and $\varepsilon$ = error ($\Delta y$)
- **Multiple linear regression**: single continuous outcome (y) but instead multiple predictor variables ($x_{1, 2, 3...k}$)
  - $y = b_0 + b_1x_1 + b_2x_2 + b_3x_3 + ...+ b_kx_k + \varepsilon$
- The predictor variables ($x_1$,$x_2$,$x_3$ …) can be continuous (age), ordinal (ASA status), and/or dichotomous (sex) in a linear regression model.
- <u>But</u> you need at least **10 observations** (study subjects) for each x variable placed in the model plus other assumptions must be met

## Three Studies Addressing the Effect of Maternal Fish Intake and Smoking on the Child Neurodevelopment

- After adjusting for 28 potential confounders, maternal seafood intake during pregnancy of < 340 gm per week was associated with increased risk of their children being in the lowest quartile for verbal intelligence quotient (IQ): No seafood consumption, odds ratio [OR] 1·48, 95% CI 1·16–1·90 (N = 11,875).
  - Hibblen JR et al: Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): An observational cohort study. Lancet 2007; 369:578-85.
- Using multivariate linear regression, in 4 year old children breast-fed for < 6 months, maternal fish intakes of > 2–3 times/week were associated with significantly higher scores on several McCarthy Scales of Children's Abilities (MSCA) subscales compared with intakes < 1 time/week (N = 392).
  - Mendez MA et al: Maternal fish and other seafood intakes during pregnancy and child neurodevelopment at age 4 years. Public Health Nutrition 2008; 12(10):1702-1710.
- Using multivariate linear regression, maternal smoking during pregnancy (in cigs/day) was associated with a decrease in child's MSCA global cognitive score [β = 0.60, (95% CI: 1.10; 0.09)] in offspring at age 4 years (N = 420).
  - Julvez Jet al: Maternal smoking habits and cognitive development of children at age 4 years in a population-based birth cohort. International Journal of Epidemiology 2007;36(4):825-32.

## Linear regression may not always work

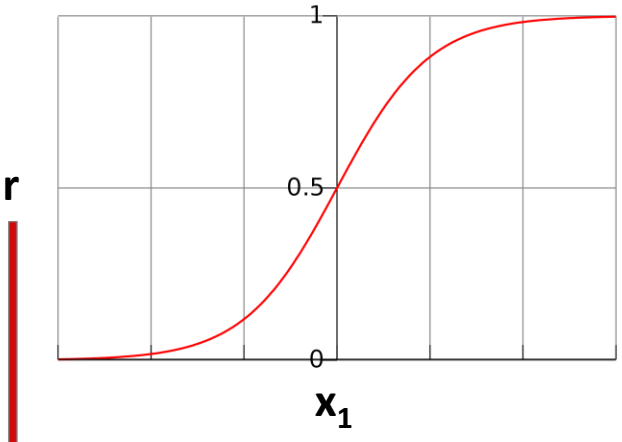
- **Simple and multiple linear regression is applied when the outcome variable (y) is continuous.**
- **But what happens if:**

1. The outcome variable (y) is not linearly related to the predictor variables (x)?
2. The outcome variable (y) is risk that ranges from 0 to 1?
3. The outcome variable (y) is not continuous but instead dichotomous/binary (0 = no, 1 = yes) like risk of death?

- **Then you apply a logistic regression model…**

## Logistic Function

$$y = 1/[1 + \exp(-b_0 - b_1x_1)]$$




$$r = \underline{risk} = 1/[1 + \exp(-b_0 - b_1x_1)]$$

# Methods of Regression II

- **Simple logistic regression**: single binary (1 = yes/0 = no) outcome variable (y) and a single predictor variable (x)
  - p = probability of outcome of interest; odds = p ÷ (1 − p)
  - **logit(p)** = $\log_e$ (odds) = $\log_e$ [p/(1 − p)] = $\log_e$ (p) − $\log_e$ (1 − p)
  - **logit(p)** = $\log_e$ [p/(1 − p)] = $\mathbf{b_0 + b_1x_1}$
  - odds ratio = $\log_e$ ($odds_1/odds_2$) = $\log_e$ ($odds_1$) − $\log_e$ ($odds_2$)
  - **odds ratio** (with $X_1 = 1$ compared to $X_1 = 0$) = $\mathbf{e^{b0 + b1x1}}$
- **Multiple logistic regression**: binary outcome (1 = yes/0 = no) but instead multiple predictor variables ($x_{1, 2, 3...k}$)
  - **logit(p)** = $\log_e$ [p/(1 − p)] = $\mathbf{b_0 + b_1x_1 + b_2x_2 + b_3x_3 + ...+ b_kx_k}$
  - **odds ratio** = $\mathbf{e^{b0 + b1x1 + b2x2 + b3x3 + ...+ bkxk}}$
- **Ordinal regression**: rank-ordered outcome (1, 2, 3, 4, 5)
- **Cox proportional hazards**: time to an event of interest

