Why many scientific findings are wrong

Joshua Naranjo

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Outline

The Vaccine Story

February 1998: *The Lancet*

Early report

Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith

Summary

Background We investigated a consecutive series of children with chronic enterocolitis and regressive developmental disorder.

Methods 12 children (mean age 6 years [range 3–10], 11 boys) were referred to a paediatric gastroenterology unit with a history of normal development followed by loss of acquired skills, including language, together with diarrhoea and abdominal pain. Children underwent gastroenterological, neurological, and developmental assessment and review of developmental records. Ileocolonoscopy and biopsy sampling, magnetic-resonance imaging (MRI), electroencephalography (EEG), and lumbar puncture were done under sedation. Barium follow-through radiography was done where possible. Biochemical,

Introduction

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Patients and methods

12 children, consecutively referred to the department of paediatric gastroenterology with a history of a pervasive developmental disorder with loss of acquired skills and intestinal symptoms (diarrhoea, abdominal pain, bloating and food intolerance), were investigated. All children were admitted to the ward for 1 week, accompanied by their parents.

Clinical investigations

The Vaccine Story

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The Vaccine Story

In eight children, the onset of behavioural problems had been linked, either by the parents or by the child's physician, with measles, mumps, and rubella vaccination. Five had had an early adverse reaction to immunisation (rash, fever, delirium; and, in three cases, convulsions). In these eight children the average interval from exposure to first behavioural symptoms was 6·3 days (range 1–14). Parents were less clear about the timing of onset of abdominal symptoms because children were not toilet

The Vaccine Story

Child	Behavioural diagnosis	Exposure identified by parents or doctor	Interval from exposure to first behavioural symptom	Features associate exposure
1	Autism	MMR	1 week	Fever/delirium
2	Autism	MMR	2 weeks	Self injury
3	Autism	MMR	48 h	Rash and fever
4	Autism? Disintegrative disorder?	MMR	Measles vaccine at 15 months followed by slowing in development. Dramatic deterioration in behaviour immediately after MMR at 4·5 years	Repetitive behaviou self injury, loss of self-help
5	Autism	None—MMR at 16 months	Self-injurious behaviour started at 18 months	
6	Autism	MMR	1 week	Rash & convulsion; avoidance & self in
7	Autism	MMR	24 h	Convulsion, gaze a
8	Post-vaccinial encephalitis?	MMR	2 weeks	Fever, convulsion, diarrhoea
9	Autistic spectrum disorder	Recurrent otitis media	1 week (MMR 2 months previously)	Disinterest; lack of
10	Post-viral encephalitis?	Measles (previously vaccinated with MMR)	24 h	Fever, rash & vomit
11	Autism	MMR	1 week	Recurrent "viral pr for 8 weeks followi
12	Autism	None—MMR at 15 months	Loss of speech development and deterioration in language skills noted at 16 months	

The Vaccine Story

Discussion

We describe a pattern of colitis and ileal-lymphoid-nodular hyperplasia in children with developmental disorders. Intestinal and behavioural pathologies may have occurred together by chance, reflecting a selection bias in a self-referred group; however, the uniformity of the intestinal pathological changes and the fact that previous studies have found intestinal dysfunction in children with autistic-spectrum disorders, suggests that the connection is real and reflects a unique disease process.

The Vaccine Story

Statistical Issues:

- Small sample
- No control group
- It temporally linked three common conditions
- Data were not collected systematically, and provided lots of opportunity for selective interpretation
  - "Exposure identified by parents or doctor"
  - "Interval from exposure to first behavioral symptoms"

The Vaccine Story

Child 4:
His medical records from the years before vaccination mentioned ‘developmental delay’, ‘general delay’, and ‘restricted vocabulary’.”

Child 8:
When she was referred to Wakefield by her physician Diana Jelley, she wrote ”...both the hospital and members of the primary care team had significant concerns about her development some months before she had her MMR.”

The Vaccine Story

Ethical Issues: (Brian Deer, The Sunday Times)

- Two years before the Lancet paper was published, Wakefield had been hired by a lawyer, Richard Barr, who hoped to raise a speculative class action lawsuit against drug companies which manufactured the triple shot
- In June 1997, Wakefield had filed a patent on products, including his own supposedly "safer" single measles vaccine
- Nearly all the children had been pre-selected through MMR campaign groups, and at the time of their admission, most of their parents were clients and contacts of the lawyer, Barr

The Vaccine Story

August '97

A new syndrome: enterocolitis and regressive behavioural disorder

Wakefield AJ, Murch S*, Anthony A#, Linnell J, Casson D*, Malik M, Berelowitz M$, Dhillon AP#, Thomson M*, Harvey P@, Valentine A+, Walker-Smith JA*

Inflammatory Bowel Disease Study Group, University Departments of Medicine and Histopathology# and the University Departments of Paediatric Gastroenterology*, Child and Adolescent Psychiatry$, Neurology@ & Radiology+, Royal Free Hospital School of Medicine, London UK

The Vaccine Story

	August 1997	February 1998
Average interval reported between MMR shot and onset of behavioural symptoms	14 days	6.3 days
Range of intervals reported between MMR shot and onset of behavioural symptoms	1 - 56 days	1 - 14 days
No. children whose parents associated onset of child's behavioural symptoms with MMR	9 of 12	8 of 12
Child 4: age of onset of behavioural problems the parent associated with MMR	2.5 years	4.5 years

The Vaccine Story

Timeline

- Oct 1988: The three-in-one MMR vaccine is introduced to the UK after successful use in the US. Previously, single measles and rubella vaccines were used, and there was no mumps vaccine.
- Feb 1998: The Lancet publishes Wakefield paper
- 2000-2002: vaccine controversy gains momentum with over 1000 media articles
- March 2004: following news of undisclosed conflict of interest, ten of Wakefield's 12 coauthors retracted the paper's interpretation section, which claimed an association in time between MMR, enterocolitis, and regressive developmental disorders.

