Sampling Methods in Scientific Studies

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Scientific studies may be

- Observational

- Randomized controlled

Scientific studies may be

- Observational
  - descriptive
  - inferential

- Randomized controlled

Scientific studies may be

- Observational
  - descriptive
  - inferential
    - cross-sectional
    - cohort
    - case control
- Randomized controlled

Descriptive Studies

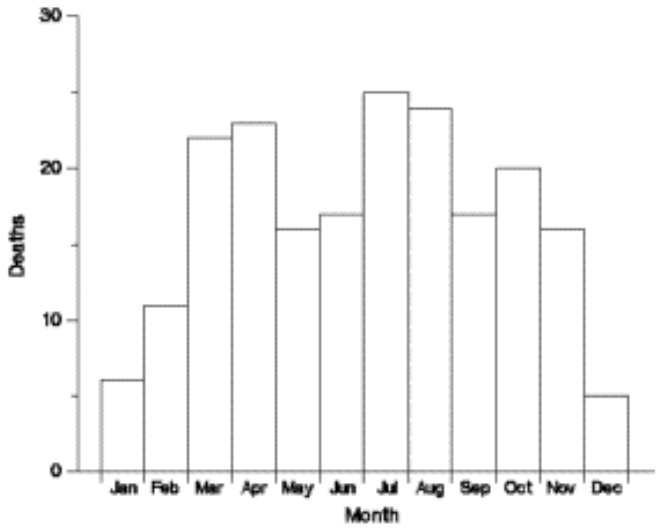
- Collect information to characterize and summarize the health event or problem

  Who? What? Where? When?

- Example: Tractor related deaths in Georgia

Example: Tractor related deaths in Georgia

Figure 1: Deaths associated with tractor injuries, by month of death



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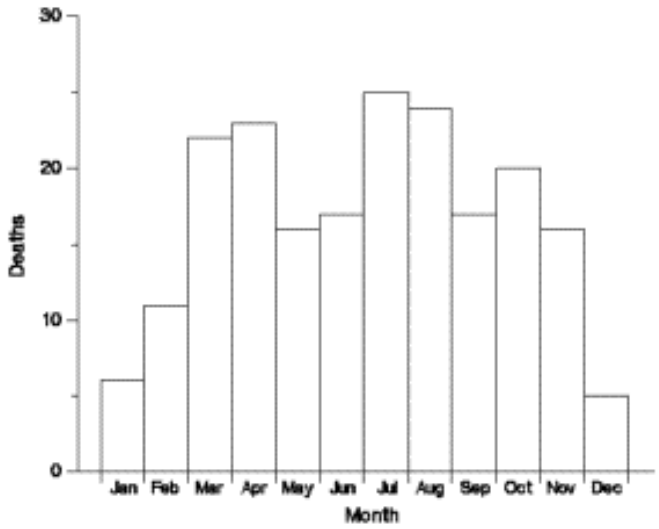
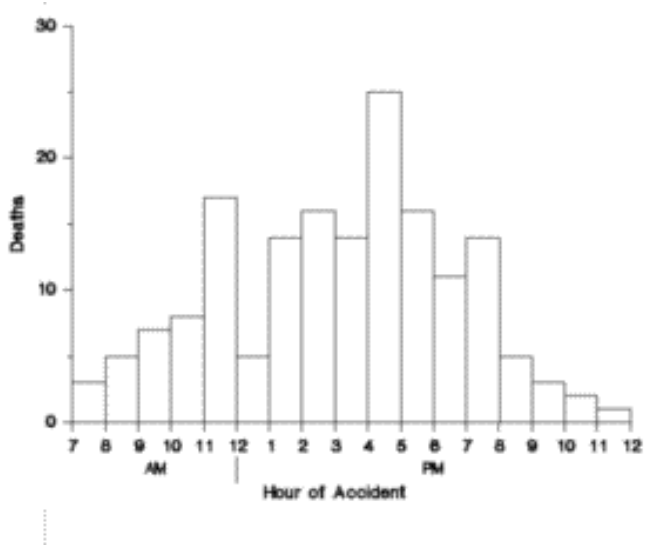


Peaks during spring and fall. Due to planting and harvest?