# Example of Regression Adjustment

**Maternal Diet and the Risk of Hypospadias and Cryptorchidism in the Offspring**

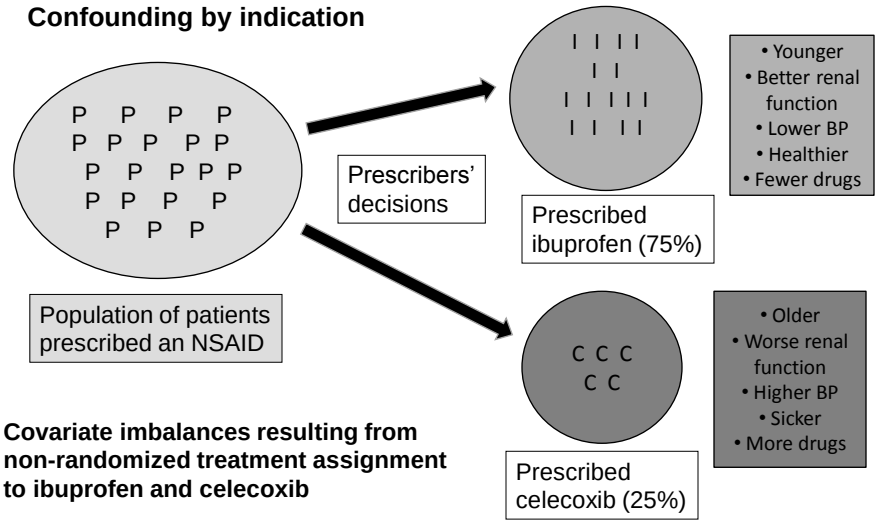
Controlling for maternal age, parity, education, & GYN disease; paternal GU disease & use of pesticides

| Factor | CRYPT Crude | CRYPT Adjust | HYPOSPAD Crude | HYPOSPAD Adjust |
|---|---|---|---|---|
| Liver & other offal (>1/week) | 3.2 (0.9, 10.7) | **5.2 (1.3, 14.2)** | | |
| Fish (>1/week) | | | 1.6 (0.8, 3.2) | **2.3 (1.0, 5.3)** |
| Mostly market fruit | | | **3.5 (1.0, 11.9)** | **5.1 (1.3, 19.8)** |
| Fried foods | **2.0 (1.0, 3.8)** | 1.5 (0.7, 3.2) | | |
| Smoked foods | **2.0 (1.1, 3.9)** | **2.5 (1.2, 5.3)** | | |
| Plastic food boxes/containers | | | **0.4 (0.2, 0.9)** | 0.5 (0.2, 1.2) |
| Mineral supplement | | | **0.5 (0.3, 1.0)** | 0.5 (0.2, 1.1) |

"This study suggests that some maternal dietary factors may play a role in the development of congenital defects of the male reproductive tract. In particular, our data indicate that further research may be warranted on the endocrine-disrupting effects resulting from the bioaccumulation of contaminants (fish, liver), pesticides (marketed fruit, wine) and/or potentially toxic food components (smoked products, wine, liver)."

Giordano et al., *Paediatric and Perinatal Epidemiology* 2008;22:249-260

# Cohort Covariate Imbalances




Modified from Perkins et al., *Pharmacoepidemiology and Drug Safety* 2000;9:94
Cavuto, Bravi, Grassi & Apolone, *Drug Development Research* 2006;67:208-216

# Propensity Scores

- Propensity score = the probability (0 to 1) that a subject would have been treated given the individual's covariates
- Intended to reduce selection bias and increase precision in **non-randomized large-scale observational studies**
- Collapse all of the background characteristics ($X_1$, $X_2$, …., Xp) or confounding covariates into a single composite value
- Propensity score (PS) is generated using logistic regression
  - PS = P(Z = 1|($X_1$, $X_2$, …., Xp)} Z = 1 if exposed, Z = 0 if not exposed
  - $$PS = \frac{\exp(b_0 + b_1x_1 + b_2x_2 + b_3x_3 + \ldots + b_kx_k)}{1 + \exp(b_0 + b_1x_1 + b_2x_2 + b_3x_3 + \ldots + b_kx_k)}$$
- Predictive strength: C-statistic from ROC curve = 0.5 to 1.0

Rubin, *Annals of Internal Medicine* 1997;127:757-763
D'Agostino, *Statistics in Medicine* 1998;17:2265-2281
Fitzmaurice, Confounding: Propensity score adjustment *Nutrition* 2006;22:1214-1216

# Propensity Scores

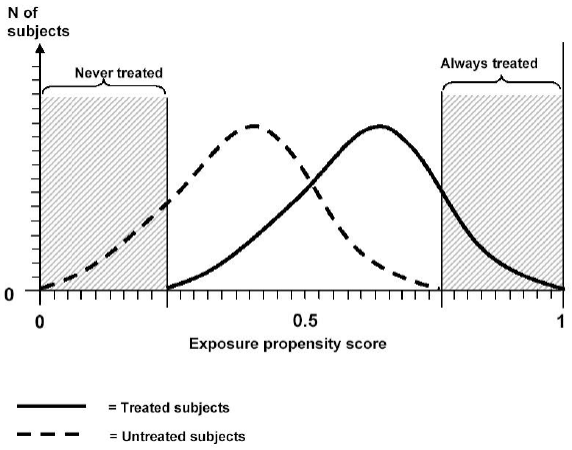
- Balancing scores ("apples to oranges" → "apples to apples")
- Can **only** adjust for **observed** confounding covariates
- Applicable for large-scale patient registry-based clinical cohort studies of longitudinal outcomes
  - Creates a "quasi-randomized study" → equal propensity score → equal likelihood to be treated or to be a control
- Requires large sample sizes to assure balance
- Requires adequate overlap of propensity distributions
- Randomization tends to balance the unmeasured covariates
  - Propensity score modeling is thus **not** intended for RCTs, but propensity scores can **possibly** be used for ANCOVA