The Vaccine Story

- 2006
  - MMR vaccination compliance: 85% (from 92% in 1998)
  - Incidence rates of measles in UK: 13 times higher than 1998
  - Incidence rates of mumps in UK: 37 times higher than 1998
- Feb 2010: Lancet "fully retracts the article from the published record"
- May 2010: Wakefield found guilty of professional misconduct by General Medical Council, medical license is revoked

The Vaccine Story

Early report

Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

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Findings Onset of behavioural symptoms was associated by the parents, with measles, mumps, and rubella vaccination in eight of the 12 children, with measles infection in one child, and otitis media in another. All 12 children had intestinal abnormalities ranging from lymphoid nodular hyperplasia to aphthoid ulceration. Histology showed patchy chronic inflammation in 11 children and reactive ileal lymphonodular hyperplasia in seven, but no granulomas. Behavioural disorders included autism (nine), disintegrative psychosis (one), and possible postviral or vaccinal encephalitis (two). There were no focal neurological abnormalities and MRI and EEG tests were normal. Abnormal laboratory results were significantly raised urinary methylmalonic acid compared with age-matched controls ($p=0.003$), low haemoglobin in four children, and low serum IgA in four children.

Interpretation We identified associated gastrointestinal disease and developmental regression in a group of previously normal children, which was generally associated in time with possible environmental triggers.

Lancet 1998; **351:** 637–41
See Commentary page

Inflammatory Bowel Disease Study Group, University Departments of Medicine and Histopathology (A J Wakefield FRCS, A Anthony MB, J Linnell PhD, A P Dhillon MRCPath, S E Davies MRCPath) **and the University Departments of Paediatric Gastroenterology** (S H Murch MB, D M Casson MRCP, M Malik MRCP, M A Thomson FRCP, J A Walker-Smith FRCP.), **Child and Adolescent Psychiatry** (M Berelowitz FRCPsych), **Neurology** (P Harvey FRCP), **and Radiology** (A Valentine FRCR), **Royal Free Hospital and School of Medicine, London NW3 2QG, UK**

Correspondence to: Dr A J Wakefield

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12 children, consecutively referred to the department of paediatric gastroenterology a history of a pervasive developmental disorder with loss of acquired skills and intestinal symptoms (diarrhoea, abdominal pain, bloating and food intolerance), were investigated. All children were admitted to the ward for a week, accompanied by their parents.

Clinical investigations

We took histories including details of immunisations and exposure to infectious diseases, and assessed the children. In 11 cases the history was obtained by the senior clinician (JW-S). Neurodevelopmental psychiatric assessments were done by consultant staff (PH, MB) with HMS-4 criteria.[1] Developmental assessments included a review of prospective developmental records from parents, health visitors, and general practitioners. Four children did not undergo psychiatric assessment in hospital; all had been assessed professionally elsewhere, so these assessments were used as the basis for their behavioural diagnosis.

After bowel preparation, ileocolonoscopy was performed by SHM or MAT under sedation with midazolam and pethidine. Paired frozen and formalin-fixed mucosal biopsy samples were taken from the terminal ileum; ascending, transverse, descending, and sigmoid colons, and from the rectum. The procedure was recorded by video or still images, and were compared with images of the previous seven consecutive paediatric colonoscopies (four normal colonoscopies and three on children with ulcerative colitis), in which the physician reported normal appearances in the terminal ileum. Barium follow-through radiography was possible in some cases.

Also under sedation, cerebral magnetic-resonance imaging (MRI), electroencephalography (EEG) including visual, brain stem auditory, and sensory evoked potentials (where compliance made these possible), and lumbar puncture were done.

Laboratory investigations

Thyroid function, serum long-chain fatty acids, and cerebrospinal-fluid lactate were measured to exclude known causes of childhood neurodegenerative disease. Urinary methylmalonic acid was measured in random urine samples from eight of the 12 children and 14 age-matched and sex-matched normal controls, by a modification of a technique described previously.[2] Chromatograms were scanned digitally on computer, to analyse the methylmalonic-acid zones from cases and controls. Urinary methylmalonic-acid concentrations in patients and controls were compared by a two-sample t test. Urinary creatinine was estimated by routine spectrophotometric assay.

Children were screened for antiendomyseal antibodies and boys were screened for fragile-X if this had not been done

Selective interpretation: The Vioxx Story

Vioxx (Rofecoxib)

- nonsteroidal anti-inflammatory drug (NSAID) made by Merck
- treatment for osteoarthritis and acute pain conditions
- approved by the FDA in May 20, 1999
- withdrawn from the market on Sept. 30, 2004

The Vioxx Story

Background

- ANSAIDS like aspirin and ibuprofen work by blocking COX-1 enzyme which helps produce pain and inflammation
- COX-1 inhibitors can cause gastrointestinal damage and decrease blood clotting
- Vioxx was a COX-2 inhibitor, specific to inflamed tissue
- COX-2 inhibitors were believed to be easier on the stomach (this was the selling point)
- The Vioxx Gastrointestinal Outcomes Research Study (VIGOR)

The Vioxx Story

The New England Journal of Medicine

COMPARISON OF UPPER GASTROINTESTINAL TOXICITY OF ROFECOXIB AND NAPROXEN IN PATIENTS WITH RHEUMATOID ARTHRITIS

CLAIRE BOMBARDIER, M.D., LOREN LAINE, M.D., ALISE REICIN, M.D., DEBORAH SHAPIRO, DR.P.H.,
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AND THOMAS J. SCHNITZER, M.D., PH.D., FOR THE VIGOR STUDY GROUP

TRACT

kground Each year, clinical upper gastrointes-
events occur in 2 to 4 percent of patients who
aking nonselective nonsteroidal antiinflammatory
s (NSAIDs). We assessed whether rofecoxib, a

NONSTEROIDAL antiinflammatory drugs (NSAIDs) are among the most commonly used medications in the world.[1] A major factor limiting their use is gastrointestinal toxicity. Although endoscopic studies reveal that

The Vioxx Story

TABLE 4. INCIDENCE OF GASTROINTESTINAL EVENTS IN THE TREATMENT GROUPS.

