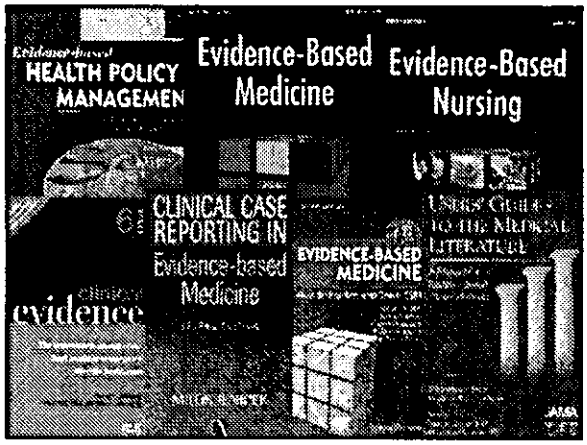
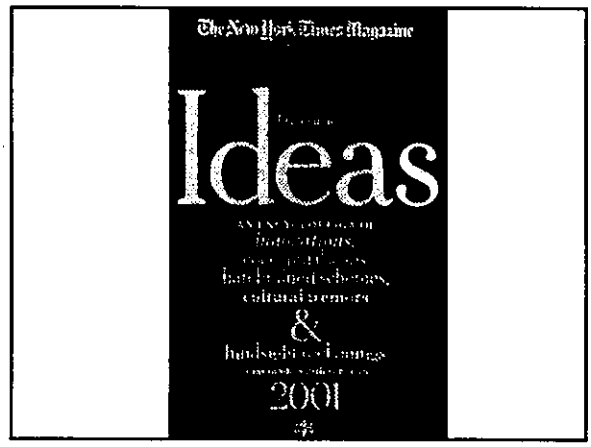




The Year in Ideas

New York Times Magazine 12/6/2001

Editors and writers included "80 ideas that shook the world (or at least jostled it a little) in 2001 . . ."

Covered: politics, medicine, sports, business, fashion, warfare, . . .

Under medicine:

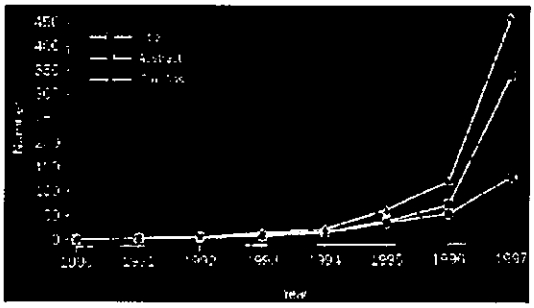
- Evidence-Based Medicine
- Pharmacogenomics
- Global antiretroviralism
- Telesurgery
- Turning a bad drug good

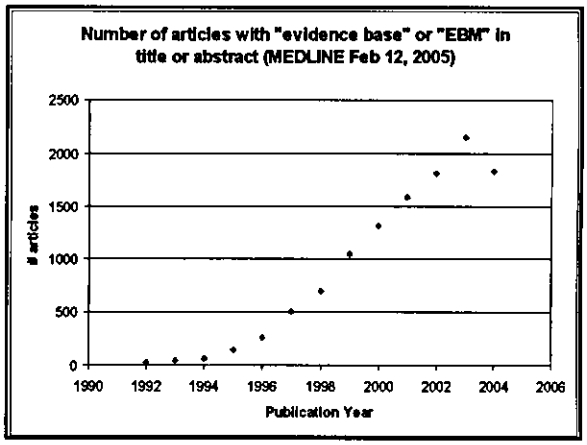
Search on the Internet

(Google January 23, 2005)

- "Evidence-based Medicine"
  - 1,190,000 items
- "Systematic review"
  - 925,000
- "Meta-analysis"
  - 1,680,000

Number of articles containing keywords evidence-based or evidence-based medicine in title (Ti), abstract (Abs), or either, by year. Lancet 1997;349:1330.





EBM articles and language
MEDLINE - February 12, 2005

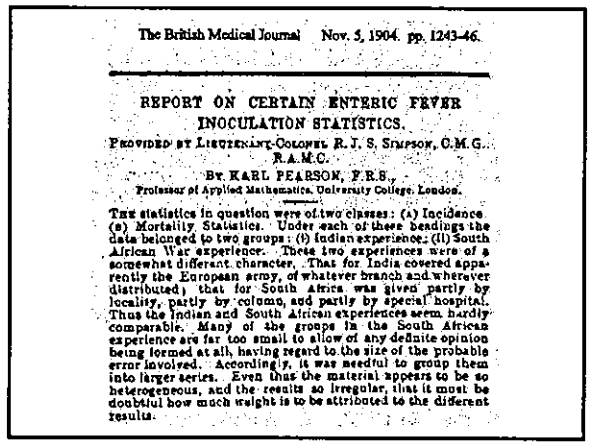
English	10,477	Hungarian	34
German	597	Chinese	28
French	206	Norwegian	24
Japanese	167	Portuguese	22
Spanish	124	Russian	12
Italian	83	Polish	11
Swedish	75	Finnish	2
Dutch	58	Turkish	1
Danish	52	Ukranian	1

Basic Tools of EBM

- Primary studies (randomized trials, cohorts, epidemiologic studies)
- Systematic review
- Meta-analysis

Applications of systematic reviews and meta-analyses in healthcare

- Interventions (most common)
- Epidemiologic (many)
- Diagnostic tests (increasing)
- Genomics (rapidly increasing)
- Health economics



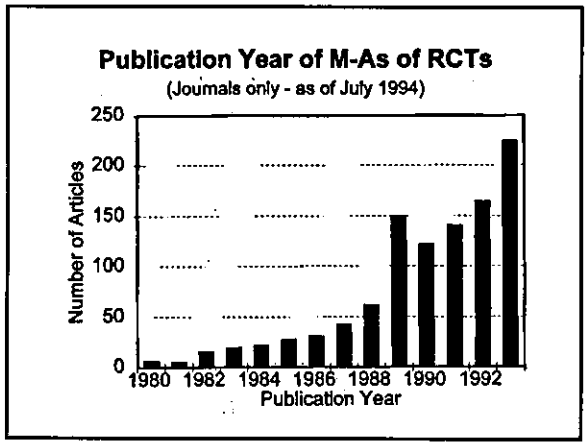
The British Medical Journal Nov. 5, 1904. pp. 1243-46.

REPORT ON CERTAIN ENTERIC FEVER INOCULATION STATISTICS.

Provided by Lieutenant-Colonel R. J. S. Simpson, C.M.G., R.A.M.C.

By KARL PEARSON, F.R.S.,
Professor of Applied Mathematics, University College, London.

The statistics in question were of two classes: (a) Incidence (b) Mortality Statistics. Under each of these headings the data belonged to two groups: (i) Indian experience; (ii) South African War experience. These two experiences were of a somewhat different character. That for India covered apparently the European army, of whatever branch and wherever distributed; that for South Africa was given partly by locality, partly by column, and partly by special hospital. Thus the Indian and South African experiences seem hardly comparable. Many of the groups in the South African experience are far too small to allow of any definite opinion being formed at all, having regard to the size of the probable error involved. Accordingly, it was needful to group them into larger series. Even thus the material appears to be so heterogeneous, and the results so irregular, that it must be doubtful how much weight is to be attributed to the different results.