Blackstone, *Journal of Thoracic and Cardiovascular Surgery* 2002;123:8-15
Glynn, Schneeweiss & Stürmer, *Basic & Clinical Pharmacology &Toxicology* 2006;98(3):253-259
Rubin, *American Journal of Ophthalmology* 2010;149(1):7-9

# Non-Overlap of Propensity Scores

**The non-overlap of the exposure propensity score distribution among treated and untreated study subjects makes the use of propensity scores questionable.**

In this example subjects with very low propensity score are never treated while subjects with very high propensity score are all treated.




Glynn, Schneeweiss & Stürmer, *Basic & Clinical Pharmacology &Toxicology* 2006;98(3):253-259

# Example of Use Propensity Scores

Ramachandran SK, Nafiu OO, Ghaferi A, Tremper KK, Shanks A, Kheterpal S. **Independent predictors and outcomes of unanticipated early postoperative tracheal intubation after nonemergent, noncardiac surgery.** Anesthesiology. 2011 Jul;115(1):44-53.

**Retrospective observational case-control study** undertaken to identify the independent predictors of unanticipated early postoperative respiratory failure requiring tracheal intubation after nonemergent, noncardiac surgery.

**Hypothesized** that unanticipated early postoperative respiratory failure is associated with a risk-adjusted increase in mortality.

Univariate **crude** odds ratios were all significant **but** confounding very likely present and interaction possibly present.

**Table 1.** Univariate Analysis for Derivation Cohort (N = 222,094)

| — | No UEPI (N = 220,241) | UEPI (N = 1,853) | *P* Value | Odds Ratio (95% CI) |
|---|---|---|---|---|
| Male sex | 92,226 (42%) | 954 (52%) | <0.001 | 1.5 (1.3–1.6) |
| White race | 162,405 (80%) | 1,430 (82%) | 0.04 | 1.1 (1.0–1.3) |
| Alcohol use | 5,940 (2.7%) | 92 (5.0%) | <0.001 | 1.9 (1.5–2.3) |
| Current smoker | 46,684 (21%) | 561 (30%) | <0.001 | 1.6 (1.5–1.8) |
| Dyspnea | 30,813 (14%) | 540 (29%) | <0.001 | 2.5 (2.3–2.8) |
| COPD | 12,527 (5.7%) | 340 (18%) | <0.001 | 3.7 (3.3–4.2) |
| Pneumonia | 822 (0.4%) | 33 (1.8%) | <0.001 | 4.8 (3.4–6.9) |
| Diabetes, no | 180,403 (82%) | 1,371 (74%) | | Reference |
| Diabetes, orally treated | 23,595 (11%) | 254 (14%) | <0.001 | 1.4 (1.2–1.6) |
| Diabetes, insulin treated | 16,243 (7%) | 228 (12%) | <0.001 | 1.8 (1.6–2.1) |
| History of CAD | 27,793 (13%) | 439 (24%) | <0.001 | 2.2 (1.9–2.4) |
| Recent CAD event | 3,299 (1.5%) | 59 (3.2%) | <0.001 | 2.2 (1.7–2.8) |
| Congestive heart failure | 2,183 (1.0%) | 83 (4.5%) | <0.001 | 4.7 (3.7–5.9) |
| Hypertension requiring medication | 115,646 (53%) | 1,341 (72%) | <0.001 | 2.4 (2.1–2.6) |
| Liver function | 8,074 (3.7%) | 132 (7.1%) | <0.001 | 2.0 (1.7–2.4) |
| Renal failure | 6,360 (2.9%) | 105 (5.7%) | <0.001 | 2.0 (1.7–2.5) |
| Sensorium or coma | 1,201 (0.5%) | 39 (2.1%) | <0.001 | 3.9 (2.8–5.4) |
| Prior neurologic condition | 20,624 (9.4%) | 292 (16%) | <0.001 | 1.8 (1.6–2.1) |
| Cancer | 10,300 (4.7%) | 149 (8.0%) | <0.001 | 1.8 (1.5–2.1) |
| Prior hospitalization | 52,415 (24%) | 773 (42%) | <0.001 | 2.3 (2.1–2.5) |
| Steroid use | 8,429 (3.8%) | 104 (5.6%) | <0.001 | 1.5 (1.2–1.8) |
| Weight loss | 7,819 (3.6%) | 161 (8.7%) | <0.001 | 2.6 (2.2–3.0) |
| Transfusion | 385 (0.2%) | 3 (0.2%) | 1.000 | 0.9 (0.3–2.9) |
| Sepsis | 13,499 (6.1%) | 259 (14%) | <0.001 | 2.5 (2.2–2.8) |
| Prior operation within 30 days | 5,789 (3.0%) | 70 (4.4%) | 0.001 | 1.5 (1.2–1.9) |
| Very–low-risk surgical procedures | 75,835 (35%) | 210 (11%) | | Reference |
| Low-risk surgical procedures | 102,460 (47%) | 900 (49%) | <0.001 | 3.2 (2.7–3.7) |
| Medium-risk surgical procedures | 25,011 (11%) | 303 (16%) | <0.001 | 4.4 (3.7–5.2) |
| High-risk surgical procedures | 16,404 (7.5%) | 438 (24%) | <0.001 | 9.6 (8.2–11.4) |
| BMI (kg/m$^2$) | 30.5 ± 9.0 | 28.8 ± 8.6 | <0.001 | — |
| Age | 57.9 ± 16.5 | 66.9 ± 13.7 | <0.001 | — |