TYPE OF EVENT	ROFECOXIB GROUP (N=4047)	NAPROXEN GROUP (N=4029)	ROFECOXIB GROUP (N=4047)	NAPROXEN GROUP (N=4029)	RELATIVE RISK (95% CI)*
	no. with event		rate/100 patient-yr		
Confirmed upper gastrointestinal events	56	121	2.1	4.5	0.5 (0.3–0.6)
Complicated confirmed upper gastrointestinal events	16	37	0.6	1.4	0.4 (0.2–0.8)
Confirmed and unconfirmed upper gastrointestinal events†	58	132	2.2	4.9	0.4 (0.3–0.6)
Complicated confirmed and unconfirmed upper gastrointestinal events‡	17	42	0.6	1.6	0.4 (0.2–0.7)
All episodes of gastrointestinal bleeding	31	82	1.1	3.0	0.4 (0.3–0.6)

The Vioxx Story

	VIOXX 50 mg N[2]=4047 n[3]	Naproxen 1000 N[2]=4029 n[3]
Any CV thrombotic event	45 *	19
Cardiac events	28**	10
Fatal MI/Sudden death	5	4
Non-fatal MI	18**	4
Unstable angina	5	2
Cerebrovascular	11	8
Ischemic stroke	9	8
TIA	2	0
Peripheral	6	1

[1]Confirmed by blinded adjudication committee, [2]N=Patients randomized, [3]n=Patients with events

* p-value <0.002 and ** p-value ≤0.006 for relative risk compared to naproxen by Cox proportional hazard

The Vioxx Story

The overall mortality rate was similar in the two groups, as were the rates of death from gastrointestinal events and from cardiovascular causes. The rate of myocardial infarction was significantly lower in the naproxen group than in the rofecoxib group (0.1 percent vs. 0.4 percent). This difference was primarily accounted for by the high rate of myocardial infarction among the 4 percent of the study population with the highest risk of a myocardial infarction, for whom low-dose aspirin is indicated.[22] The difference in the

The Vioxx Story

UPPER GASTROINTESTINAL TOXICITY OF ROFECOXIB AND

results are consistent with the theory that naproxen has a coronary protective effect and highlight the fact that rofecoxib does not provide this type of protection owing to its selective inhibition of cyclooxygenase-2 at its therapeutic dose and at higher doses. The finding that naproxen therapy was associated with a lower rate of myocardial infarction needs further confirmation in larger studies.

The Vioxx Story

Timeline

- May 1999: The FDA approves Vioxx
- March 2000: Merck gets results of the VIGOR trial
- Nov. 23, 2000: The VIGOR results are published in NEJM
- February 2001: FDA holds advisory meeting on the VIGOR trials, publishes VIGOR data on web
- Aug. 22, 2001: Cardiologists Debabrata Mukherjee et al publish JAMA paper based on their own analysis of VIGOR data at FDA web site. They cast serious doubt on the hypothesis that naproxen protects the heart.

The Vioxx Story

- January 2002 to August 2004: Numerous epidemiological studies point to Vioxx's increased risk of cardiovascular problems
- September 2004: A colon-polyp prevention study, called APPROVe, shows that the drug raises the risk of heart attacks after 18 months. Merck withdraws Vioxx from market.
- June 2006: The seventh trial against Merck begins. Merck has won three and lost three.
- November 2007: Merck announces $4.85 billion settlement fund to end thousands of lawsuits

Sampling Bias: 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).

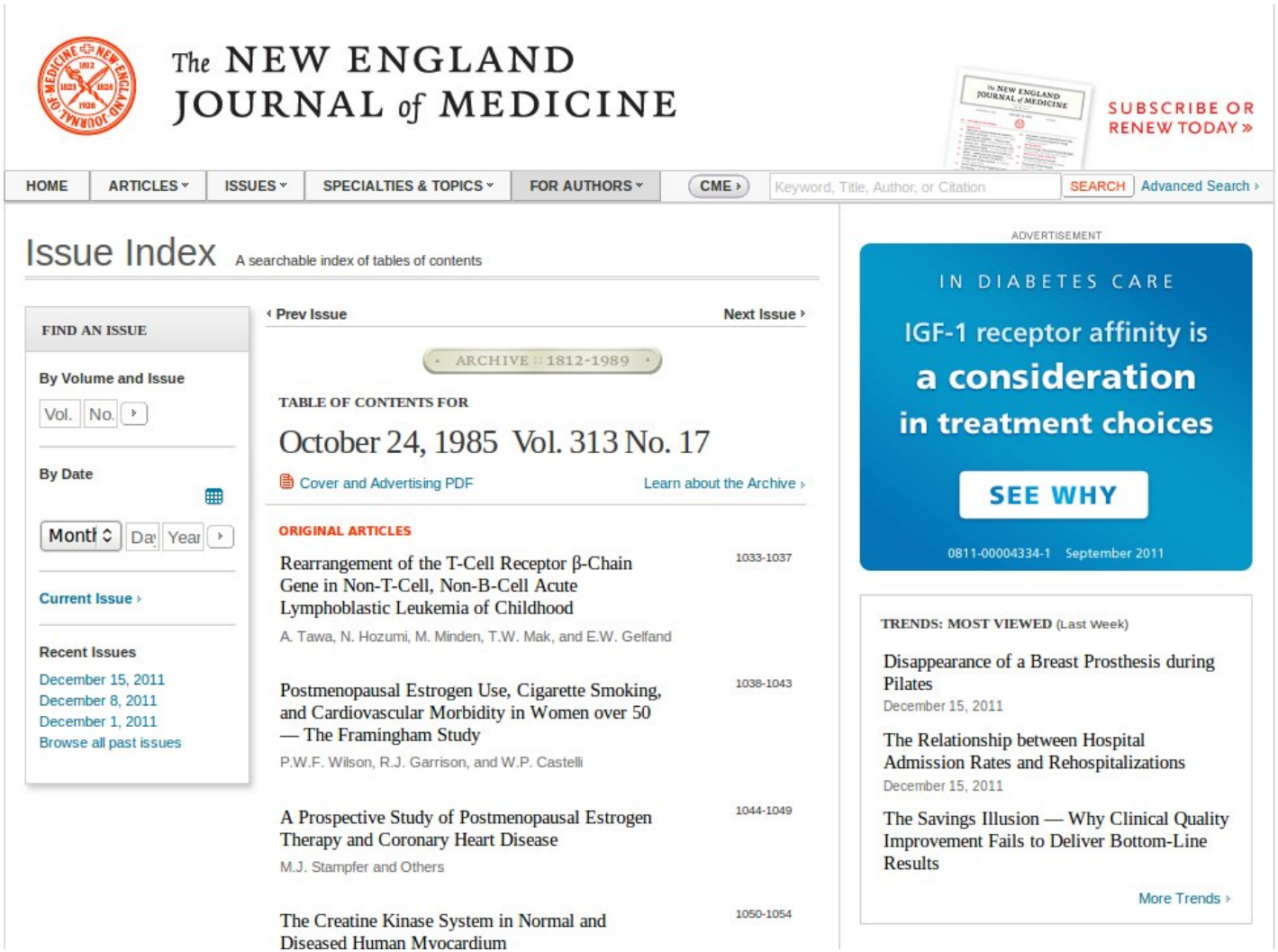
Ads targeted the menopausal woman as suffering from 'estrogen deficiency', which can be cured by taking estrogen ("remain vital beyond middle age").