Types of EBM Products

- Systematic reviews/meta-analysis
- Decision analysis/cost-effectiveness analysis
- Evidence reports
- Clinical practice guidelines
- Technology assessments
- Databases (trial registries, Cochrane Library)
- Websites
- Training: courses/workshops (schools, society meetings) critical appraisal of literature
- Methodological research

EBM uses

- Patient care (medicine, dentistry, nursing)
- Healthcare financing
- Public health
  - Nutrition policies
  - Regulatory
  - Surveillance
- Medical research
  - Funding decisions
- Evidence and society
  - Law
  - Ethics
- Veterinary Medicine

Groups involved in EBM activities

- Government agencies
- Academic institutions
- Professional organizations
- Medical journals
- Managed care companies/health care insurers
- Pharmaceutical companies
- Interest groups (consumer organizations)
- Individuals
- Courts

Types of EBM activities
(students and clinicians)

- Attend courses/workshops (schools, society meetings)/participate in journal clubs
- Visit websites for information
- Learn critical appraisal of literature and interpretation of results
- Use information from evidence syntheses for clinical decision making

Types of EBM activities
(policy decision makers)

- Use evidence reports / systematic reviews / meta-analyses / technology assessments / decision analysis / cost-effectiveness analysis to formulate policies
  - Drug approval (FDA)
  - Managed care
- Use information to decide future research
  - NIH, MRC
- Produce clinical practice guidelines
  - Professional organizations

Types of EBM activities
(researchers and teachers)

- Conducts evidence reports / systematic reviews / meta-analyses
- Produce clinical practice guidelines
- Conducts technology assessments
- Perform decision analysis / cost-effectiveness analysis
- Create EBM websites
- Conduct courses/workshops (schools, society meetings)
- Perform methodological research

US Government Agencies
(examples)

- Agency for Healthcare Research and Quality (AHRQ)
  - Evidence-based Practice Centers (EPC)
  - National Guidelines Clearinghouse
- Centers for Medicare and Medicaid Services (CMS)
  - Technology assessments
  - Drug class evaluations
  - Medicare coverage decisions
- Social Security Administration (SSA) – disability in children, kidney failure
- FDA – conducts meta-analyses and accepts meta-analyses for NDA
  - Food related health claims
    - Chromium may prevent development of diabetes

US Government Agencies
(examples)

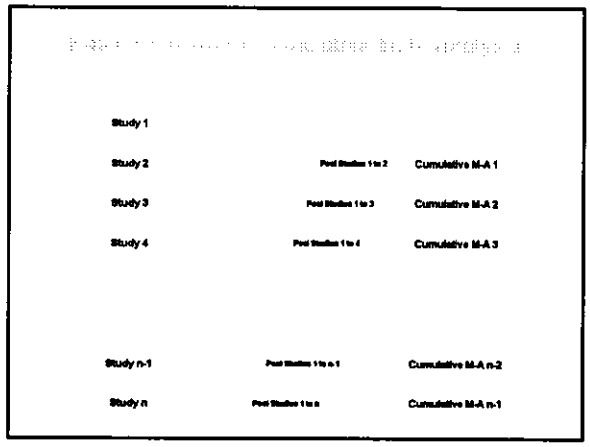
- National Institute of Health (NIH)
  - Consensus Development Conference
  - NICHD: Cochrane perinatal medicine
- Veteran Affairs - Cochrane prostate group
- Center for Disease Control (CDC)
  - Human Genome Epidemiology (HuGE net)
  - Diabetes prevention and translation branch
  - Reproductive health

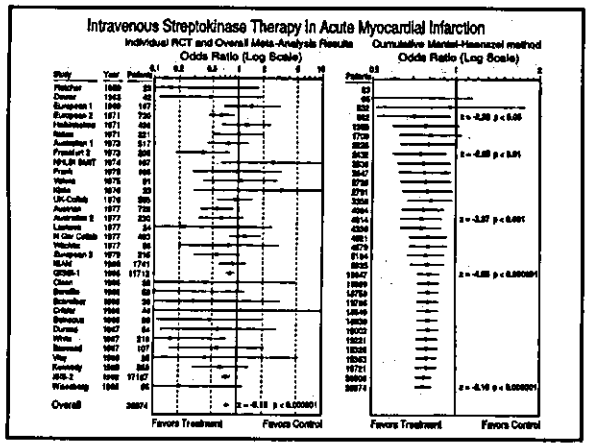
Examples of meta-analysis

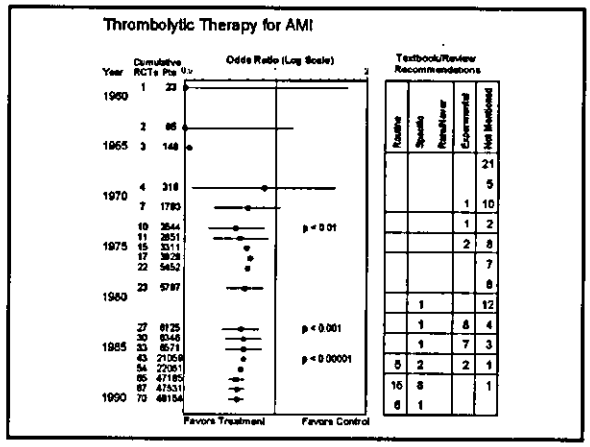
Cumulative meta-analysis

Lau J, Antman EM, Jiminez-Silva J, Kupelnick B, Mosteller F, Chalmers TC. Cumulative meta-analysis of therapeutic trials for myocardial infarction. N Engl J Med. 1992; 327:248-54.

Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomzied control trials and recommendations of clinical experts: Treatment for myocardial infarction. JAMA. 1992; 268:240-48.



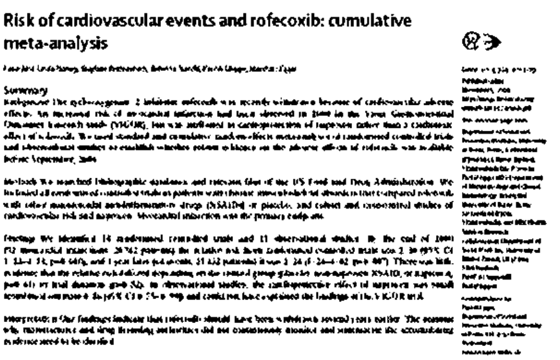




Benefits of systematic reviews and meta-analyses

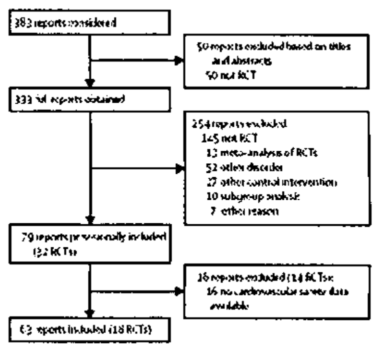
- Continuously updated meta-analysis can efficiently identify efficacious treatments
- As well as treatments that should not be used
- Identify areas of research gaps

Cumulative M-A of the adverse effects of Vioxx

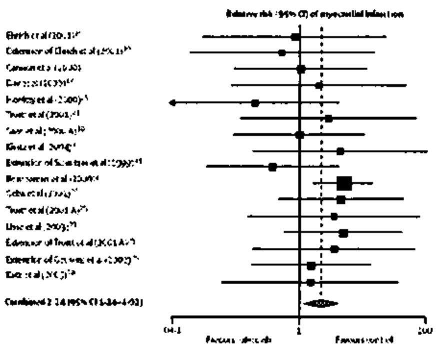

Risk of cardiovascular events and rofecoxib: cumulative meta-analysis

Summary

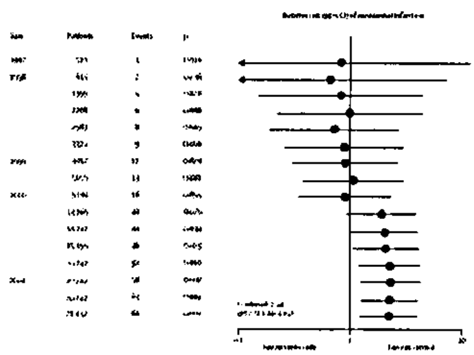
Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. Juni et al. Lancet 2004;364:2021-29.



Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. Juni et al. Lancet 2004;364:2021-29.



Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. Juni et al. Lancet 2004;364:2021-29.



Meta-Analysis: High-Dosage Vitamin E Supplementation May Increase All-Cause Mortality

Edgar R. Miller III, MD, PhD; Roberto Pastor-Barriuso, PhD; Dariush Dalal, MD, MPH; Rudolph A. Riemersma, PhD, FRCPE; Lawrence J. Appel, MD, MPH; and Eliseo Guallar, MD, DrPH

Background: Experimental models and observational studies suggest that vitamin E supplementation may prevent cardiovascular disease and cancer. However, several trials of high-dosage vitamin E supplementation showed non-statistically significant increases in total mortality.

Purpose: To perform a meta-analysis of the dose–response relationship between vitamin E supplementation and total mortality by using data from randomized, controlled trials.

Patients: 135 967 participants in 19 clinical trials. Of these trials, 9 tested vitamin E alone and 10 tested vitamin E combined with other vitamins or minerals. The dosages of vitamin E ranged from 16.5 to 2000 IU/d (median, 400 IU/d).

Data Sources: PubMed search from 1966 through August 2004, complemented by a search of the Cochrane Central Trials Database and review of citations of published reviews and meta-analyses. No language restrictions were applied.

Data Extraction: 2 investigators independently abstracted study reports. The investigators of the original publications were contacted if required information was not available.

Data Synthesis: In all 11 trials testing high-dosage vitamin E (≥400 IU/d) showed increased risk (risk difference > 0% for all-cause mortality in comparisons of vitamin E versus control. The pooled all-cause mortality risk difference in high-dosage vitamin E trials was 39 per 10 000 persons (95% CI, 3 to 74 per 10 000 persons; $P = 0.035$). For low-dosage vitamin E trials, the risk difference was −16 per 10 000 persons (CI, −41 to 10 per 10 000 persons; $P > 0.2$). A dose–response analysis showed a statistically significant relationship between vitamin E dosage and all-cause mortality, with increased risk of dosages greater than 150 IU/d.

Limitations: High-dosage (≥400 IU/d) trials were often small and were performed in patients with chronic disease. The generalizability of the findings to healthy adults is uncertain. Precise estimation of the threshold at which risk increases is difficult.

Conclusion: High-dosage (≥400 IU/d) vitamin E supplements may increase all-cause mortality and should be avoided.

Ann Intern Med. 2005;142:000-000. www.annals.org
For article affiliation, see end of text.
For the editorial comment, see pp 000-000.

Meta-Analysis: High-dosage vitamin E supplementation may increase all-cause mortality. Miller ER, et al. Ann Intern Med 2005.

- Experimental models and observational studies suggest that vitamin E supplementation may prevent cardiovascular disease and cancer. However, several trials of high-dosage vitamin E supplementation showed non–statistically significant increases in total mortality.
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Meta-Analysis: High-dosage vitamin E supplementation may increase all-cause mortality. Miller ER, et al. Ann Intern Med 2005.

- A dose–response analysis showed a statistically significant relationship between vitamin E dosage and all-cause mortality, with increased risk of dosages greater than 150 IU/d.
- High-dosage (>400 IU/d) vitamin E supplements may increase all-cause mortality and should be avoided.

Figure 2. Risk difference in all-cause mortality for randomized, controlled trials of vitamin E supplementation and pooled results for low-dosage (<400 IU/d) and high-dosage (>400 IU/d) vitamin E trials.

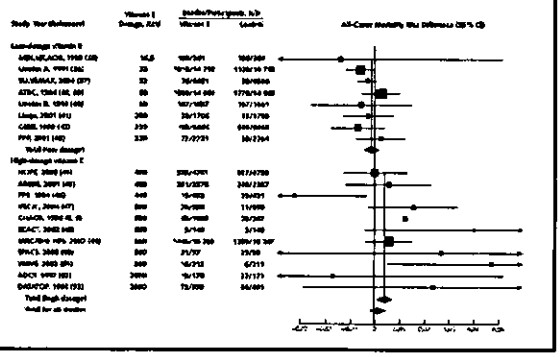
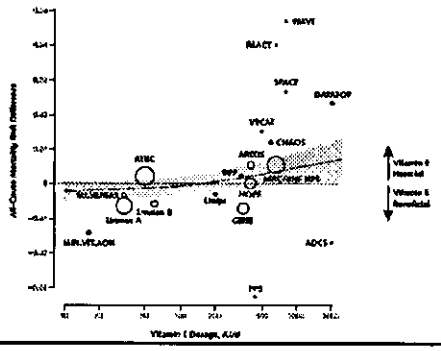


Figure 3. Dose–response relationship between vitamin E supplementation and all-cause mortality in randomized, controlled trials.



Vitamin E meta-analysis

- Question that individual studies that were not originally designed to address
- The high end of 1000 mg/day UL was assumed to be safe

Example of using systematic reviews to purchase healthcare

- Since 1995, Australia has mandated that pharmaceutical companies that want their products listed in the national formulary must include a systematic review of the available evidence with their submission
- The national Pharmaceutical Benefits Advisory Committee evaluates the evidence and makes recommendations to the federal government

Does the practice of EBM using systematic reviews and meta-analyses have an impact on health outcome?

How do you measure impact?

Different domains
- Clinical practice
- Medical research
- Medical education
- Healthcare financing
- Public health policy
- Public (consumers/patients) support

Some possible ways to assess impact?

- Interest in the topic
  - Increasing number of people interested
  - Increasing number of publications
  - Citation analysis of the literature
  - Adoption of the paradigm
- Use of systematic reviews by authoritative bodies / decision makers
  - Clinical practice guidelines
  - Healthcare / public health recommendations
- Demonstrated benefits

Limited Data at Present

Mostly anecdotal case reports

Historical controls

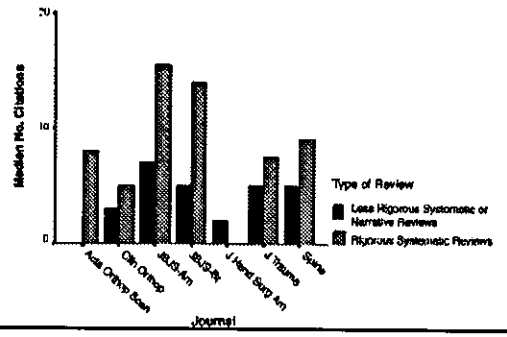
Stages and Prevalence of Chronic Kidney Disease (US pop Age ≥ 20)

Stage	Description	GFR (mL/min/1.73 m²)	Prevalence N (1000s)	Prevalence %
1	Kidney damage with normal or ↑ GFR	≥ 90	5,900	3.3
2	Kidney damage with mild ↓ GFR	60 – 89	5,300	3.0
3	Moderate ↓ GFR	30 – 59	7,600	4.3
4	Severe ↓ GFR	15 – 29	400	0.2
5	Kidney failure	< 15 (or dialysis)	300	0.1