Example: Tractor related deaths in Georgia

Figure 2: Deaths associated with tractor injuries, by time of day



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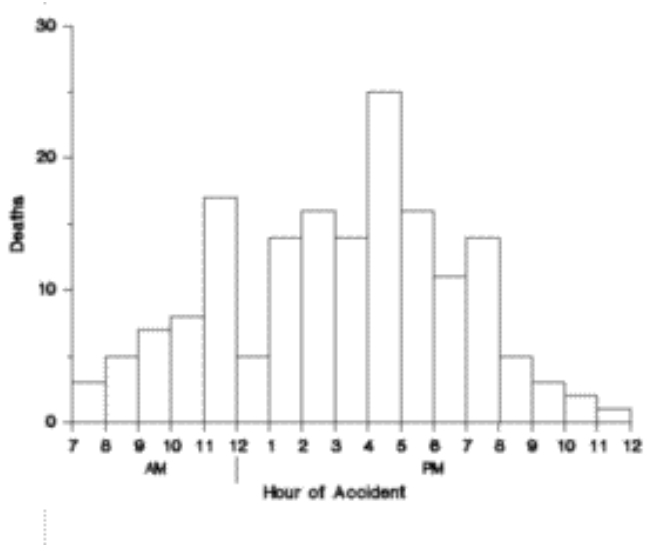

Increasing before lunch. Fatigue?

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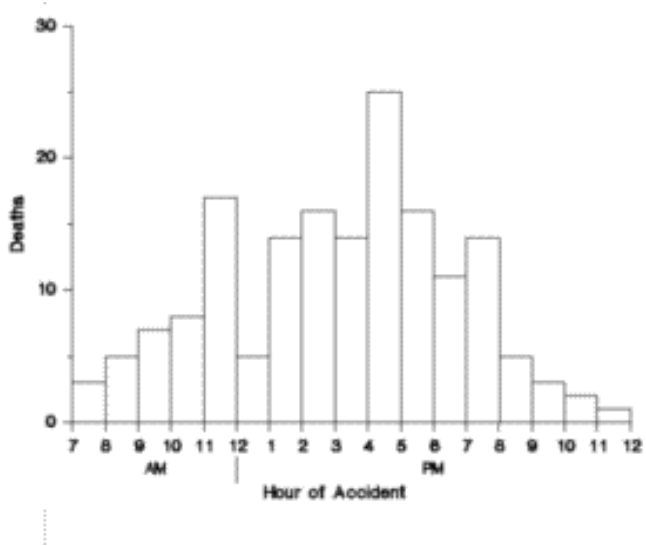

Increasing before lunch. Fatigue?
Peak at 4-5. Fatigue? Hunger? Darkness?

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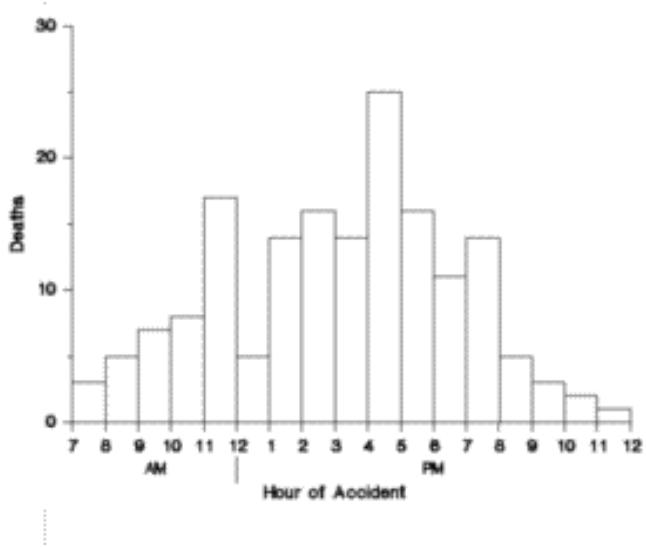


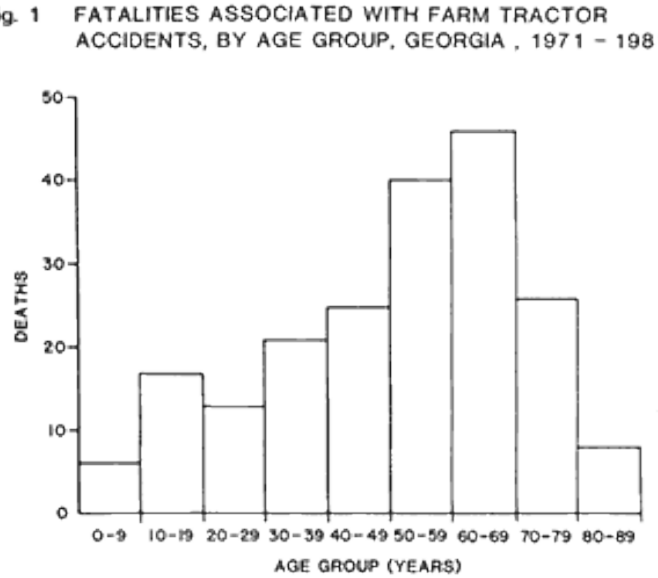
Increasing before lunch. Fatigue?

Peak at 4-5. Fatigue? Hunger? Darkness?

Children home from school.

Example: Tractor related deaths in Georgia

Figure 3: Deaths associated with tractor injuries, by age



Peak in older age group. Tractor users older? Less likely to survive an accident?
Small peak for school-age group.