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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IN DIABETES CARE

IGF-1 receptor affinity is a consideration in treatment choices

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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: 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

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 CHD. 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

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 the years spanned by both studies, the 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.

i.e., "Healthy Cohort Effect"

The HRT Story: 2002

In 1991, the NIH had a new director, cardiologist Bernadine Healy

She had an ambitious goal: a large, randomized, placebo-controlled multi-endpoint clinical trial on women's health covering

-heart disease, breast and colon cancer, bone fractures

-role of hormone therapy, diet, vitamins, calcium in prevention

The study was called the Women's Health Initiative (WHI).

The HRT Story: 2002

One arm of WHI:
16,608 healthy women aged 50-79 were recruited from 1993-1998 and randomly assigned to receive either a daily intake of Prempro (estrogen-progesterone) or a placebo.

Another arm of WHI:
10,739 women who had had a hysterectomy were randomly assigned to receive either a daily intake of 0.625 mg Premarin (estrogen-only) or a placebo

The HRT Story: 2002

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-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.

The HRT Story: 2002

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)

The HRT Story: 2002

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)

The HRT Story: 2017

September 12, 2017

JAMA | Original Investigation

Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality

The Women's Health Initiative Randomized Trials

JoAnn E. Manson, MD, DrPH; Aaron K. Aragaki, MS; Jacques E. Rossouw, MD; Garnet L. Anderson, PhD; Ross L. Prentice, PhD; Andrea Z. LaCroix, PhD; Rowan T. Chlebowski, MD, PhD; Barbara V. Howard, PhD; Cynthia A. Thomson, PhD; Karen L. Margolis, MD, MPH; Cora E. Lewis, MD, MSPH; Marcia L. Stefanick, PhD; Rebecca D. Jackson, MD; Karen C. Johnson, MD, MPH; Lisa W. Martin, MD; Sally A. Shumaker, PhD; Mark A. Espeland, PhD; Jean Wactawski-Wende, PhD; for the WHI Investigators

IMPORTANCE Health outcomes from the Women's Health Initiative Estrogen Plus Progestin and Estrogen-Alone Trials have been reported, but previous publications have generally not focused on all-cause and cause-specific mortality.

OBJECTIVE To examine total and cause-specific cumulative mortality, including during the intervention and extended postintervention follow-up, of the 2 Women's Health Initiative

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Author Video Interview and JAMA Report Video

Supplemental content

CME Quiz at jamanetwork.com/learning

The HRT Story: 2017

"Previous WHI reports have focused on incident diagnoses such as coronary heart disease, stroke, breast cancer, hip fracture, and other major outcomes, all of which are serious but predominantly nonfatal and led to fewer than half of the deaths.

In view of the complex balance of benefits and risks of hormone therapy, the all-cause mortality outcome provides an important summary measure, representing the net effect of hormone therapy use for 5 to 7 years on life-threatening outcomes."

The HRT Story: 2017

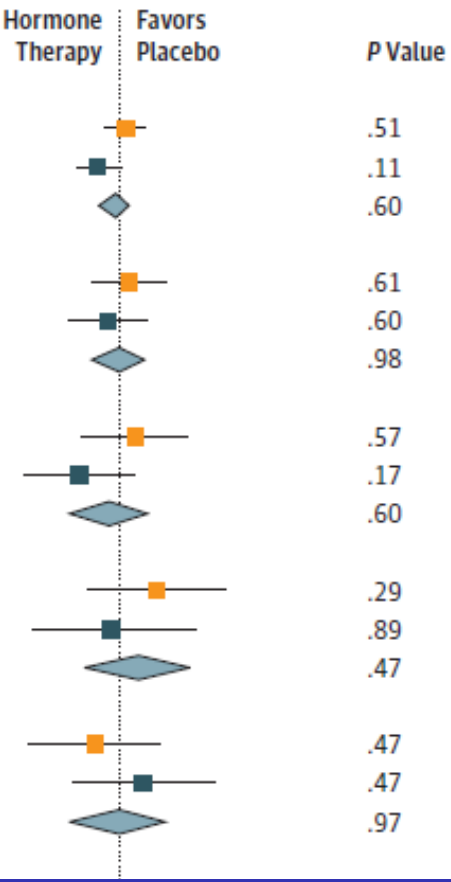
Results: During the cumulative 18-year follow-up, 7489 deaths occurred: 1088 deaths during the intervention phase and 6401 deaths during postintervention follow-up.

- Pooled cohort: All-cause mortality was 27.1% in the hormone therapy group vs 27.6% in the placebo group: HR was 0.99 (95% CI, 0.94-1.03)
- CEE plus MPA: HR was 1.02 (95% CI, 0.96-1.08)
- CEE alone: HR was 0.94 (95% CI, 0.88-1.01)

The HRT Story: 2017

Figure 2. Mortality Outcomes in the Women's Health Initiative Hormone Therapy Trials During the 18-Year Cumulative Follow-up

End Points	No. of Deaths, Annualized Rates (%): Hormone Therapy	Placebo	HR (95% CI)	*P* Value
All-cause mortality				
CEE plus MPA vs placebo	2244 (1.58)	2110 (1.57)	1.02 (0.96-1.08)	.51
CEE alone vs placebo	1505 (1.73)	1630 (1.83)	0.94 (0.88-1.01)	.11
Pooled trials			0.99 (0.94-1.03)	.60
CVD mortality[a]				
CEE plus MPA vs placebo	688 (0.49)	644 (0.48)	1.03 (0.92-1.15)	.61
CEE alone vs placebo	547 (0.63)	577 (0.65)	0.97 (0.86-1.09)	.60
Pooled trials			1.00 (0.92-1.08)	.98
CHD mortality				
CEE plus MPA vs placebo	310 (0.22)	285 (0.21)	1.05 (0.89-1.23)	.57
CEE alone vs placebo	240 (0.28)	277 (0.31)	0.89 (0.75-1.05)	.17
Pooled trials			0.97 (0.86-1.09)	.60
Stroke mortality				
CEE plus MPA vs placebo	188 (0.13)	161 (0.12)	1.12 (0.91-1.38)	.29
CEE alone vs placebo	126 (0.14)	132 (0.15)	0.98 (0.77-1.26)	.89
Pooled trials			1.06 (0.90-1.24)	.47
Other known CVD mortality				
CEE plus MPA vs placebo	188 (0.13)	195 (0.14)	0.93 (0.76-1.13)	.47
CEE alone vs placebo	174 (0.20)	164 (0.18)	1.08 (0.87-1.34)	.47
Pooled trials			1.00 (0.86-1.15)	.97
Cancer mortality				