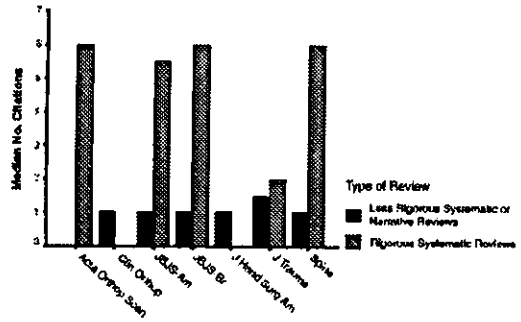
Citations of systematic reviews

- Bhandari M, et al. (McMaster Univ.) Doubling the impact: Publication of systematic review articles in orthopaedic journals. J Bone Joint Surg 2004;86-A:1012-16.
- Selected 15 high Science Citation Index impact factors orthopedic journals
- 2331 original or review articles published in 2000
- 110 qualified as review articles
- 17 of 110 met criteria for rigorous systematic reviews
- Systematic review articles received more citations compared with narrative reviews (mean 13.8 vs 6.0, p=0.008)

Median number of subsequent citations in orthopedic journals according to type of review



Median number of subsequent citations in non-orthopedic journals according to type of review



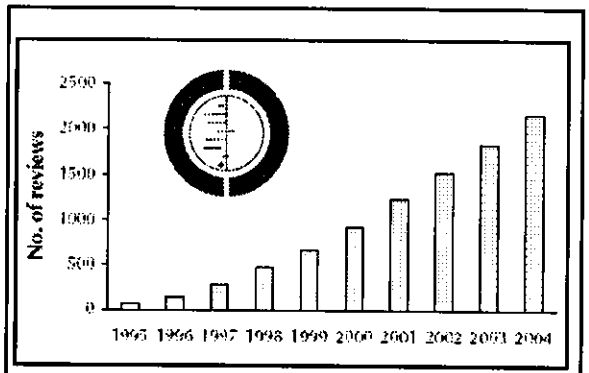


Fig. 1: Number of reviews in the Cochrane Database of Systematic Reviews.

Grimshaw J. So what has the Cochrane Collaboration ever done for us? A report card on the first 10 years. CMAJ 2004;171:747-749.

- Over 2074 completed systematic reviews (2004, issue 3)
- Covering top 10 causes of disability in both developed and developing countries
- Reviews authored by about 7000 volunteers worldwide

Dissemination and uses of Cochrane Library

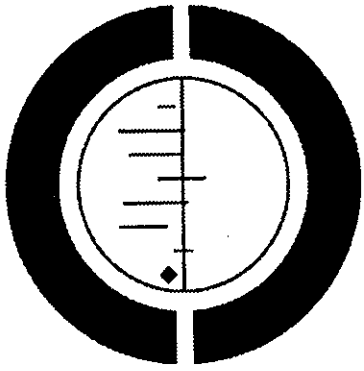
- National licenses: free to users in Australia, Denmark, England, Finland, Ireland, Norway, Northern Ireland, South Africa, Spain, Wales
- Free (via Health InterNetwork Access to Research Initiative) to low- or middle- income countries classified by World Bank.
- Through Ovid Technologies; > 5000 institutional customers worldwide (with > 2.5 million individual users)

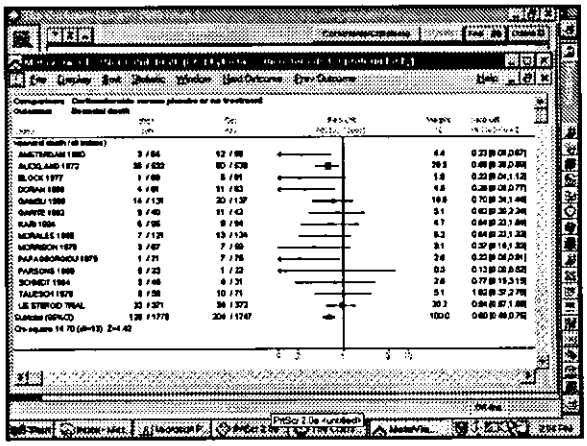
Examples of how Cochrane reviews are used? (*Cochrane Inside*)

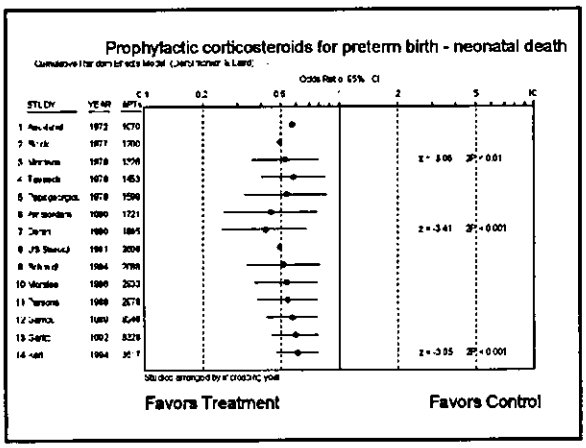
- Reproductive Health Library – WHO-sponsored (English and Spanish) electronic publication distributed free to over 34,000 healthcare professionals and organizations in low- and middle-income countries
- Clinical Evidence – BMJ publication, summaries (many using Cochrane reviews) to provide reliable and relevant information to clinical practice. Free to 50,000 healthcare professionals in UK National Health Service, 500,000 in US (funded by United Health Foundation), and via Internet to over 100 low- and middle- income countries.

Impact of systematic reviews and meta-analyses on clinical practice

The Cochrane Collaboration







Efficacy and toxicity of single daily dose vs. multi-dose aminoglycoside: a meta-analysis.

Barza M, Ioannidis JPA, Cappelleri JC, Lau J.
BMJ 1996;312:338-45.

Efficacy and toxicity of single daily dose vs. multi-dose aminoglycoside: a meta-analysis. Barza M, Ioannidis JPA, Cappelleri JC, Lau J. BMJ 1996;312:338-45.

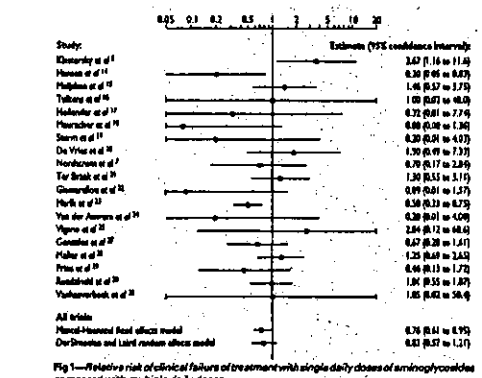


Fig 1—*Relative risk of clinical failure of treatment with single daily doses of aminoglycosides compared with multiple daily doses*

Efficacy and toxicity of single daily dose vs. multi-dose aminoglycoside: a meta-analysis. Barza M, Ioannidis JPA, Cappelleri JC, Lau J. BMJ 1996;312:338-45.