Detailed definitions of all American College of Surgeons–National Surgical Quality Improvement Program data elements are available in appendix 1. All patient and operative characteristics were compared using Mann–Whitney U test for continuous variables and chi-square for categorical variables.

BMI = body mass index; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; UEPI = unanticipated early postoperative intubation.

**Baseline** characteristics of patients with no unanticipated early postoperative intubation (No UEPI) vs. patients with unanticipated early postoperative intubation (UEPI)

# Example of Use Propensity Scores

Ramachandran SK, Nafiu OO, Ghaferi A, Tremper KK, Shanks A, Kheterpal S. **Independent predictors and outcomes of unanticipated early postoperative tracheal intubation after nonemergent, noncardiac surgery.** Anesthesiology. 2011 Jul;115(1):44-53.

Patients from the derivation cohort were risk-matched based on the **propensity score** of a logistic regression model.

**Matching** was performed on a one-to-one basis for the outcome variable UEPI, and all predictor univariates were reassessed after matching to assure sufficient matching (a p > 0.05).

This **controlled for confounding**.

**Table 4.** Univariate Analysis for Matched Cohort (N = 1,958)

| | No UEPI (N = 979) | UEPI (N = 979) | *P* Value |
|---|---|---|---|
| Male sex | 462 (47%) | 474 (48%) | 0.587 |
| White race | 757 (83%) | 752 (82%) | 0.609 |
| Alcohol use | 17 (1.7%) | 17 (1.7%) | 1.000 |
| Current smoker | 252 (26%) | 252 (26%) | 1.000 |
| Dyspnea | 181 (19%) | 181 (19%) | 1.000 |
| COPD | 97 (9.9%) | 97 (9.9%) | 1.000 |
| Pneumonia | 2 (0.2%) | 5 (0.5%) | 0.288 |
| Diabetes, no | 786 (80%) | 786 (80%) | Reference |
| Diabetes, orally treated | 128 (13%) | 128 (13%) | 1.000 |
| Diabetes, insulin treated | 65 (6.6%) | 65 (6.6%) | 1.000 |
| History of CAD | 175 (18%) | 175 (18%) | 1.000 |
| Concurrent CAD event | 21 (2.1%) | 15 (1.5%) | 0.313 |
| Congestive heart failure | 3 (0.3%) | 3 (0.3%) | 1.000 |
| Hypertension | 703 (72%) | 703 (72%) | 1.000 |
| Liver function | 14 (1.4%) | 14 (1.4%) | 1.000 |
| Renal failure | 14 (1.4%) | 14 (1.4%) | 1.000 |
| Altered sensorium or coma | 7 (0.7%) | 10 (1.0%) | 0.465 |
| Prior neurological condition | 128 (13%) | 153 (16%) | 0.107 |
| Cancer | 34 (3.5%) | 34 (3.5%) | 1.000 |
| Prolonged hospitalization | 271 (28%) | 271 (28%) | 1.000 |
| Steroid use | 45 (4.6%) | 49 (5.0%) | 0.672 |
| Weight loss | 24 (2.5%) | 24 (2.5%) | 1.000 |
| Transfusion | 0 (0.0%) | 0 (0.0%) | 1.000 |
| Sepsis | 44 (4.5%) | 44 (4.5%) | 1.000 |
| Prior operation <30 days | 16 (1.8%) | 18 (2.1%) | 0.668 |
| Very–low-risk procedures | 149 (15%) | 149 (15%) | Reference |
| Low-risk procedures | 520 (53%) | 520 (53%) | 1.000 |
| Medium-risk procedures | 119 (12%) | 119 (12%) | 1.000 |
| High-risk procedures | 191 (20%) | 191 (20%) | 1.000 |
| BMI (kg/m$^2$) | 29.3 ± 8.2 | 29.3 ± 8.7 | 0.848 |
| Age | 66.7 ± 13.9 | 66.7 ± 13.9 | 1.000 |
| Mortality, 30-day all-cause | 19 (1.9%) | 149 (15%) | <0.001 |
| | | | 9.1 (5.6–14.8)* |

Detailed definitions of all American College of Surgeons-National Surgical Quality Improvement Program data elements are available in appendix 1. All patient and operative characteristics were compared using Mann–Whitney U test for continuous variables and chi-square for categorical variables.

* Odds ratio with 95% confidence interval.

BMI = body mass index; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; UEPI = unanticipated early postoperative intubation.