Inferential Studies

Inferential studies test hypotheses using

- Observational study
  - cross-sectional
    -data represent a point in time
  - cohort
    -subjects selected according to exposure
  - case-control
    -subjects selected according to outcome: cases and controls
    (necessarily restrospective)
- Randomized experiment

Cross-sectional studies

- Cross-sectional studies are primarily surveys
- intended to look at prevalence rates and risk factors
- Example: National Health and Nutrition Examination Survey (NHANES)
- Example: Wisconsin Epidemiologic Study of Diabetic Retinopathy
- Example: Baltimore Eye Survey

Example: NHANES

- to assess the health and nutritional status of adults and children in the US
- combines interviews and physical examinations (including lab tests)
- responsible for producing vital and health statistics for the US
- sample of about 5,000 persons from 15 counties each year
- determine the prevalence of major diseases and risk factors
- the basis for national standards of height, weight, blood pressure, etc.

Example: NHANES

Major Findings:

- pediatric growth charts
- Federal nutrition recommendations, school lunch programs
- iron fortification of grain and cereal products (1973)
- iodine fortification of salt has virtually eliminated goiter and stillbirths
- Recommended Daily Allowance (RDA) of vitamins and minerals
- vaccine policy (e.g. 1-in-4 females aged 14-59 infected with HPV, 2003-04)

Example: NHANES

Major Findings:

- prevalence estimates of
  - malnutrition, obesity
  - cholesterol, hypertension
  - diabetes, arthritis, osteoporosis
  - hepatitis, HPV, other infectious diseases
  - dental health, visual health
  - exposures to lead, mercury, asbestos

Smaller, more targeted cross-sectional studies:

- Wisconsin Epidemiologic Study of Diabetic Retinopathy
  - studied prevalence of retinopathy among diabetics
  - identified risk factors such as hyperglycemia or hypertension
- Baltimore Eye Survey
  - confirmed that rate of primary open-angle glaucoma in black Americans was found to be four to five times higher than whites
- European Youth Heart Study
  - physical activity levels should be higher than current guidelines to prevent CVD risk factors.

Cohort studies

- A *cohort* is a group of people who share something in common
  - students enrolled in Stat 5630
  - WMU students 20 years and older
  - adult men and women residents of Framingham, Massachusetts
- the cohort may be chosen according to exposure patterns, but must be identified *before* disease status has been determined (this is crucial)
- determination of disease status may be prospective or retrospective
- allows calculation of relative risk

Cohort studies

- Example: A Cohort Study of Childhood Asthma Followed to Adulthood
  - children born from April 1972 through March 1973 in Dunedin, New Zealand
  - assess risk factors for persistence and relapse
- Example: A Retrospective Cohort Study of Measles, Mumps, and Rubella Vaccination and Autism
  - 537,303 children born in Denmark from January 1991 through December 1998
  - risk of autism was similar in MMR vaccinated and unvaccinated children

- Example: Framingham Heart Study
  - began in 1948 with 5,209 adults from Framingham, Mass.
  - now on its third generation of participants (1971 and 2002)
  - assess risk factors for cardiovascular disease
- Example: Nurses' Health Study
  - began in 1976, has followed 121,700 female registered nurses
  - assess risk factors for cancer and cardiovascular disease

Example: Framingham Heart Study

Major Findings:

1960s Smoking, high cholesterol and BP increase risk of coronary heart disease (CHD).
Exercise decreases risk, obesity increases it.

1970s Elevated BP increases risk of stroke.

1980s High levels of HDL cholesterol *reduces* risk of heart disease.

1990s Framingham Risk Score is published, and correctly predicts 10-year risk of future CHD events.

2000s Lifetime risk of developing elevated BP is 90%.
Lifetime risk for obesity is approximately 50%.
Social contacts are relevant to whether a person is obese.
Four risk factors for a precursor of heart failure are discovered.
Some genes increase risk of atrial fibrillation.
Parent dementia increases risk of poor memory.

Example: Nurses' Health Study

Major Findings:

	Breast Cancer	CHD/Stroke
Smoking	No association	Strong positive association
Oral Contraceptives	Current use increases risk	Current use increases risk
Alcohol	Increases risk	Reduces CHD risk
Diet	Red meat increases risk	Fish reduces risk of stroke. Nut/wholegrain reduce CHD risk Trans fats increase risk

Case-control studies

- Case-control studies select subjects according to disease outcome (cases and controls)
- then the investigator looks back to determine exposure or risk factors
- necessarily retrospective (there is no waiting for disease outcome)
- relative risk is not valid

Example: Effectiveness of Bicycle Safety Helmets

Thompson et al. (1989):

- Cases: 235 persons with bicycling head injuries, who sought emergency care at one of five hospitals
- Controls:

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- Controls: 433 persons who received emergency care at the same hospitals for bicycling injuries not involving the head