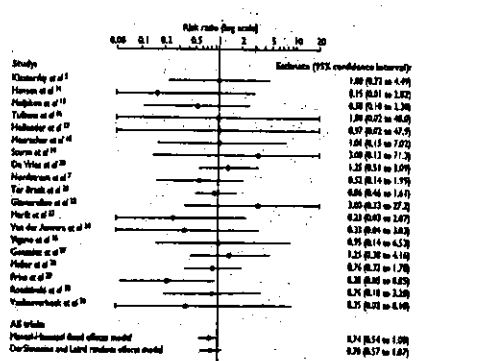


Fig 2—*Relative risk of nephrotoxicity with single daily doses of aminoglycosides compared*

Published meta-analyses of single daily doses of aminoglycosides

First author	Pub. date	Journal	# Trials	Patients (#, type)
Gaffoe	Jan 1995	Eur J Clin Pharm	16	1200 all
Blaser	Dec 1995	Eur J Clin Microbiol Infect Dis	24	3181 all
Barza	Feb 1996	BMJ	21	3091 all
Hatala	April 1996	Ann Intern Med	14	1625 immuno-competent
Munckhof	April 1996	J Antimicrob Chemo	19	2881 all
Ferriols-Lisart	May 1996	Am J Health-Syst Pharm	18	2317 all
Freeman	June 1996	Pharmacotherapy	15	2933 all
Hatala	May 1997	Clin Infect Dis	4	811 immuno-compromised
Bailey	May 1997	Clin Infect Dis	22	2649 all
Zaki Ali	May 1997	Clin Infect Dis	26	? all

Editorial Response:

Meta-analyses are no longer required for determining the efficacy of single daily dosing of aminoglycosides.

David N. Gilbert
Clinical Infectious Diseases
May, 1997

Daily dosage of aminoglycosides.

Urban AW, Craig WA. Curr Clin Top Infect Dis 1997;17:238-55.

CONCLUSIONS

An enormous body of data now exists, including pharmacodynamic studies, animal infection models, human comparative trials, and literature meta-analyses, to support the practice of once-daily dosage of aminoglycosides. . .

Regulatory Agency

FDA and Ephedra

Ephedra (ma huang)

- A dietary supplement – in the US, under Dietary Supplements Health Education Act (DSHEA) 1994, it is considered as a food, therefore presumed to be safe, until proven otherwise
- People have used it for weight loss, athletic performance enhancement
- Deaths and other adverse events have been attributed to it
- Attempts by FDA to regulate it in the past have failed

RAND EPC ephedra report

- The RAND Evidence-based Practice Center (EPC) was commissioned by the NIH to review recent evidence on the risks and benefits of ephedra and ephedrine
- The study found limited evidence of an effect of ephedra on short-term weight loss, and minimal evidence of an effect on performance enhancement in certain physical activities

RAND EPC ephedra report

- It found that ephedra is associated with higher risks of mild to moderate side effects such as heart palpitations, psychiatric and upper gastrointestinal effects, and . . . .
- The study reviewed over 16,000 adverse events reported after ephedra use and found about 20 "sentinel events" including heart attack, stroke, and death that occurred in the absence of other contributing factors.
- The RAND study adds significantly to the evidence suggesting that ephedra as currently marketed may be associated with unreasonable safety risks.

RAND EPC Ephedra report

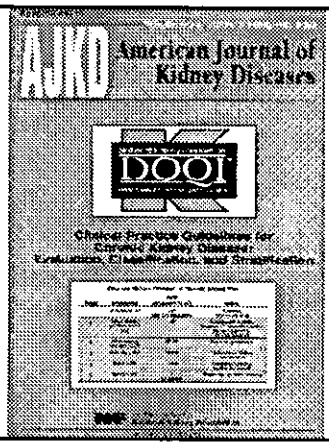
Table 2. Adverse Events Associated with Ephedra and Ephedrine

Event	Number of Events	Number of Sentinel Events	Number of Possible Sentinel Events
Death	84	6	12
Myocardial infarction (heart attack)	28	5	7
Other cardiac	30	0	3
Cerebrovascular event (stroke)	58	11	12
Seizure	40	4	7
Other neurological	8	0	1
Psychiatric event	91	6	8

FDA and Ephedra

- FDA issued regulations in 2003 to cease marketing of products containing ephedra

Evidence-based Clinical Practice Guidelines on Kidney Diseases and Impact on Public Health



Conclusions

- EBM, along with it key methods systematic review and meta-analysis, is here to stay
- The practice and of healthcare and medical education are changing because of it and will continue to do so
- Hopefully, the term EBM will disappear, because it will be the norm of healthcare

Future Challenges

- Need to find ways to demonstrate the impact of evidence-based practice
- Real-time production of reviews
- From passive recipient of data to active advocates; need to take more of an active role in directing the production of evidence
- Dissemination of ideas and methods to other scientific disciplines

Meta-analysis in molecular medicine

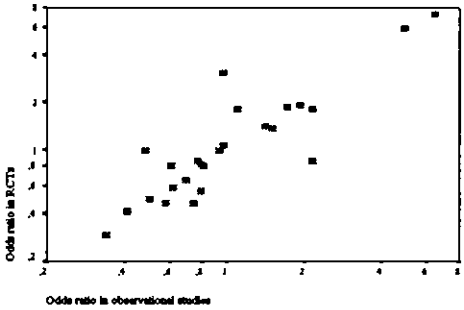
John P.A. Ioannidis, MD

Professor and Chairman, Department of Hygiene and Epidemiology
University of Ioannina School of Medicine, Ioannina, Greece
Professor of Medicine (adjunct), Tufts-New England Medical Center, Boston, USA

The revolution of molecular research

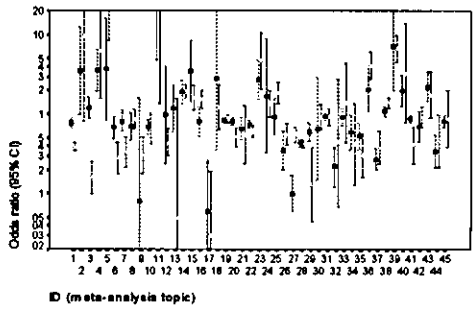
- Apocalyptic promises of bio-information
- Reductionism
- Discovery-oriented approaches
- Massive data
- Globalization of research
- Analysis still largely based on traditional epidemiological principles of non-randomized studies

How reliable is epidemiology at large? RCTs vs. observational studies



Ioannidis, Haidich and Lau, BMJ 2001 based on Concato et al. and Benson et al. NEJM 2000

Randomized trials vs. epidemiology



Ioannidis et al. JAMA 2001

Major postulated problems of molecular research

- Small sample sizes
- Small effect sizes
- Large number of biological factors
- Old-epidemiology problems: confounding, misclassification
- Questionable replication validity

Background issues

- Assay development
- Standardization
- Independence
- Diagnostic and predictive performance
- Validation
- Clinical use
- Integration in clinical care
- Cost-effectiveness

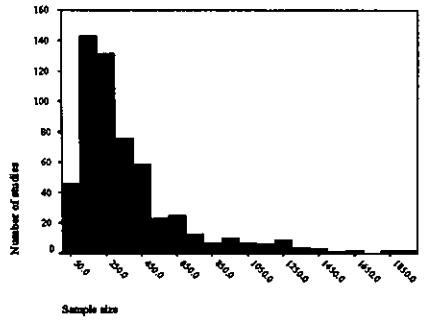
The good news and the bad news

- The good news is that we have many promising discoveries
- It is great to know more and more
- The bad news is that we have too many promising discoveries
- It is a pity to think that we know more