Characteristics of the **matched** cohort (subset) of patients with No UEPI vs. patients with UEPI

# Example of Use Propensity Scores

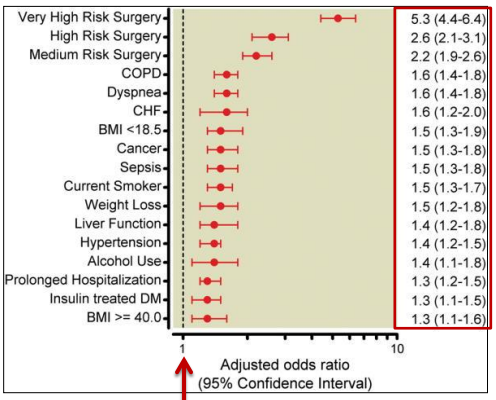
Ramachandran SK, Nafiu OO, Ghaferi A, Tremper KK, Shanks A, Kheterpal S. **Independent predictors and outcomes of unanticipated early postoperative tracheal intubation after nonemergent, noncardiac surgery.** Anesthesiology. 2011 Jul;115(1):44-53.

**Table 2.** Independent Risk Factors for Unanticipated Early Postoperative Intubation—Derivation Cohort

| Risk Factor | *P* Value | Adjusted Odds Ratio (95% CI) |
|---|---|---|
| BMI <18.5 kg/m$^2$ | <0.001 | 1.5 (1.3–1.9) |
| BMI ≥40.0 kg/m$^2$ | 0.011 | 1.3 (1.1–1.6) |
| Alcohol use | 0.004 | 1.4 (1.1–1.8) |
| Current smoker | <0.001 | 1.5 (1.3–1.7) |
| Dyspnea | <0.001 | 1.6 (1.4–1.8) |
| Chronic obstructive pulmonary disease | <0.001 | 1.6 (1.4–1.8) |
| Diabetes, insulin treated | 0.003 | 1.3 (1.1–1.5) |
| Congestive heart failure | 0.001 | 1.6 (1.2–2.0) |
| Hypertension | <0.001 | 1.4 (1.2–1.5) |
| Liver function | <0.001 | 1.4 (1.2–1.8) |
| Cancer | <0.001 | 1.5 (1.3–1.8) |
| Prolonged hospitalization | <0.001 | 1.3 (1.2–1.5) |
| Weight loss | <0.001 | 1.5 (1.2–1.8) |
| Sepsis | <0.001 | 1.5 (1.3–1.8) |
| Medium-risk surgery | <0.001 | 2.2 (1.9–2.6) |
| High-risk surgery | <0.001 | 2.6 (2.1–3.1) |
| Very–high-risk surgery | <0.001 | 5.3 (4.4–6.4) |

Detailed definitions of all American College of Surgeons–National Surgical Quality Improvement Program data elements are available in appendix 1. Any variable with a $P < 0.05$ and an adjusted odds ratio <0.8 or >1.2 was established as an independent predictor of unanticipated early postoperative intubation.
BMI = body mass index.

**After controlling for the other risk factors**, based upon the **adjusted odds ratios**, all of these co-morbidities were **significant risk factors** for unanticipated early postoperative intubation.




Null value of 1.0 for an **odds** ratio

# Example of Use Propensity Scores

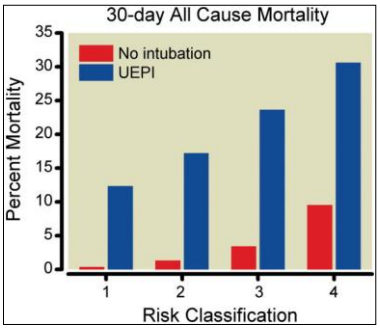
Ramachandran SK, Nafiu OO, Ghaferi A, Tremper KK, Shanks A, Kheterpal S. **Independent predictors and outcomes of unanticipated early postoperative tracheal intubation after nonemergent, noncardiac surgery.** Anesthesiology. 2011 Jul;115(1):44-53.

**Table 3.** Unanticipated Early Postoperative Intubation Risk Class Index

| — | Derivation (N = 222,094) | | | Validation (N = 109,636) | | |
|---|---|---|---|---|---|---|
| | n | UEPI n (%) | Odds Ratio (95% CI) | n | UEPI n (%) | Odds Ratio (95% CI) |
| Class I (0 or 1 risk factors) | 70,166 | 144 (0.2) | Reference | 34,799 | 82 (0.2) | Reference |
| Class II (2 risk factors) | 64,120 | 349 (0.5) | 2.7 (2.2–3.2) | 31,751 | 173 (0.5) | 2.3 (1.8–3.0) |
| Class III (3 risk factors) | 46,282 | 466 (1.0) | 4.9 (4.1–6.0) | 22,667 | 262 (1.2) | 5.0 (3.9–6.3) |
| Class IV (4 or 5 risk factors) | 35,619 | 675 (1.9) | 9.4 (7.8–11.3) | 17,495 | 333 (1.9) | 8.2 (6.4–10.5) |
| Class V (6+ risk factors) | 5,907 | 219 (3.7) | 18.7 (15.1–23.1) | 2,924 | 125 (4.3) | 18.9 (14.3–25.0) |

Patients are assigned to a risk class based on the number of preoperative risk factors they possess: very–high-risk surgery, high-risk surgery, medium-risk surgery, chronic obstructive pulmonary disease, dyspnea, congestive heart failure, body mass index <18.5 or ≥40.0 kt/m$^2$, cancer, sepsis, current smoker, weight loss, abnormal liver function, hypertension, alcohol use, previous hospitalization, and insulin-treated diabetes mellitus. Detailed definitions of all American College of Surgeons–National Surgical Quality Improvement Program data elements are available in appendix 1.
UEPI = unanticipated early postoperative intubation.