The HRT Story: 2017

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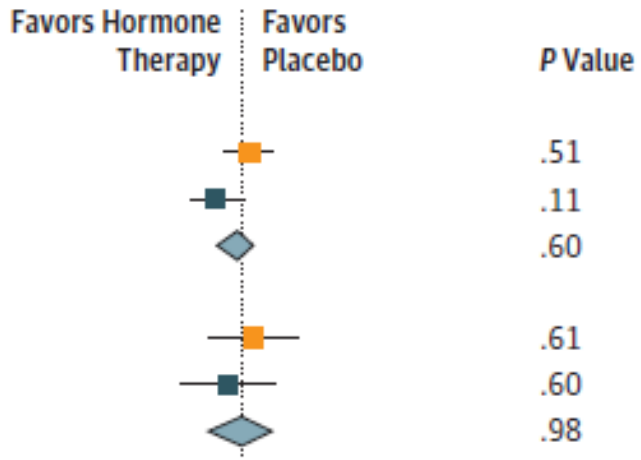
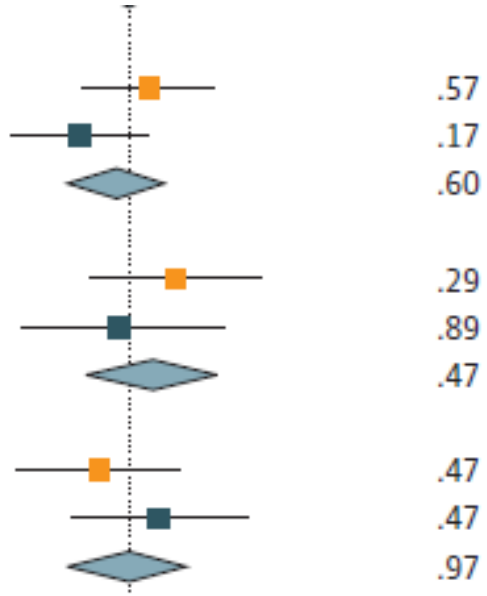
Pooled trials			0.99 (0.94-1.03)	.60
CVD mortality[a]				
CEE plus MPA vs placebo	688 (0.49)	644 (0.48)	1.03 (0.92-1.15)	.61
CEE alone vs placebo	547 (0.63)	577 (0.65)	0.97 (0.86-1.09)	.60
Pooled trials			1.00 (0.92-1.08)	.98



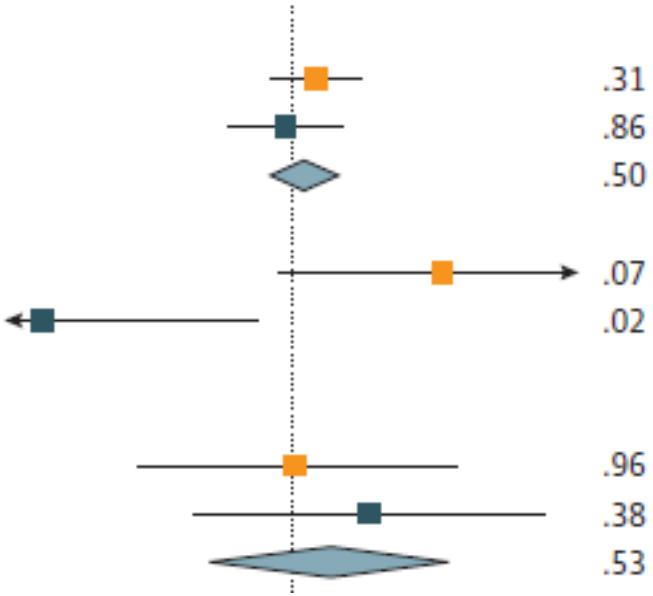
The HRT Story: 2017

CHD mortality			
CEE plus MPA vs placebo	310 (0.22)	285 (0.21)	1.05 (0.89-1.23)
CEE alone vs placebo	240 (0.28)	277 (0.31)	0.89 (0.75-1.05)
Pooled trials			0.97 (0.86-1.09)
Stroke mortality			
CEE plus MPA vs placebo	188 (0.13)	161 (0.12)	1.12 (0.91-1.38)
CEE alone vs placebo	126 (0.14)	132 (0.15)	0.98 (0.77-1.26)
Pooled trials			1.06 (0.90-1.24)
Other known CVD mortality			
CEE plus MPA vs placebo	188 (0.13)	195 (0.14)	0.93 (0.76-1.13)
CEE alone vs placebo	174 (0.20)	164 (0.18)	1.08 (0.87-1.34)
Pooled trials			1.00 (0.86-1.15)



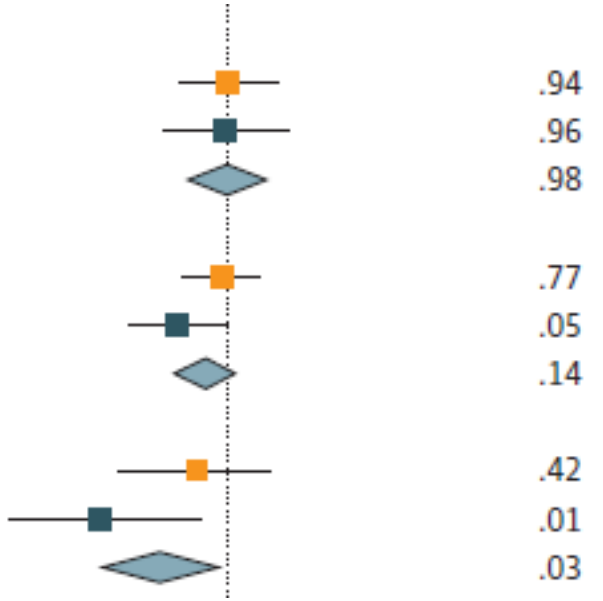
The HRT Story: 2017

Cancer mortality			
CEE plus MPA vs placebo	706 (0.50)	638 (0.47)	1.06 (0.95-1.18)
CEE alone vs placebo	424 (0.49)	439 (0.49)	0.99 (0.86-1.13)
Pooled trials			1.03 (0.95-1.12)
Breast cancer mortality			
CEE plus MPA vs placebo	61 (0.043)	40 (0.030)	1.44 (0.97-2.15)
CEE alone vs placebo	22 (0.025)	41 (0.046)	0.55 (0.33-0.92)
Pooled trials			NR[b]
Colorectal cancer mortality			
CEE plus MPA vs placebo	53 (0.037)	50 (0.037)	1.01 (0.69-1.49)
CEE alone vs placebo	47 (0.054)	40 (0.045)	1.21 (0.79-1.84)
Pooled trials			1.10 (0.82-1.46)