Example: Effectiveness of Bicycle Safety Helmets

Thompson et al. (1989):

- Cases: 235 persons with bicycling head injuries, who sought emergency care at one of five hospitals
- Controls: 433 persons who received emergency care at the same hospitals for bicycling injuries not involving the head

Results:

Head Injury: 7 percent were wearing helmets

No head injury: 24 percent were wearing helmets

Example: Effectiveness of Bicycle Safety Helmets

How effective are helmets in preventing head injury?

$$\text{RR} = \frac{.07}{.24} = .29 = \frac{P[\text{Helmet}|\text{Head Inj}]}{P[\text{Helmet}|\text{No Head Inj}]}$$

"Head injury reduces your risk of wearing a helmet by 71%"

Example: Effectiveness of Bicycle Safety Helmets

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"Head injury reduces your risk of wearing a helmet by 71%"

We want:

$$\text{RR}^* = \frac{P[\text{Head Inj}|\text{Helmet}]}{P[\text{Head Inj}|\text{No Helmet}]}$$

But $\text{RR}^* \neq \text{RR}$.

Recall:

$$\text{Odds}(E|D) = \frac{P(E|D)}{1 - P(E|D)}$$

It is easy to show

$$\frac{\text{Odds}(E|D)}{\text{Odds}(E|\text{not D})} = \frac{P(E \cap D) \cdot P(E^c \cap D^c)}{P(E^c \cap D) \cdot P(E \cap D^c)} = \frac{\text{Odds}(D|E)}{\text{Odds}(D|\text{not E})}$$

Example: Effectiveness of Bicycle Safety Helmets

Implication?

$$\frac{\text{Odds[Head Inj|Helmet]}}{\text{Odds[Head Inj|No Helmet]}} = \frac{\text{Odds[Helmet|Head Inj]}}{\text{Odds[Helmet|No Head Inj]}}$$

$$= \frac{.07/(1-.07)}{.24/(1-.24)} = .25$$

"Wearing a helmet reduces your odds of head injury by 75%"

Example: Effectiveness of Bicycle Safety Helmets

It is interesting to note the evolution of methodology

- Problem: the event is rare, and randomization is unethical
- Solution: sampling methodology ("Let's sample the accident cases instead.")
- Problem: the wrong rates are estimated.
- Solution: statistical theory (risk ratios are wrong, but odds ratios are correct)

"Wearing a helmet reduces your odds of head injury by 75%"

The HRT Story

Hormone Replacement Therapy:

Since the 1940's, when pharmaceutical companies had successfully manufactured estrogen, estrogen was sold as a way to cure the symptoms of menopause (hot flashes, night sweats, irritability, osteoporosis, etc).

Ads targeted the menopausal woman as suffering from 'estrogen deficiency', which can be cured by taking estrogen ("remain vital beyond middle age").

By 1975, Premarin had become the fifth leading prescription drug in the United States

The HRT Story

1975: Published studies linked estrogen use to higher rates of uterine cancer

1976: The FDA required that each package of estrogen contain an insert warning of the risks of estrogen

Progesterone was added to estrogen to offset the risks of uterine cancer

The HRT Story

1976: Breast cancer was linked to estrogen therapy in menopausal women

Taking a possible carcinogen for hot flashes was not reason enough and sales dropped.

By 1980, estrogen use had declined by 50% of its 1975 peak.

The HRT Story

Early 1980s: several studies showed that estrogen was effective in slowing bone loss