Like the Lee Revised Cardiac Risk Index, an UEPI risk index was created.




Significant increases in death rate in patients with unanticipated early postoperative intubation (UEPI) across increasing risk classes.

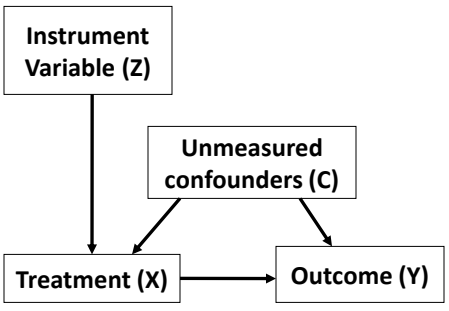
# Instrumental Variables Analysis (IVA)

- Covariate analysis **cannot** adjust for potential confounding variables that are **unknown** or not easily quantifiable.
- IVA exploits quasi-experimental variation in treatment assignment that is incidental to the studied health outcome.
- **Three assumptions** for IVA:
  1. The IV must predict treatment but that prediction does not have to be perfect. An IV that does a poor job of prediction is said to be weak.
  2. A valid IV will not be directly related to outcome, except through the effect of the treatment.
  3. A valid IV will also not be related to outcome through either measured or unmeasured paths.

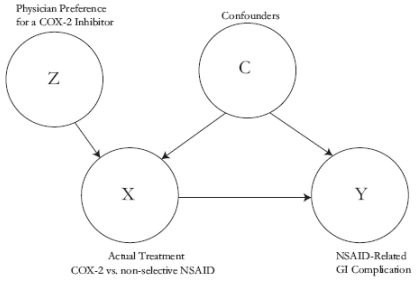
Johnston, Gustafson, Levy & Grootendorst, *Statistics in Medicine* 2008; 27:1539–1556
Rassen et al., *Journal of Clinical Epidemiology* 2009;62:1226-1232

# Causal Relations in IVA

**General instrumental variable analysis (IVA) model**




**Example of IVA with physician-specific prescribing preference**




Bennett, *Methods in Neuroepidemiology* 2010;35(3):237-240
Brookhart, Wang, Solomon & Scheeweiss, *Epidemiology* 2006;17(3):268-275

# Instrumental Variables Model

- **Two-stage least-squares regression**
  1. $Y = \alpha_0 + \alpha_1 X + \varepsilon_1$ } Y = outcome, X = exposure
  2. $X = \beta_0 + \beta_1 Z + \varepsilon_2$ } X = exposure, Z = instrument variable
  - Substituting equation 2 into equation 1:
  - $Y = \alpha_0 + \alpha_1 (\beta_0 + \beta_1 Z + \varepsilon_2) + \varepsilon_1 \rightarrow Y_i = \gamma_0 + \gamma_1 Z_i + \varepsilon_i$
  - Estimate direct treatment effect ($\beta_1$) of treatment ($T_i$) on outcome ($Y_i$): $\beta_1 = \gamma_1 / \alpha_1$
- Examples of instrumental variables
  - Physician prescribing preference for NSAID
  - Smoking cessation program in pregnant mothers
  - Distance to hospital with cardiac catherization laboratory

Bennett, *Methods in Neuroepidemiology* 2010;35(3):237-240
Schneeweiss et al., *Arthritis & Rhematism* 2006;54(11):3390-3398
Brookhart, Rassen & Schneeweiss, *Pharmacoepidemiology and Drug Safety* 2010;19:537-554

# Analysis of Covariance (ANCOVA)

- Compares several means (like an ANOVA) but adjusts for the effect of one or more other variables (covariates)
- These covariates <u>can</u> be the presumed confounders.
- May use the propensity score as a single covariate (?)
- Two key <u>but</u> often violated assumptions for an ANCOVA:
  - Independence of the covariate and experimental effect (x)
  - Homogeneity of regression slopes: the relationship between the covariate and dependent outcome (y) is true for all of the subgroups of study subjects
- Use of ANCOVA is quite controversial – it is not a quick fix.