The HRT Story: 2017

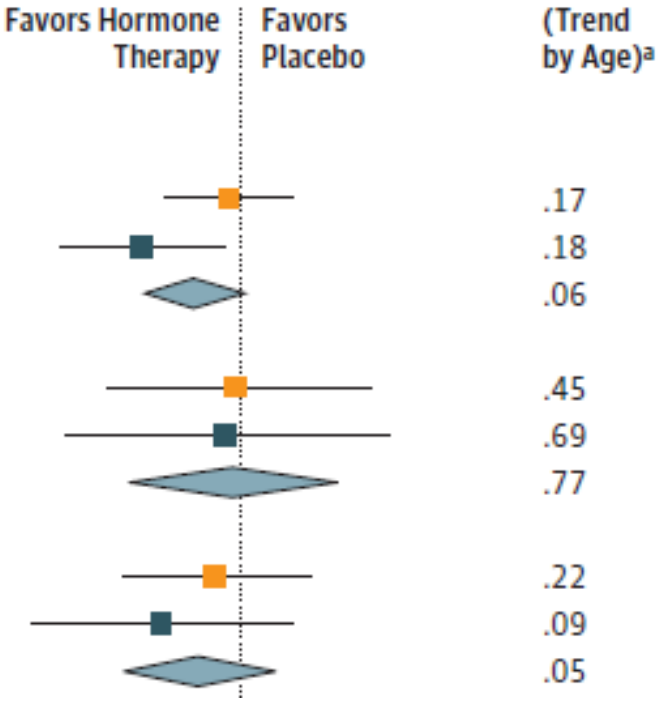
Other known cancer mortality			
CEE plus MPA vs placebo	548 (0.39)	521 (0.39)	1.00 (0.89-1.13)
CEE alone vs placebo	336 (0.39)	345 (0.39)	1.00 (0.86-1.16)
Pooled trials			1.00 (0.91-1.10)
Other mortality			
CEE plus MPA vs placebo	850 (0.60)	828 (0.61)	0.99 (0.90-1.08)
CEE alone vs placebo	534 (0.61)	614 (0.69)	0.89 (0.79-1.00)
Pooled trials			0.95 (0.88-1.02)
Alzheimer's or dementia mortality			
CEE plus MPA vs placebo	223 (0.16)	233 (0.17)	0.93 (0.77-1.11)
CEE alone	127 (0.15)	175 (0.20)	0.74 (0.59-0.94)
Pooled trials			0.85 (0.74-0.98)



The HRT Story: 2017

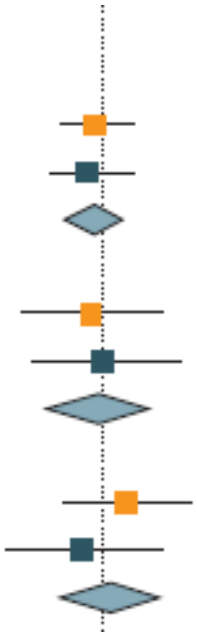
Treatment by age interaction

Outcome by Age	No. of Deaths, Annualized Rates (%)		HR (95% CI)	P Value (Trend by Age)[a]
	Hormone Therapy	Placebo		
Age 50-59 y				
All-cause mortality				
CEE plus MPA vs placebo	307 (0.60)	294 (0.62)	0.97 (0.83-1.14)	.17
CEE alone vs placebo	170 (0.58)	218 (0.73)	0.79 (0.64-0.96)	.18
Pooled trials	477 (0.60)	512 (0.66)	0.89 (0.79-1.01)	.06
CVD mortality[b]				
CEE plus MPA vs placebo	75 (0.15)	70 (0.15)	0.99 (0.72-1.38)	.45
CEE alone vs placebo	48 (0.16)	50 (0.17)	0.97 (0.65-1.44)	.69
Pooled trials	123 (0.15)	120 (0.16)	0.98 (0.76-1.27)	.77
Cancer mortality				
CEE plus MPA vs placebo	145 (0.29)	144 (0.30)	0.94 (0.75-1.19)	.22
CEE alone vs placebo	70 (0.24)	85 (0.29)	0.83 (0.60-1.14)	.09
Pooled trials	215 (0.27)	229 (0.30)	0.90 (0.75-1.09)	.05



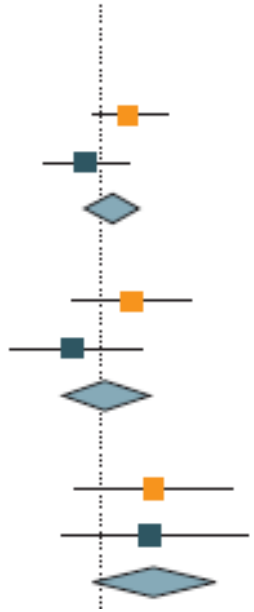
The HRT Story: 2017

Age 60-69 y			
All-cause mortality			
CEE plus MPA vs placebo	964 (1.50)	919 (1.51)	0.98 (0.90-1.08)
CEE alone vs placebo	650 (1.66)	694 (1.71)	0.97 (0.88-1.08)
Pooled trials	1614 (1.56)	1613 (1.59)	0.98 (0.91-1.05)
CVD mortality[b]			
CEE plus MPA vs placebo	256 (0.40)	246 (0.40)	0.97 (0.82-1.16)
CEE alone vs placebo	226 (0.58)	233 (0.58)	1.01 (0.84-1.21)
Pooled trials	482 (0.47)	479 (0.47)	0.99 (0.87-1.12)
Cancer mortality			
CEE plus MPA vs placebo	348 (0.54)	310 (0.51)	1.06 (0.91-1.24)
CEE alone vs placebo	199 (0.51)	216 (0.53)	0.96 (0.79-1.16)
Pooled trials	547 (0.53)	526 (0.52)	1.02 (0.90-1.15)