Fields to discuss

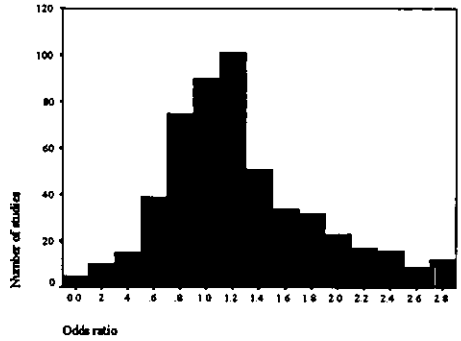
- Disease susceptibility - Genetics
- Disease susceptibility - Genomics
- Prognosis – Single factors
- Prognosis – Microarrays and discovery research
- All of the above – response to treatment

Most studies assessing genetic risk factors are small in terms of sample size



Ioannidis, Trends Mol Med 2003

Most genetic effects in multigenetic diseases are small



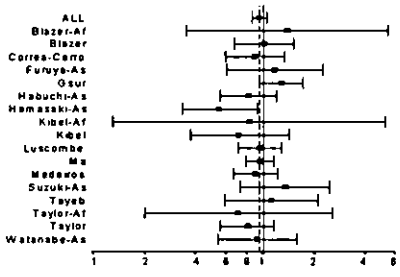
Complicating factors

- Too many genes to consider
- Dominant/recessive/co-dominant effects
- Gene-gene interactions
- Gene-environment interactions
- Time-dependent effects
- Measurement errors for genotyping and for clinical and laboratory phenotype
- Unconscious bias
- Conscious bias

Why meta-analysis?

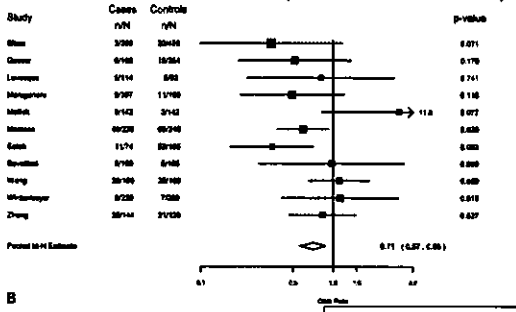
- To improve power
- To assess for heterogeneity
- To explain heterogeneity
- To detect and/or exclude bias
- To allow meaningful evaluation of multivariate molecular models
- To allow meaningful evaluation of interactions

No effect overall: t vs. T TaqI VDR and prostate cancer

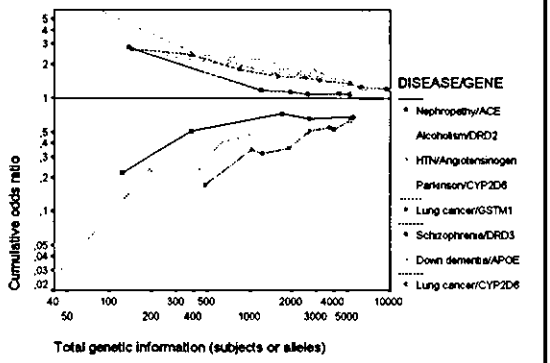


Ntais, Polyzos and Ioannidis, Cancer Epidemiol Biomarkers Prev 2003

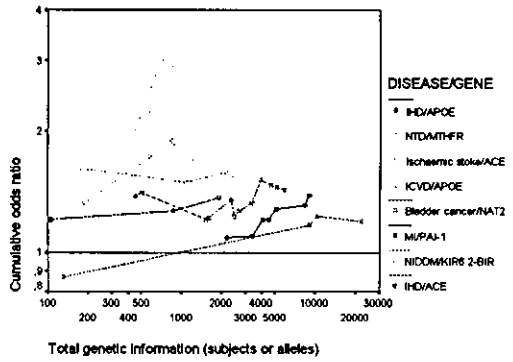
Effect: UCHL1 S18Y and Parkinson's disease (Y/Y vs. others)



Maraganore et al, Ann Neurol 2004



Ioannidis et al, Nature Genetics 2001



Counting fish in the sea of association analyses

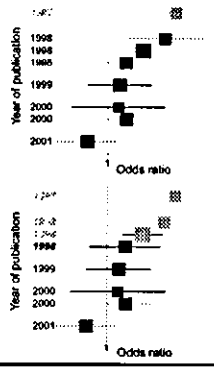
Multiplier	Parameter
>10000000	Gene variants
>1000	Diseases
>10	Outcomes
>10	Subgroups
>10	Genetic contrasts
>10	Investigators
1 quadrillion	**Candidate analyses**

The legend of focusing "based on biological plausibility"

- Just in the year 2002 studies were published addressing the relationship of the APOE epsilon polymorphism with familial Alzheimer's disease; sporadic Alzheimer's disease; colorectal cancer; fatty liver; atherosclerosis; hyperlipidemia; acute ischemic stroke; spina bifida; coronary artery disease; normal tension glaucoma; hypertension; Parkinson's disease, diabetic nephropathy; pre-eclampsia; hepatitis C-related liver disease; cerebrovascular disease; coronary artery disease post-renal transplantation; non-specified cognitive impairment; childhood nephrotic syndrome; spontaneous abortion; multiple sclerosis; alcohol withdrawal; cognitive dysfunction after coronary artery surgery; alcoholic chronic pancreatitis; alcoholic cirrhosis; macular toxicity from chloroquine; macular edema; aortic valve stenosis; vascular dementia; type II diabetes mellitus; and migraine.

Would you place your money on...

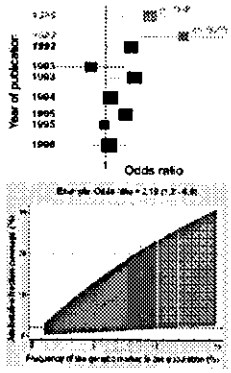
- Presence of a statistically significant ("positive") first study
  - 35 vs 20 meta-analyses
- At least half among several (≥3) early-published studies "positive"
  - 15 vs 33 meta-analyses



Trikalinos et al, Eur J Human Genet 2004

Or, would you rather bet on these?...

- Presence of at least 2 "highly significant" early-published studies
  - 9 vs 39 meta-analyses
- Presence of a 1st study claiming an attributable fraction of at least 2%
  - 19 vs 36 meta-analyses

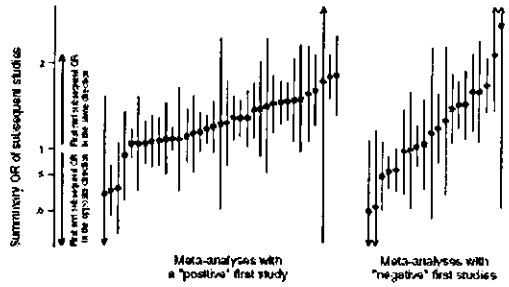


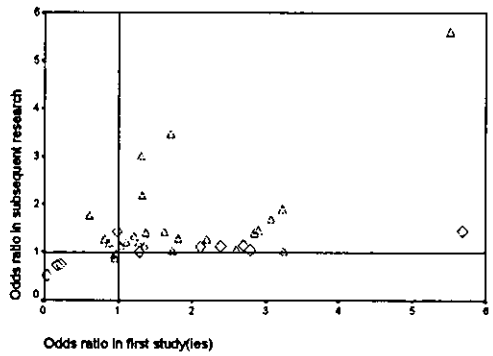
Diagnostic performances

Assessment	Sensitivity (95% CI)	Specificity (95% CI)	LR+	LR-
Very or early-published studies excluded from the meta-analysis				
First study with $P<0.05$ (35/55)	0.63 (0.49, 0.84)	0.38 (0.21, 0.56)	1.1	0.92
At least half of early-published studies with $P<0.05$ (15/48)	0.40 (0.16, 0.68)	0.73 (0.54, 0.87)	1.5	0.82
Very low P-values in early-published studies* (9/48)	0.20 (0.04, 0.48)	0.82 (0.65, 0.93)	1.1	0.98
Attributable fraction in first study ≥ 2% based on 95% CI coverage (19/55)	0.39 (0.26, 0.61)	0.69 (0.56, 0.84)	1.3	0.88
All studies included in the meta-analysis				
First study with $P<0.05$ (35/55)	0.67 (0.46, 0.83)	0.39 (0.22, 0.59)	1.1	0.85
At least half of early-published studies with $P<0.05$ (15/48)	0.52 (0.31, 0.72)	0.91 (0.77, 0.99)	5.8	0.53
Very low P-values in early-published studies* (9/48)	0.47 (0.23, 0.72)	0.96 (0.78, 1.00)	11	0.55
Attributable fraction in first study ≥ 2% based on 95% CI coverage (19/55)	0.64 (0.25, 0.65)	0.75 (0.55, 0.89)	1.8	0.75

