Contradicted Medical Studies

Joshua Naranjo

Department of Statistics,
Western Michigan University

Outline

Applications

Statistics - data science (collection, analysis, decision-making)

- Actuarial science
- Business analytics (finance, sales)
- Census and sample surveys (population stats)
- Government statistics (labor, economy)
- Clinical trials (drug development, therapy assessment)
- Engineering (manufacturing, reliability)
- Economics (health of the market, financial institutions)
- Epidemiology (population health)

Scientific studies may be

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

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 5680
  - premenopausal women in Kalamazoo 20 years and older
  - adult men and women residents of Framingham, Massachusetts
  - nurses
- 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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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

To do: (bicycle odds ratios, then silicon 2x2, then simpsons paradox NJ vs Nebraska

1. Cannot estimate risk: P(wear helmets), P(injury given helmet), P(injury given no helnet)
2. Cannot do relative risk: P(injury given helmet)/P(no injury given helmet)

What you have:

3. P(helmet given injury) = 7 percent
4. P(no helmet given injury) = 93 percent
5. P(helmet given no injury) = 24 percent
6. P(no helmet given no injury) = 76 percent

Example: Effectiveness of Bicycle Safety Helmets

Bambach et al (2013) The effectiveness of helmets in bicycle collisions with motor vehicles
Cases: 372 helmet vs 267 No helmet (58.2 were wearing helmets)
Controls: 924 helmet vs 296 No helmet (75.7 were wearing helmets)

Example: Effectiveness of Bicycle Safety Helmets

Estimate of the "risk difference" $p_1 - p_2$:

$$\text{psample1 - psample2} = .24 - .07 = .17$$

95% confidence interval for $p_1 - p_2$:

$$(.12, .22)$$

Epidemiologists prefer the "risk ratio":

$$\text{RR} = \frac{\text{psample1}}{\text{psample2}} = \frac{.07}{.24} = .29$$

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

How effective are helmets in preventing head injury?

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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%"

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).

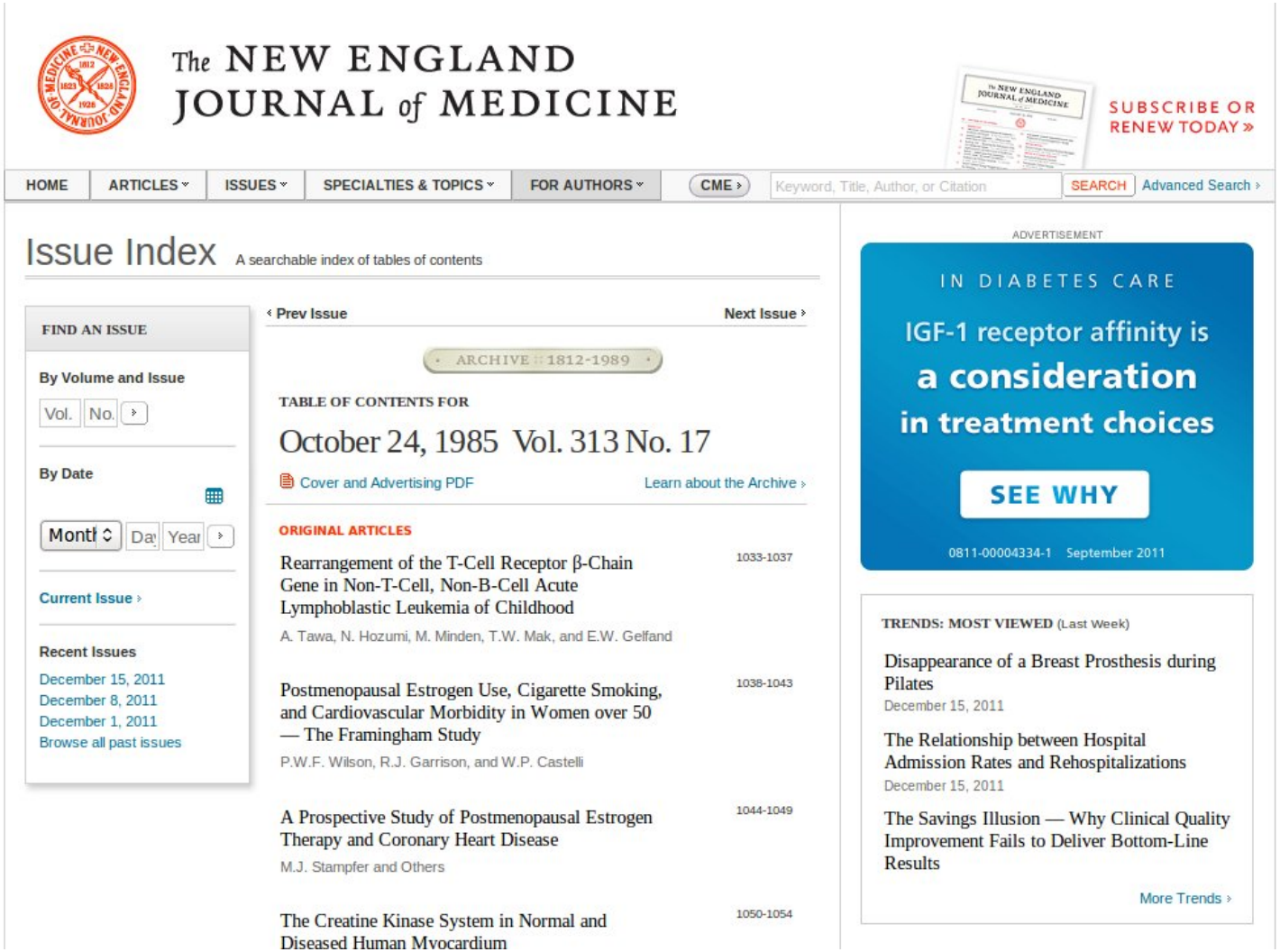
Ads targeted the menopausal woman as suffering from 'estrogen deficiency', which can be cured by taking estrogen ("remain vital beyond middle age").