Miller & Chapman, Journal of Abnormal Psychology 2001;110:40-48
Leech, Barrett, & Morgan (2005): *SPSS for Intermediate Statistics: Use and Interpretation* (2nd edition)
Field (2009): *Discovering Statistics Using SPSS* (3rd edition)

## Johns Hopkins Bloomberg School of Public Health's OPENCOURSEWARE (OCW) Project

- "…provides access to content of the School's most popular courses. As challenges to the world's health escalate daily, the School feels a moral imperative to provide equal and open access to information and knowledge about the obstacles to the public's health and their potential solutions."
- Funded by the William and Flora Hewlett Foundation
- **Introduction to Biostatistics:** http://ocw.jhsph.edu/courses/introbiostats/
- **Methods in Biostatistics I:** http://ocw.jhsph.edu/courses/MethodsInBiostatisticsI/
- **Methods in Biostatistics II:** http://ocw.jhsph.edu/courses/methodsinbiostatisticsii/
- **Fundamentals of Epidemiology I:** http://ocw.jhsph.edu/courses/FundEpi/
- **Fundamentals of Epidemiology II:** http://ocw.jhsph.edu/courses/fundepiii/

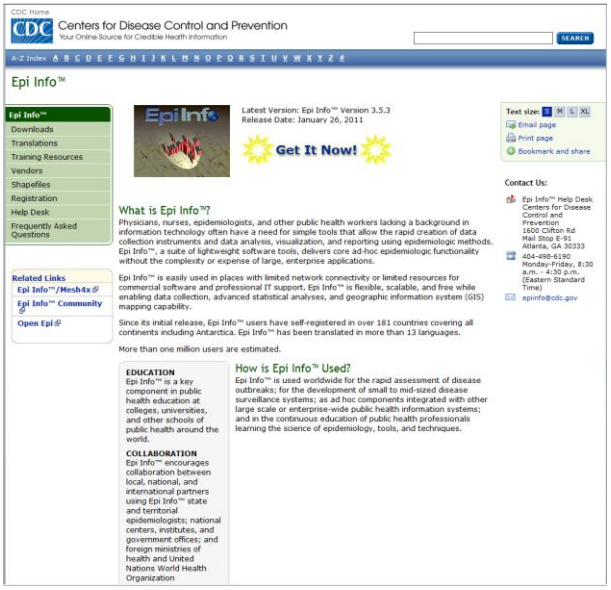
## ActivEpi: www.activepi.com

- **"*ActivEpi*** is a collection of innovative tools for learning epidemiology.**"**
- Multimedia approach to learning basic and some intermediate epidemiology
- Extensive series of online, downloadable PowerPoint presentations (free)
- "Epi for Clinicians" section provides a population-based perspective on clinical medicine.

# Epi Info 3.5.3: www.cdc.gov/epiinfo

**"**Physicians, nurses, epidemiologists, and other public health workers lacking a background in information technology often have a need for simple tools that allow the rapid creation of data collection instruments and data analysis, visualization, and reporting using epidemiologic methods.

Epi Info™, a suite of lightweight software tools, delivers core ad-hoc epidemiologic functionality without the complexity or expense of large, enterprise applications.**"**




## Journal References I


- McCrum-Gardner, E. (2008). Which is the correct statistical test to use? *Br J Oral Maxillofac Surg, 46*(1), 38-41.

**********

- Overholser, B. R., & Sowinski, K. M. (2007). Biostatistics primer: Part I. *Nutr Clin Pract, 22*(6), 629-635.
- Overholser, B. R., & Sowinski, K. M. (2008). Biostatistics primer: Part 2. *Nutr Clin Pract, 23*(1), 76-84.

**********

- Whitley, E., & Ball, J. (2002a). Statistics review 1: Presenting and summarising data. *Crit Care, 6*(1), 66-71.
- Whitley, E., & Ball, J. (2002b). Statistics review 2: Samples and populations. *Crit Care, 6*(2), 143-148.
- Whitley, E., & Ball, J. (2002c). Statistics review 3: Hypothesis testing and P values. *Crit Care, 6*(3), 222-225.
- Whitley, E., & Ball, J. (2002d). Statistics review 4: Sample size calculations. *Crit Care, 6*(4), 335-341.
- Whitley, E., & Ball, J. (2002e). Statistics review 5: Comparison of means. *Crit Care, 6*(5), 424-428.
- Whitley, E., & Ball, J. (2002f). Statistics review 6: Nonparametric methods. *Crit Care, 6*(6), 509-513.
- Bewick, V., Cheek, L., & Ball, J. (2003). Statistics review 7: Correlation and regression. *Crit Care, 7*(6), 451-459.
- Bewick, V., Cheek, L., & Ball, J. (2004a). Statistics review 8: Qualitative data - tests of association. *Crit Care, 8*(1),
- Bewick, V., Cheek, L., & Ball, J. (2004b). Statistics review 9: One-way analysis of variance. *Crit Care, 8*(2), 130-136.
- Bewick, V., Cheek, L., & Ball, J. (2004c). Statistics review 10: Further nonparametric methods. *Crit Care, 8*(3), 196-199.
- Bewick, V., Cheek, L., & Ball, J. (2004d). Statistics review 11: Assessing risk. *Crit Care, 8*(4), 287-291.
- Bewick, V., Cheek, L., & Ball, J. (2004e). Statistics review 12: Survival analysis. *Crit Care, 8*(5), 389-394.
- Bewick, V., Cheek, L., & Ball, J. (2004f). Statistics review 13: Receiver operating characteristic curves. *Crit Care, 8*(6), 508-512.
- Bewick, V., Cheek, L., & Ball, J. (2005). Statistics review 14: Logistic regression. *Crit Care, 9*(1), 112-118.

## Journal References II


- De Muth, J. E. (2008). Preparing for the first meeting with a statistician. *Am J Health Syst Pharm, 65*(24), 2358-2366.