*Refers to the presence of ≥ 7 studies with P-values < 0.01, or the presence of ≥ 7 statistically significant studies, one of which has P < 0.001 among the early-published studies
CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio
CIs were derived using exact methods.

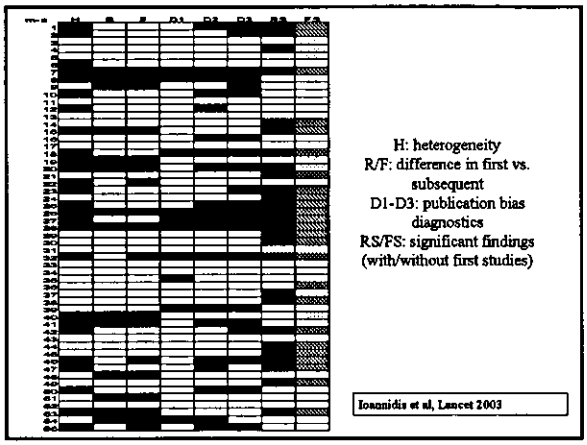
Subsequent magnitude of the genetic effect





Predictors of statistically significant discrepancies between the first and subsequent studies on the same genetic association.

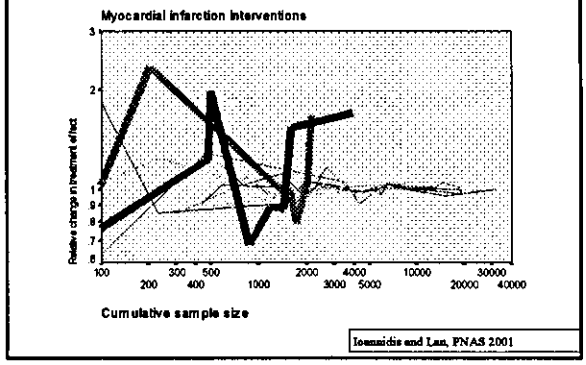
Predictor of discrepancy	Univariate regressions	
	OR (95% CI)	*P*-value
Total number of studies (per study)	1.17 (1.03-1.33)	.020
Sample size of first study(ies) (doubling)	0.42 (0.17-0.98)	.046
Single first study with clear genetic contrast	9.33 (1.01-86.3)	.044



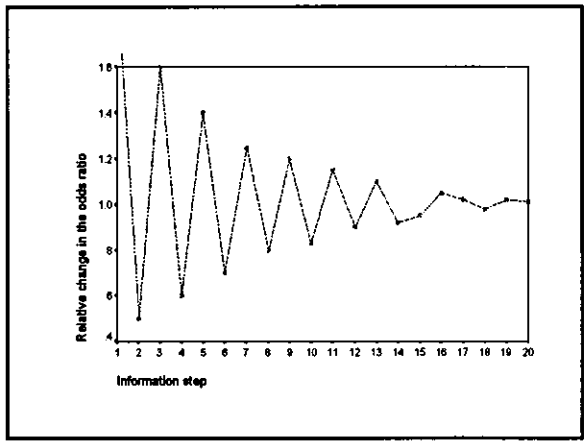
H: heterogeneity
R/F: difference in first vs. subsequent
D1-D3: publication bias diagnostics
RS/FS: significant findings (with/without first studies)

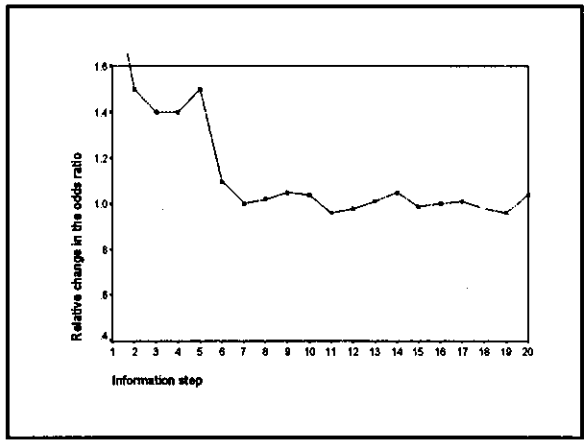
Ioannidis et al, Lancet 2003

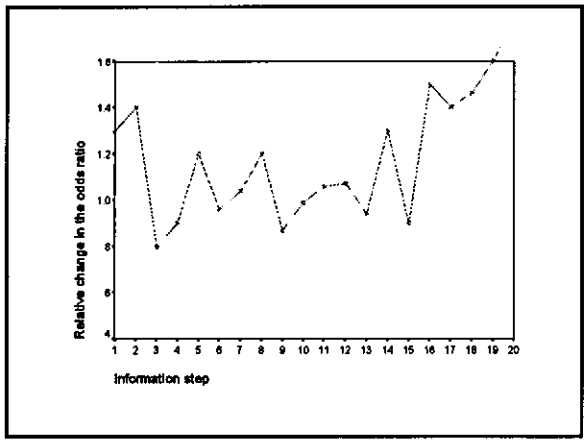
Discrepancies over time occur even in randomized trials