1986: the FDA approved estrogen as a treatment for postmenopausal osteoporosis

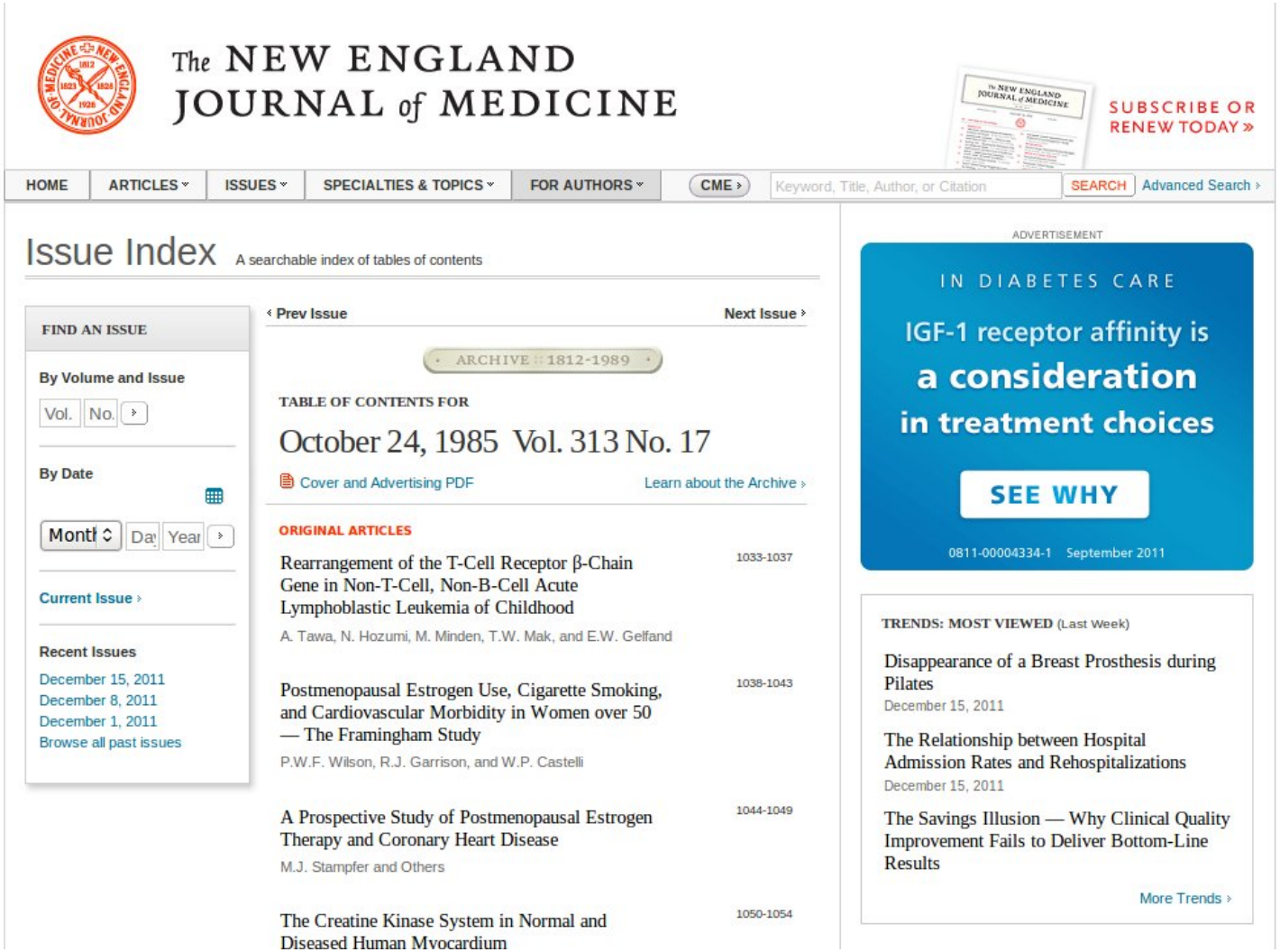
The HRT Story

1985: Nurses Health Study showed that registered nurses who were currently using estrogen had 70 percent lower risk of developing coronary heart disease

The HRT Story

1985: Nurses Health Study showed that registered nurses who were currently using estrogen had 70 percent lower risk of developing coronary heart disease

1985: Framingham Heart Study showed that women who had taken estrogen were 50 percent more likely to develop heart disease



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Vol. No.

By Date

Month Day Year

Current Issue

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Browse all past issues

Prev Issue | Next Issue

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TABLE OF CONTENTS FOR

October 24, 1985 Vol. 313 No. 17

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ORIGINAL ARTICLES

Rearrangement of the T-Cell Receptor β-Chain Gene in Non-T-Cell, Non-B-Cell Acute Lymphoblastic Leukemia of Childhood — 1033-1037
A. Tawa, N. Hozumi, M. Minden, T.W. Mak, and E.W. Gelfand

Postmenopausal Estrogen Use, Cigarette Smoking, and Cardiovascular Morbidity in Women over 50 — The Framingham Study — 1038-1043
P.W.F. Wilson, R.J. Garrison, and W.P. Castelli

A Prospective Study of Postmenopausal Estrogen Therapy and Coronary Heart Disease — 1044-1049
M.J. Stampfer and Others

The Creatine Kinase System in Normal and Diseased Human Myocardium — 1050-1054

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IN DIABETES CARE

IGF-1 receptor affinity is a consideration in treatment choices

SEE WHY

0811-00004334-1 September 2011

TRENDS: MOST VIEWED (Last Week)

Disappearance of a Breast Prosthesis during Pilates
December 15, 2011

The Relationship between Hospital Admission Rates and Rehospitalizations
December 15, 2011

The Savings Illusion — Why Clinical Quality Improvement Fails to Deliver Bottom-Line Results

More Trends

The HRT Story: Nurses' Health Study

A Prospective Study of Postmenopausal Estrogen Therapy and Coronary Heart Disease - The Nurses' Health Study
by Stampfer, et al. (NEJM 313:1044-9, October 24, 1985)