**********

- Chan, Y. H. (2003a). Biostatistics 101: Data presentation. *Singapore Med J, 44*(6), 280-285.
- Chan, Y. H. (2003b). Biostatistics 102: Quantitative data--parametric & non-parametric tests. *Singapore Med J, 44*(8), 391-396.
- Chan, Y. H. (2003c). Biostatistics 103: Qualitative data - tests of independence. *Singapore Med J, 44*(10), 498-503.
- Chan, Y. H. (2003d). Biostatistics 104: Correlational analysis. *Singapore Med J, 44*(12), 614-619.
- Chan, Y. H. (2004a). Biostatistics 201: Linear regression analysis. *Singapore Med J, 45*(2), 55-61.
- Chan, Y. H. (2004b). Biostatistics 202: Logistic regression analysis. *Singapore Med J, 45*(4), 149-153.
- Chan, Y. H. (2004c). Biostatistics 203. Survival analysis. *Singapore Med J, 45*(6), 249-256.
- Chan, Y. H. (2004d). Biostatistics 301. Repeated measurement analysis. *Singapore Med J, 45*(8), 354-368; quiz 369.
- Chan, Y. H. (2004e). Biostatistics 301A. Repeated measurement analysis (mixed models). *Singapore Med J, 45*(10), 456-461.
- Chan, Y. H. (2004f). Biostatistics 302. Principal component and factor analysis. *Singapore Med J, 45*(12), 558-565, quiz 566.
- Chan, Y. H. (2005a). Biostatistics 303. Discriminant analysis. *Singapore Med J, 46*(2), 54-61; quiz 62.
- Chan, Y. H. (2005b). Biostatistics 304. Cluster analysis. *Singapore Med J, 46*(4), 153-159; quiz 160.
- Chan, Y. H. (2005c). Biostatistics 305. Multinomial logistic regression. *Singapore Med J, 46*(6), 259-268; quiz 269.
- Chan, Y. H. (2005d). Biostatistics 306. Log-linear models: poisson regression. *Singapore Med J, 46*(8), 377-385; quiz 386.
- Chan, Y. H. (2005e). Biostatistics 307. Conjoint analysis and canonical correlation. *Singapore Med J, 46*(10), 514-517; quiz 518.
- Chan, Y. H. (2005f). Biostatistics 308. Structural equation modeling. *Singapore Med J, 46*(12), 675-679; quiz 680.


## Journal References III


- Barratt, A., Wyer, P. C., Hatala, R., et al. (2004). Tips for learners of evidence-based medicine: 1. Relative risk reduction, absolute risk reduction and number needed to treat. *CMAJ, 171*(4), 353-358.
- Montori, V. M., Kleinbart, J., Newman, T. B., et al. (2004). Tips for learners of evidence-based medicine: 2. Measures of precision (confidence intervals). *CMAJ, 171*(6), 611-615.
- Hatala, R., Keitz, S., Wyer, P., & Guyatt, G. (2005). Tips for learners of evidence-based medicine: 4. Assessing heterogeneity of primary studies in systematic reviews and whether to combine their results. *CMAJ, 172*(5), 661-665.

**********

- Fitzmaurice, G. (1999a). Confidence intervals. *Nutrition, 15*(6), 515-516.
- Fitzmaurice, G. (1999b). Meta-analysis. *Nutrition, 15*(2), 174-176.
- Fitzmaurice, G. (2000a). The meaning and interpretation of interaction. *Nutrition, 16*(4), 313-314.
- Fitzmaurice, G. (2000b). The odds ratio: Impact of study design. *Nutrition, 16*(11-12), 1114-1115.
- Fitzmaurice, G. (2000c). Regression to the mean. *Nutrition, 16*(1), 80-81.
- Fitzmaurice, G. (2000d). Some aspects of interpretation of the odds ratio. *Nutrition, 16*(6), 462-463.
- Fitzmaurice, G. (2001a). Clustered data. *Nutrition, 17*(6), 487-488.
- Fitzmaurice, G. (2001b). A conundrum in the analysis of change. *Nutrition, 17*(4), 360-361.
- Fitzmaurice, G. (2001c). How to explain an interaction. *Nutrition, 17*(2), 170-171.
- Fitzmaurice, G. (2002a). Measurement error and reliability. *Nutrition, 18*(1), 112-114.
- Fitzmaurice, G. (2002b). Sample size and power: How big is big enough? *Nutrition, 18*(3), 289-290.
- Fitzmaurice, G. (2002c). Statistical methods for assessing agreement. *Nutrition, 18*(7-8), 694-696.
- Fitzmaurice, G. (2003). Confused by confounding? *Nutrition, 19*(2), 189-191.
- Fitzmaurice, G. (2004). Adjusting for confounding. *Nutrition, 20*(6), 594-596.
- Fitzmaurice, G. (2006a). Confounding: Propensity score adjustment. *Nutrition, 22*(11-12), 1214-1216.
- Fitzmaurice, G. (2006b). Confounding: Regression adjustment. *Nutrition, 22*(5), 581-583.
- Fitzmaurice, G. (2008). Missing data: Implications for analysis. *Nutrition, 24*(2), 200-202.