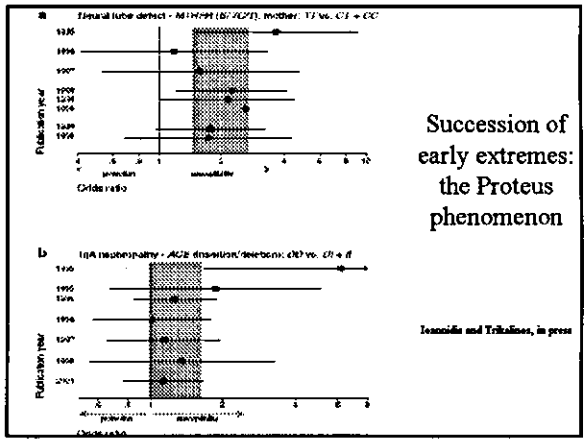


Ioannidis and Lau, PNAS 2001





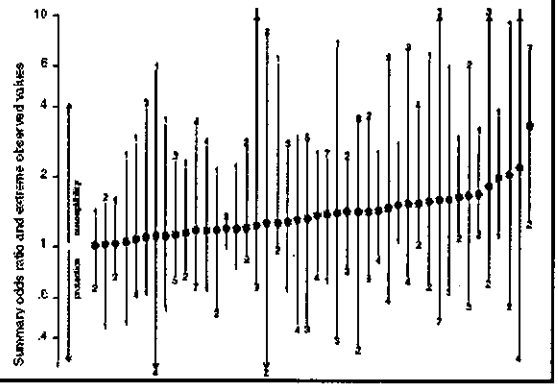


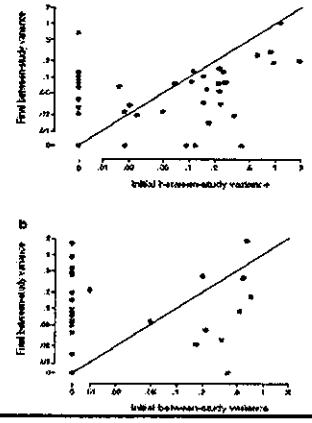


Succession of early extremes: the Proteus phenomenon

Ioannidis and Trikalinos, in press

Extreme results are common





Genetics

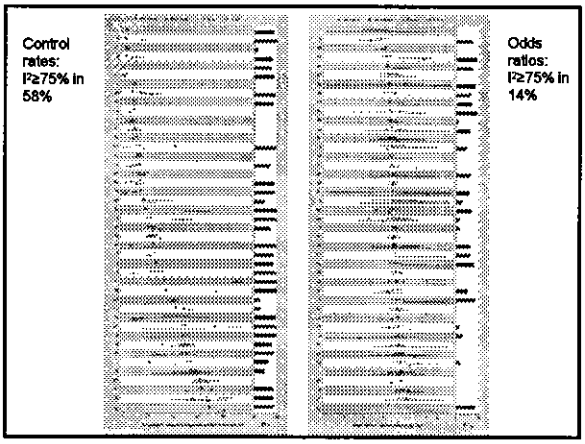
Changes in between-study variance over time

Health care interventions

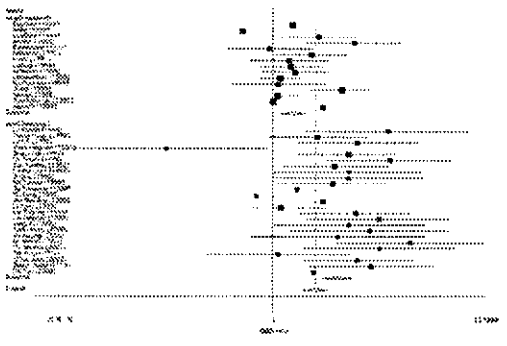
Racial (or other subgroup) differences?

- Empirical evidence suggest that while allele frequencies differ a lot (I-squared≥75%) in 58% of postulated gene-disease associations, differences in the effect sizes (odds ratios) occur in 14%.
- No differences in race-specific odds ratios have been recorded once we have exceeded a total sample size of N=10,000

Ioannidis et al, Nat Genet 2004



ACE D/I polymorphism and MI: Language bias - reverse language bias?



Problems of standardization

- Polymorphic markers
- Variable techniques
- Time-to-event outcomes
- Multivariate analyses
- Intermediate and surrogate outcomes

Advantages of MIPD

Advantages
- Data
  - More information
  - Inclusion of data from unpublished studies
  - Better standardization of information
    - Categorization of eligible participants
    - Outcomes
    - Definition of follow-up period and censoring criteria
- Analysis
  - Better time-to-event analyses
    - Standardized statistical models
  - Better adjusted/multivariate analyses
- Interpretation
  - Assessment of heterogeneity
- Other

Ioannidis et al, Am J Epidemiol 2002

Disadvantages of MIPD

Data
- Data may not be made available from all published studies

Interpretation
- Potential post hoc conflicts with collaborators regarding findings

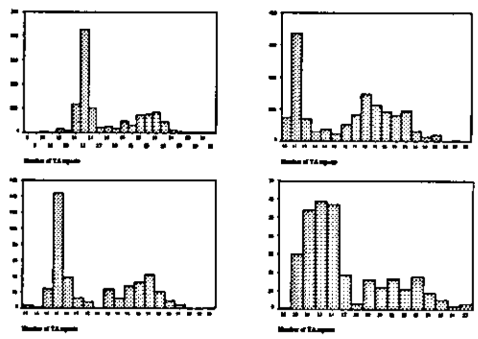
Resources
- Substantial effort and infrastructure required to:
  - Develop and administer a standardized protocol
  - Collect, manage, and analyze data
  - Communicate with collaborators

A prospective MIPD: GENOMOS

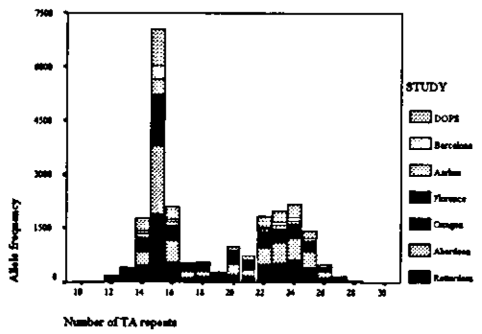
- Meta-analysis of individual-level data on osteoporosis on approximately 25,000 subjects with prospective genotyping
- 10 institutions involved across Europe
- A unique opportunity to evaluate the genetics of osteoporosis with rigorous large scale evidence

Ioannidis et al, JAMA 2004

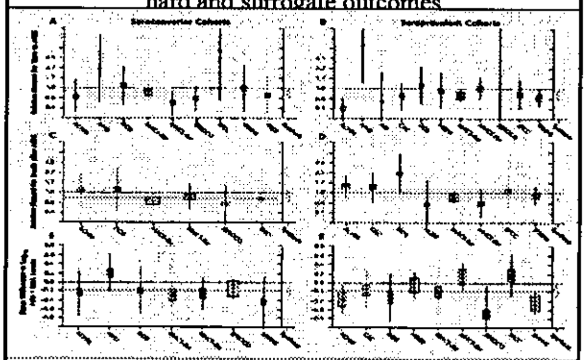
Distribution of TA alleles of the ER alpha gene in 4 populations



Standardization of genotypes in a prospective MIPD

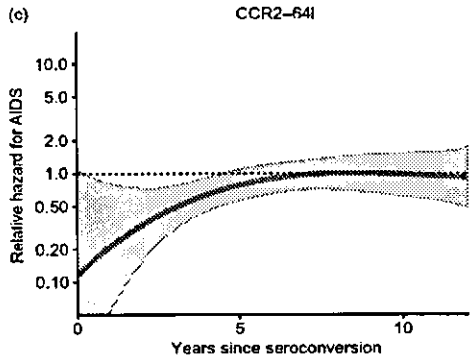


CCR5-delta32 and HIV disease progression: hard and surrogate outcomes



Ioannidis et al, Ann Intern Med 2001

Time-dependent effects

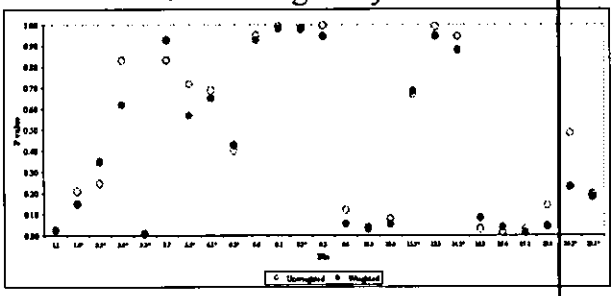


Mulherin et al. AIDS 2003

Other challenges

- Whole genome association meta-analyses
- Whole genome searches meta-analysis

GSMA – heterogeneity testing for low heterogeneity



Zintzaras and Ioannidis. Genetic Epidemiology 2005

Prognostic factor meta-analyses: Readily available, available, hidden, and very well hidden data