- surveyed 32,317 postmenopausal female nurses, aged 30 to 55 years
- 4 years of follow-up
- RR of CHD in those who had ever used hormones was 0.5 (0.3 and 0.8; P = 0.007)
- RR of CHD in current users was 0.3 (0.2 and 0.6; P = 0.001)

The HRT Story: Nurses' Health Study

Conclusion:

> *"The relative risks were similar for fatal and nonfatal disease and were unaltered after adjustment for cigarette smoking, hypertension, diabetes, high cholesterol levels, a parental history of myocardial infarction, past use of oral contraceptives, and obesity. These data support the hypothesis that the postmenopausal use of estrogen reduces the risk of severe coronary heart disease."*

The HRT Story: Framingham Study

Postmenopausal Estrogen Use and Cardiovascular Morbidity in Women over 50 – The Framingham Study
by Wilson et al (NEJM; 313:1038-1043, October 24, 1985)

- surveyed 1234 postmenopausal women, aged 50 to 83 years
- eight years of follow-up
- 50 per cent elevated risk of cardiovascular morbidity ($P<0.01$) among those who had used hormones
- more than a twofold risk for cerebrovascular disease ($P<0.01$)

The HRT Story: Framingham Study

Conclusion:

> *"Increased rates for myocardial infarction ($P<0.05$) were observed particularly among the estrogen users who smoked cigarettes. Conversely, among nonsmokers estrogen use was associated only with an increased incidence of stroke ($P<0.05$). No benefits from estrogen use were observed in the study group."*

The HRT Story

Since the Framingham study

1. involved older women (who were thus at greater risk)
2. had received higher doses of estrogen
3. had a smaller sample size (1234 vs 32,317)
4. were not replicated by other studies

the results were largely dismissed by the media and medical community

The HRT Story

Subsequent studies were conducted investigating the true effects of HRT on CHD. Most supported Stampfer's study that HRT was protective against CRD. In Stampfer's own words (*International Journal of Epidemiology, 1990*), :

> *"Of 16 prospective studies, 15 found decreased relative risks, in most instances, statistically significant. The Framingham study alone observed an elevated risk, which was not statistically significant when angina was omitted. Overall, the bulk of the evidence strongly supports a protective effect of estrogens that is unlikely to be explained by confounding factors. "*

The HRT Story

More researchers kept producing positive studies about hormones preventing heart attacks and bone loss, while not increasing cancer, stroke, or blood clots.

1992: Premarin was the number one prescribed drug in the United States

Major medical professional organizations were recommending long-term use of HRT. E.g., the American of College of Physicians issued guidelines to practicing physicians recommending that "all women. . . should consider preventive hormone therapy," and that 10 to 20 years of therapy were recommended for "maximum benefit"

The HRT Story

Too good to be true?

Elizabeth Barrett-Connor (UCSD Div. of Epidemiology):
"I thought there were two or three very strong biases

1. women taking estrogen were better educated and wealthier
2. there was compliance bias – that is, people who are compliant in clinical trials, even with a placebo, have less disease.
3. during many of the years covered in these studies, the standard Physicians Desk Reference suggested estrogen should not be prescribed to women with heart disease, hypertension, or diabetes. So women with heart risks were not receiving the drug.

"Healthy Cohort Effect"

The HRT Story

Posthuma et al. (1994): *Cardioprotective effect of hormone replacement therapy in post-menopausal women: is the evidence biased?*

Vandenbroucke JP (1995): *How much of the cardioprotective effect of postmenopausal estrogens is real?*

Sturgeon et al. (1995): *Evidence of a healthy estrogen user survivor effect.*

Matthews et al. (1996): *Prior to estrogen replacement therapy, are users healthier than nonusers?*

Randomized Study: The Women's Health Initiative

In the early 1990s, the NIH initiated a large-scale randomized controlled clinical trial on womens health covering heart disease, breast and colon cancer, bone fractures, and the role of hormone therapy, diet, vitamins, and calcium in preventing these diseases.

Between 1993 and 1998, the WHI randomized 16,608 postmenopausal women aged 50-79 years into receiving estrogen plus progestin therapy or placebo.

A second arm of the study involving 10,739 women compared estrogen only against placebo.

Randomized Study: The Women's Health Initiative

Results:

On May 31, 2002, after a mean of 5.2 years of follow-up, the data and safety monitoring board recommended stopping the trial of estrogen plus progestin vs placebo. The test statistic for breast cancer exceeded the stopping boundary, and the global index statistic indicated 'risks exceeding benefits'.

On February 2, 2004, the data and safety monitoring board recommended stopping the trial of estrogen only vs placebo. Estrogen alone does not appear to affect the risk of heart disease or breast cancer, but it did increase the risk of stroke.