The HRT Story: 2017

Age 70-79 y			
All-cause mortality			
CEE plus MPA vs placebo	973 (3.64)	897 (3.42)	1.07 (0.98-1.18)
CEE alone vs placebo	685 (3.66)	718 (3.77)	0.97 (0.87-1.07)
Pooled trials	1658 (3.65)	1615 (3.57)	1.03 (0.96-1.10)
CVD mortality[b]			
CEE plus MPA vs placebo	357 (1.34)	328 (1.25)	1.08 (0.93-1.25)
CEE alone vs placebo	273 (1.46)	294 (1.54)	0.94 (0.80-1.11)
Pooled trials	630 (1.39)	622 (1.37)	1.01 (0.91-1.13)
Cancer mortality			
CEE plus MPA vs placebo	213 (0.80)	184 (0.70)	1.14 (0.94-1.39)
CEE alone vs placebo	155 (0.83)	138 (0.72)	1.14 (0.91-1.44)
Pooled trials	368 (0.81)	322 (0.71)	1.14 (0.98-1.33)



The HRT Story: 2017

"Although these findings lend support to use of hormone therapy for recently menopausal women with moderate-to-severe symptoms, the attenuation of age differences with longer follow-up would not support use of hormone therapy for reducing chronic disease or mortality."

The HRT Story: 2017

Looking back: The HRT Story 1985

The Framingham Study

- n=1234 postmenopausal women, aged 50 to 83 years
- eight years of follow-up

The Nurses' Health Study

- n=32,317 postmenopausal female nurses, aged 30 to 55 years
- 4 years of follow-up

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)

"... 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."

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

Contradicted study	Current state of knowledge
1. Nurses Health 2. PEPI	Etrogen/progestin do not protect but increase CAD risk in postmenopausal women.
3. Health Pros	Vitamin E supplement does not reduce CAD in men.
4. Nurses Health	Vitamin E supplement does not reduce CAD in women.

Contradicted research outcomes

Table 1: Contradicted research and current state of knowledge

Contradicted study	Current state of knowledge
5. CHAOS	Vitamin E supplement does not prevent coronary events
6. HA-1A Sepsis	HA-1A did not improve survival in gram-negative sepsis.
7. Rossaint et al (nitric oxide)	Nitric oxide does not improve survival in respiratory distress.

Contradicted research outcomes

Table 2: Contradicted research designs

Contradicted study	Contradicted 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 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)

Common threats to correct outcomes

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

- Low sample size
- Heterogeneous cohort (population variance)

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

- Confounded effects (cohort vs RCT)
  (e.g. the type of subjects who assigned themselves to estrogen turns out to be heart healthier than thse who did not.)
- Surrogate endpoint (Y) and surrogate markers (X)

Common threats to correct outcomes

Kim and Prasad (2015) survey:

"...examined all cancer drug marketing approvals by the FDA from 2008 through 2012."

- 54 approvals were made, with 36 drugs (67%) approved on the basis of a surrogate end point, such as tumor response rate or progression-free survival
- With several years of follow-up, 31 (86%) of these have unknown effects on overall survival or fail to show gains in survival

Modeling the probability that a research finding is true

Ioannidis (2005):
Let R=ratio of "true" to "false" relationships (this is field specific). Then $R = \#T/\#F$.

The prior probability of any relationship being true (i.e. before the study is conducted) is

$$P[T] = \frac{\#T}{\#T + \#F} = \frac{\#T/\#F}{(\#T + \#F)/\#F} = \frac{R}{R+1}$$

DIABETES RESEARCH AND CLINICAL PRACTICE 120 (2016) 65–72

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Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Correlation of body muscle/fat ratio with insulin sensitivity using hyperinsulinemic-euglycemic clamp in treatment-naïve type 2 diabetes mellitus

Noboru Kurinami [a,1], *Seigo Sugiyama* [a,b,1], *Akira Yoshida* [a], *Kunio Hieshima* [a], *Fumio Miyamoto* [a], *Keizo Kajiwara* [a], *Tomio Jinnouchi* [a], *Hideaki Jinnouchi* [a,*]

[a] *Diabetes Care Center, Jinnouchi Hospital, Kumamoto, Japan*
[b] *Division of Cardiovascular Medicine, Diabetes Care Center, Jinnouchi Hospital, Kumamoto, Japan*

Table 2 – Results of simple regression analysis for the M/I ratio.

	B	R^2
Weight (kg)	−0.633	0.3900
Height (cm)	−0.156	0.0244
BMI (kg/m^2)	−0.699	0.4890
Waist circumference (cm)	−0.744	0.5534
Muscle quantity (kg)	−0.297	0.0885
Body fat quantity (kg)	−0.754	0.5692
Body fat percentage (%)	−0.744	0.5535
Muscle quantity/Body fat quantity	0.806	0.6503
HbA1c (%)	−0.218	0.0474
Fasting plasma glucose (mmol/L)	−0.263	0.0690
Fasting blood insulin (pmol/L)	−0.476	0.2261
QUICKI	0.751	0.563
HOMA-IR	−0.511	0.2613
HDL-cholesterol (mmol/L)	0.332	0.1100
Triglycerides (mmol/L)	−0.402	0.1612
eGFR (mL/min/1.73 m^2)	0.155	0.0241

BMI, body mass index; GFR, estimated glomerular filtration rate; HDL, high-density lipopr
insulin resistance; QUICKI, Quantitative insulin sensitivity check index.