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

The HRT Story

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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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. "*

Table 4 Prospective studies with internal controls

Study	Age at baseline (mean or range)	Number in population	Percentage estrogen users	Follow-up (years) (mean or range)	Endpoint (number of cases)	Relative risk (95% CI)	
						Age-adjusted	Risk factor-adjusted
Potocki (21)	60–70	158	52%	10 ?	MI (4)	0.31 (0.04–2.57)[a]	
Hammond *et al.* (24)	46.3	619	49%	1.3	CHD (58)	0.33 (0.19–0.56)[a]	
Nachtigall *et al.* (25)	55	168	50%	10	MI (4)	0.33 (0.04–2.82)[a]	
Lafferty and Helmuth (26)	45–60 (53.7)	124	49%	3–16 (8.6)	MI (7)	0.17 (0.03–1.06)[a]	
Stampfer *et al.* (27)	30–55	32 317	Past 18% Current 35% Ever 57%	3.3	Nonfatal MI and CHD death (90)	Past 0.7 (0.4–1.2) Current 0.3 (0.2–0.6) Ever 0.5 (0.3–0.8)	0.59 (0.33–1.06) 0.30 (0.14–0.64) 0.52 (0.34–0.80)
Framingham Heart Study[b]							
Wilson *et al.* (28)	50–84	1234	Past 14% Current 10%	8	All CVD (194) CVD death (48) MI (51)	1.76 ($P < 0.01$)[c] 1.94 ($P > 0.05$)[c] 1.87 ($P > 0.05$)[c]	
Eaker and Castelli (29)	50–59 60–69	695 602	15% 8%	10	CHD no angina (35) (51)	0.26 (0.06–1.22)[c,d] 1.68 (0.71–4.00)[c,d]	0.4 ($P > 0.05$)[c] 2.2 ($P > 0.05$)[c]
Bush *et al.* (30)	40–69	2270	26%	8.5	CVD death (50)	0.34 (0.12–0.81)	0.37 (0.16–0.88)
Petitti *et al.* (31)	18–54	6093	Ever 44%	10–13	CVD death	0.9 (0.2–3.3)	0.6 (0.3–1.1)
Criqui *et al.* (32)	50–79	1868	39%	12	CHD death (87)	0.75 (0.45–1.24)	0.99 (0.59–1.67)
Henderson *et al.* (33)	40–101 (median = 73)	8807	Past 43% Current 14%	4.6	MI deaths (149)	Past 0.62 (0.43–0.90) Current 0.47 (0.20–2.00) Ever 0.59 (0.42–0.82)	No change No change No change
Croft and Hannaford (34)	20–60	Nested	Ever 6.5%	19	MI (9)	0.8	0.8 (0.3–1.8)
Avila *et al.* (37)	50–64	24 900	Current 14%	5	MI (120)	0.7 (0.4–1.3)	0.7 (0.4–1.4)
Sullivan *et al.* (38)	?	2268	Ever 10.5%	10	Death		0.16 (0.04–0.66)

[a] The crude odds ratio and confidence intervals are derived from data given in the text.

[b] The results based on the analysis of Eaker and Castelli (29) are not included in the quantitative overview.

[c] This includes high-density lipoprotein cholesterol in the regression analysis.

[d] These results are taken as the average of findings using examinations 11 and 12 as baseline.