Randomized Study: The Women's Health Initiative

Risk findings for estrogen plus progestin (cases per 10,000 women):

- Breast cancer: 26% increased risk (38 cases vs 30 on placebo)
- Stroke: 41% increased risk (29 vs 21)
- Heart attack: 29% increased risk (37 vs 30)
- Blood clots (legs, lungs): Doubled rates (34 vs 16)
- Colorectal Cancer: 37% less risk (10 vs 16)
- Fractures: 37% fewer hip fractures (10 vs 15)

Randomized Study: The Women's Health Initiative

Risk findings for estrogen only (cases per 10,000 women):

- Stroke: 39% increase in strokes (44 cases 32 on placebo)
- Blood clot: 47% higher risk (21 vs 15)
- Coronary heart disease: No significant difference (49 vs 54)
- Colorectal cancer: No significant difference (17 vs 16)
- Breast cancer: No significant difference (26 vs 33)
- Bone fractures: 39% fewer hip fractures (11 vs 17)

Contradicted research outcomes

Questions:

1. How often do medical studies result in wrong findings?
2. What are the primary causes of wrong findings?
   - Statistical
   - Otherwise

Paper:
"*Contradicted and Initially Stronger Effects in Highly Cited Clinical Research*", by Ioannidis (2005)

Methods: Authors looked at all original research studies published in 3 major clinical journals (*NEJM*, *JAMA*, *Lancet*) in 1990-2003 and cited more than 1000 times in the literature.

Contradicted research outcomes

Results: Of 49 highly cited original clinical research studies, 45 claimed that the intervention was effective. Of these,

- 7 were contradicted by subsequent studies
- 7 found effects stronger than those of subsequent studies
- 20 found effect confirmed by subsequent studies
- 11 remained largely unchallenged

Conclusion: Contradiction and initially stronger effects are not unusual in highly cited research of clinical interventions and their outcomes.

Contradicted research outcomes

Table 1: Contradicted research and current state of knowledge

Highly Cited Study	Current state of knowledge
1. Nurses Health 2. PEPI	Estrogen does not protect, but increases CAD risk in postmenopausal women
3. Health Pros	Vit E supplement does not reduce CAD in men
4. Nurses Health	Vit E supp. does not reduce CAD in women
5. CHAOS	Vit E supp. does not prevent CAD events
6. HA-1A Sepsis	HA-1A does not improve survival in sepsis
7. Rossaint et al	Nitric oxide does not improve survival in respiratory distress

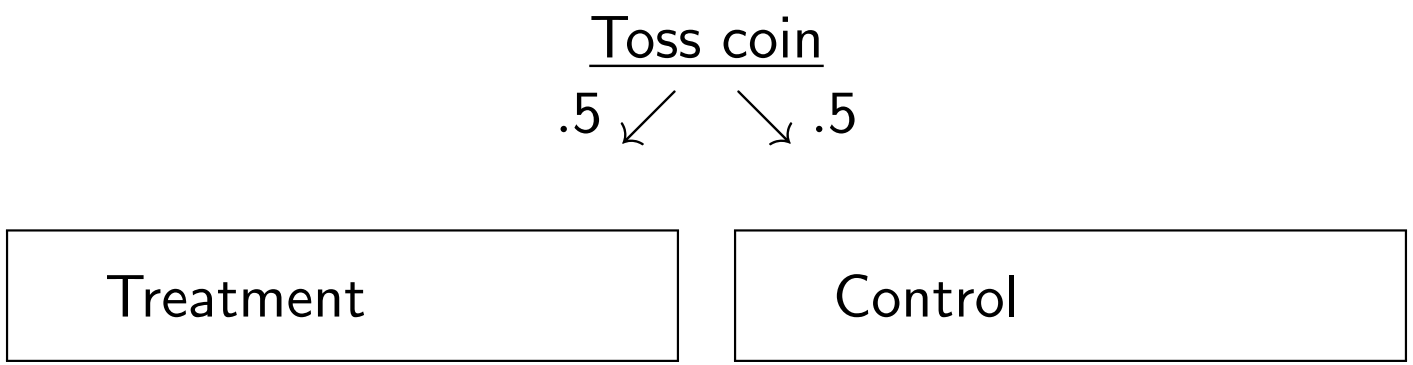
Contradicted research outcomes

Table 2: Contradicted research designs

Highly Cited Study	Highly cited study design	Contradicting study design
1. Nurses Health	Cohort (n=48,470)	RCT (n=16,608)
2. PEPI	RCT (n=875)	RCT (n=16,608)
3. Health Pros	Cohort (n=39,910)	RCT (n=6,996)
4. Nurses Health	Cohort (n=87,245)	RCT (n=2,545)
5. CHAOS	RCT (n=2,002)	RCT (n=9,541)
6. HA-1A Sepsis	RCT (n=200)	RCT (n=2,199)
7. Rossaint et al	Case series (n=9)	MA RCT (n=535)

Observational vs randomized studies

Recall Women's Health Initiative: 10,000 women randomized into estrogen or placebo



Age profile of the two groups? Balanced!
Education? Income? Race? Balanced!
Diet? Exercise? Health attitudes?