Modeling the probability that a research finding is true

Let $\alpha = P[\text{Type I error}]$ of each test in a study
Let $1 - \beta = 1 - P[\text{Type II error}] =$ power of each test in a study
Let c=number of relationships being tested in a study

Table : 2×2 table of expected counts

Research finding	Relationship: True	Relationship: False	Total
Yes			
No			
Total	$c\frac{R}{R+1}$	$c\frac{1}{R+1}$	c

Modeling the probability that a research finding is true

Let $\alpha = P[\text{Type I error}]$ of each test in a study
Let $1 - \beta = 1 - P[\text{Type II error}] =$ power of each test in a study
Let c=number of relationships being tested in a study

Table : 2×2 table of expected counts

Research finding	Relationship: True	Relationship: False	Total
Yes		$c\frac{1}{R+1}\alpha$	
No		$c\frac{1}{R+1}(1-\alpha)$	
Total	$c\frac{R}{R+1}$	$c\frac{1}{R+1}$	c

Modeling the probability that a research finding is true

Let $\alpha = P[\text{Type I error}]$ of each test in a study
Let $1 - \beta = 1 - P[\text{Type II error}] =$ power of each test in a study
Let c=number of relationships being tested in a study

Table : 2×2 table of expected counts

Research finding	Relationship: True	Relationship: False	Total
Yes	$c\frac{R}{R+1}(1-\beta)$	$c\frac{1}{R+1}\alpha$	
No	$c\frac{R}{R+1}\beta$	$c\frac{1}{R+1}(1-\alpha)$	
Total	$c\frac{R}{R+1}$	$c\frac{1}{R+1}$	c

Modeling the probability that a research finding is true

Let $\alpha = P[\text{Type I error}]$ of each test in a study
Let $1 - \beta = 1 - P[\text{Type II error}] =$ power of each test in a study
Let c=number of relationships being tested in a study

Table : 2×2 table of expected counts

Research finding	Relationship: True	Relationship: False	Total
Yes	$c\frac{R}{R+1}(1-\beta)$	$c\frac{1}{R+1}\alpha$	$\frac{c(R(1-\beta)+\alpha)}{R+1}$
No	$c\frac{R}{R+1}\beta$	$c\frac{1}{R+1}(1-\alpha)$	$\frac{c(R\beta+1-\alpha)}{R+1}$
Total	$c\frac{R}{R+1}$	$c\frac{1}{R+1}$	c

Modeling the probability that a research finding is true

After a research finding has been claimed based on statistical significance, the post-study probability that the relationship is true is

$$\text{PPV} = \frac{R(1-\beta)}{R(1-\beta)+\alpha}$$

where PPV stands for *positive predictive value*.
A research finding is more likely true than false if

$$R(1-\beta) > \alpha$$

Modeling the probability that a research finding is true

Multiple studies:

Suppose there are n independent studies targeting the same questions. The question-wise Type I and Type II error rates are

$$\beta^* = P[\text{0 significant findings}|\text{True}] = \beta \cdot \beta \cdots \beta = \beta^n$$
$$\alpha^* = P[\geq 1 \text{ sig}|\text{False}] = 1 - p[\text{0 sig}|\text{False}] = 1 - (1-\alpha)^n$$

Finding	True	False	Total
Yes	$c\frac{R}{R+1}(1-\beta^*)$	$c\frac{1}{R+1}\alpha^*$	$\frac{c(R(1-\beta^*)+\alpha^*)}{R+1}$
No	$c\frac{R}{R+1}\beta^*$	$c\frac{1}{R+1}(1-\alpha^*)$	$\frac{c(R\beta^*+1-\alpha^*)}{R+1}$
Total	$c\frac{R}{R+1}$	$c\frac{1}{R+1}$	c

Modeling the probability that a research finding is true

Bias:

Let u be the proportion of explored analyses that would not have been research findings but end up reported as such because of bias. (E.g. p-hacking, selective exclusion of subjects, selective reporting.)

Finding	True	False	Total
Yes	$c\frac{R}{R+1}(1-\beta^*)+c\frac{R}{R+1}\beta^* u$	$c\frac{1}{R+1}\alpha^*+c\frac{1-\alpha^*}{R+1}u$	
No	$c\frac{R}{R+1}\beta^*\ (1-u)$	$c\frac{1-\alpha^*}{R+1}\ (1-u)$	
Total	$c\frac{R}{R+1}$	$c\frac{1}{R+1}$	c

Modeling the probability that a research finding is true

$$\text{PPV} = \frac{(1-\beta^*)R + u\beta^* R}{R + \alpha^* - \beta^* R + u - u\alpha^* + u\beta^* R}$$

is a function of

- pre-study probability R
- α and β
- number of teams n
- bias u

Modeling the probability that a research finding is true

Corollary 1: The smaller the sample sizes conducted in a scientific field, the less likely the research findings are to be true.
Small sample size means smaller power. The PPV for a true research finding decreases as power decreases.

Corollary 2: The smaller the effect sizes in a scientific field, the less likely the research findings are to be true.
Small effect sizes mean smaller power.

Modeling the probability that a research finding is true

Corollary 3: The greater the number and the lesser the selection of tested relationships, the less likely the research findings are to be true.

Fields like genetics that use microarrays and other high-throughput discovery-oriented research, have lower R and correspondingly lower PPV.

Modeling the probability that a research finding is true

Corollary 4: The greater the flexibility in designs, definitions, outcomes, and analytical methods in a scientific field, the less likely the research findings are to be true.

Flexibility increases the potential for transforming what would be *negative* results into *positive* results, hence increasing u.

Modeling the probability that a research finding is true

Corollary 5: The greater the financial interests and prejudices in a scientific field, the less likely the research findings are to be true.

Conflicts of interest are very common in biomedical research, and increase the potential for bias u. Prejudice may not necessarily have financial roots. Findings that may or may not refute global warming, or evolution, or efficacy of vaccines, may be censored by self, or colleagues, or the peer-review process.

Modeling the probability that a research finding is true

Corollary 6: The hotter a scientific field (with more teams involved), the less likely the research findings are to be true. This may explain why we occasionally see major excitement, inevitably followed by disappointment, in fields like cancer studies or genetics.

Modeling the probability that a research finding is true

Suppose that
$\alpha = .05$, $\beta = .20$,
$u = .10$ rate of no-findings reported as findings
$n = 10$ teams conducting research,

R	1:100	1:10	1:5	1:2	1:1	2:1	5:1
PPV	.02	.16	.27	.48	.65	.79	.90

where R =ratio of true to false relationships

Modeling the probability that a research finding is true

Suppose that
$\alpha = .05$, $\beta = .20$,
$u = .10$ rate of no-findings reported as findings

	R	1:100	1:10	1:5	1:2	1:1	2:1	5:1
	$n = 10$	.02	.16	.27	.48	.65	.79	.90
PPV	$n = 20$	.01	.11	.20	.38	.55	.71	.86
	$n = 40$	.01	.09	.16	.32	.49	.65	.83