The HRT Story

Postmenopausal Estrogen Therapy and Cardiovascular Disease – Ten-Year Follow-up from the Nurses' Health Study
by Stampfer et al (NEJM, September 12, 1991)

> *Abstract: Our earlier report of a benefit from estrogen use in terms of the risk of coronary disease, based on four years of follow-up, was accompanied by a report from the Framingham Study that came to the opposite conclusion. We now report results for both coronary disease and stroke, based on 10 years of follow-up in the Nurses' Health Study, that included 48,470 postmenopausal women with 337,252 person-years of follow-up.*

The HRT Story

Results:

After adjustment for age and other risk factors,

- the overall relative risk of major coronary disease in women currently taking estrogen was 0.56 (95% CI, 0.40 to 0.80)
- The relative risk for current and former users of estrogen as compared with those who had never used it was 0.89 (95% CI, 0.78 to 1.00) for total mortality and 0.72 (95% CI, 0.55 to 0.95) for mortality from cardiovascular disease.
- The relative risk of stroke when current users were compared with those who had never used estrogen was 0.97 (95% CI, 0.65 to 1.45)

The HRT Story

Conclusions:

> *"Current estrogen use is associated with a reduction in the incidence of coronary heart disease as well as in mortality from cardiovascular disease, but it is not associated with any change in the risk of stroke."*

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 10,739 postmenopausal women aged 50-79 years into receiving estrogen therapy or placebo.

Randomized Study: The Women's Health Initiative

Results:

On February 2, 2004, the data and safety monitoring board recommended stopping the trial. Estrogen therapy does not appear to affect the risk of heart disease or breast cancer, but it increased the risk of stroke.

Randomized Study: The Women's Health Initiative

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

- Stroke: 39% increase in strokes (44 cases vs 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)

Randomized Study: The Women's Health Initiative

Bottom line? All those studies were wrong!

- The data: Estrogen group had less coronary disease
- False conclusion: Estrogen decreases risk.
- Correct:
  - Estrogen increases risk.
  - Estrogen group was healthier than non-estrogen group.

The HRT Story

Today:

Estrogen is still on the market.

Primarily prescribed for short-term treatment of menopausal symptoms and osteoporosis, and long term use is not recommended.

Litigation

- October 11, 2007:
  A Nevada jury awarded $35 million in compensatory and $99 million in punitive damages to 3 plaintiffs. Judge reduced verdict to $23 million in compensatory and $35 million in punitive damages.
- October 27, 2009: The jury awarded Connie Barton of Illinois $3.7 million in compensatory and $75 million in punitive damages.
- November 24, 2009: The jury awarded Donna Kendall of Illinois $6.3 million in compensatory and $28 million in punitive damages
- About 10,000 similar cases are pending

2005 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 clinical research studies published in 3 major general clinical journals (*NEJM, JAMA, Lancet*) or high-impact-factor specialty journals in 1990-2003 and cited more than 1000 times in the literature.

2005 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.

2005 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

2005 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)

The Vitamin E study

Health Professionals Study (Rimm et al, 1993):

An observational study of 51,529 male health professionals ranging in ages 40-75 in 1986. Those who consume more than 100 IU of vitamin E a day for a period of 2 years saw a reduction in the risk of coronary heart disease.

Contradicted by:

Heart Outcomes Prevention Evaluation Study (Yusuf et al, 2000):

2,545 women and 6,996 men were randomly given either a placebo or 400 IU of vitamin E daily for a mean of 4.5 years. There was no significant difference between the number of deaths in either group.

The Vitamin E study

Statistical explanation for contradiction:

The Health Professionals study is an observational study and vulnerable to the 'healthy cohort' effect where subjects who choose to take Vitamin E is as a group healthier than those who don't.

Moral:
Large sample size does not protect a study from biased sampling. The bias is simply repeated on a larger scale.

The Nitric Oxide study

The Nitric Oxide Study (Rossaint et al. 1993):

Consisted of 9 patients with severe ARDS (Adult Respiratory Distress Syndrome). Concluded that inhalation of nitric oxide in those with severe ARDS reduces pulmonary-artery pressure and increases arterial oxygenation.

Contradicted by:

Nitric Oxide Inhalation for Acute Hypoxemic Respiratory Failure (Sokol et al, 2009)

535 patients with acute hyperemic respiratory failure. Nitric oxide had no effect on mortality rates.

The Nitric Oxide study

Statistical explanation for contradiction:

- Sample Size (n=9)
- No Control Group
  - Placebo Effect
  - Regression Effect
    All patients started with extremely low oxygenation
- Heterogeneous Cohort
  4 patients had pneumonia, 4 had trauma and lung contusion.
  Some had kidney or liver failures.
- Surrogate endpoint (oxygenation, not mortality)

Threats to correct outcomes

Threats to study reliability: (*Are the results repeatable?*)

- Low sample size
- Heterogeneous cohort (population variance)
- Instrument reliability (e.g. pain scale, anxiety scale)

Threats to study validity: (*Does it do what is intended?*)

- Confounded effects (cohort vs RCT)
- Surrogate endpoint (Y) and surrogate markers (X) (e.g. urinary sodium $\rightarrow$ BP)
- Instrument validity (e.g. anxiety vs stress, memory loss)

Lessons

- Association is not causation (sometimes not even association)
- Beware of the limitations of 'adjusting for risk factors'
  - covariate adjustment
  - propensity analysis
- Persistence of the healthy cohort effect
  - systematic selection of subjects that would favor the treatment
  - systematic removal of subjects who show early symptoms

Need a healthy cynicism for results of observational studies.
Without randomized trials, keep thinking "maybe".