Observational vs randomized studies

Q: Why not do this for all studies?
A: Not always possible.

Ex. "Smoking decreases life span"

Smokers	*Nonsmokers*

Cannot randomize. Group membership is *observed* rather than *assigned*.

Observational vs randomized studies

Observational studies

$\Downarrow$

Apples and Oranges

Smokers are different from nonsmokers in other ways besides smoking!
(e.g. Drink more coffee, exercise less, stand out in the cold more, etc.)

If estrogen group has lower disease rates than no-estrogen, does this mean that estrogen is protective, or is the estrogen group just fundamentally healthier?
$\Rightarrow$ "The healthy volunteer effect"

Observational vs randomized studies

Simpson's Paradox: (Comparing aggregate scores)

NAEP 1992 8th Grade Math Scores

	State	White	Black	Other
Nebraska	**277**	281	236	259
New Jersey	**271**	283	242	260

Percentage of population

Nebraska	87%	5%	8%
New Jersey	66%	15%	19%

Observational vs randomized studies

Simpson's Paradox: (Comparing aggregate scores)

Basketball

	Shot %	FT	3-pt
Me	**.540**	.600	.300
You	**.460**	.700	.400

Percentage of population

Me	80%	20%
You	20%	80%

Observational vs randomized studies

Simpson's Paradox: (Comparing aggregate scores)

NAEP Study

Nebraska	*New Jersey*

-Race, etc.: Not Balanced

Driver Leg Injury Study

Men	*Women*

-Height: Not Balanced

Observational vs randomized studies

Clofibrate Study

Clofibrate is a cholesterol lowering drug. The study looked at mortality rates of patients with heart disease over a period of 5 years.

	Clofibrate		Placebo	
	Number	Deaths	Number	Deaths
Total	1103	20%	2789	21%
Adherers	708	15%		
Non-adherers	357	25%		

Observational vs randomized studies

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1. Clofibrate is not effective
2. Adherers are different from non-adherers

Anecdotal Studies

Silicone Breast Implants Story

1960s
The first silicone breast implants

1977
First lawsuit: Cleveland woman claims ruptured implants and subsequent operations had caused pain and suffering. Dow Corning settles, $170,000.

1984
San Francisco woman's systemic autoimmune disease is found by a jury to be caused by her silicone implants. Jury awards $1.5 million in punitive damages.

Anecdotal Studies

June 1988
FDA classifies the implants into Class III.
Requires manufacturers to prove their safety
in order to keep them on the market.

December 1990
Congressional hearing on safety of silicone implants.

December 1991
A San Francisco woman wins $7.3 million from Dow Corning. Jury concludes her mixed connective-tissue disease is linked to her ruptured silicone implants.

Anecdotal Studies

January 1992
FDA Commissioner David Kessler calls for a voluntary moratorium on the use of silicone implants until the FDA and the advisory panel have an opportunity to consider newly available information. The manufacturers agree.

February 1992
Class action lawsuit is filed in Cincinnati.

December 1993
12,359 lawsuits have been filed against Dow Corning.

Anecdotal Studies

June 1994
Mayo Clinic epidemiologic study finds no increased risk of connective-tissue or other disorders.

December 1994
19,092 lawsuits have been filed against Dow Corning.

May 1995
Dow Corning files for Chapter 11 bankruptcy.

June 1995
Harvard Nurses Epidemiologic Study published in NEJM. Finds no increased risk of connective-tissue disease.

Anecdotal Studies

December 1995
By now more than 20 studies in the U.S. and internationally fail to support a causal relationship .

Today
Silicone implants remain off the market. Available only to women who will have breast surgery for a medical condition, and only if they agree to be part of a scientific study.

Anecdotal Studies

The Harvard Nurses Study

New England Journal of Medicine, June 22, 1995

Data: 87,501 nurses followed for other research purposes from 1976 through May 31, 1990. None of the women had connective tissue disease at the start of the study.

During the time frame of the study, 3 women with breast implants developed connective tissue diseases.

Number of women with breast implants who developed disease:

3

Anecdotal Studies

The Harvard Nurses Study

Data is missing!

	Disease	No Disease
Implant	3	
No Implant		

Anecdotal Studies

The Harvard Nurses Study

Data is missing!

	Disease	No Disease
Implant	3	
No Implant		

	Disease	No Disease	
Implant	3	1,180	.0025
No Implant	513	85,805	.0059

> *"Don't ask whether B follows A. Ask whether B follows A* more frequently *than A^c."*

Anecdotal vs Observational vs Randomized studies

Summary:

Show me the study!

IF	THEN	ASK
Anecdotal	No comparisons.	Coincidence?
Observational	Lurking variables.	Similar groups?
Randomized	Best.	