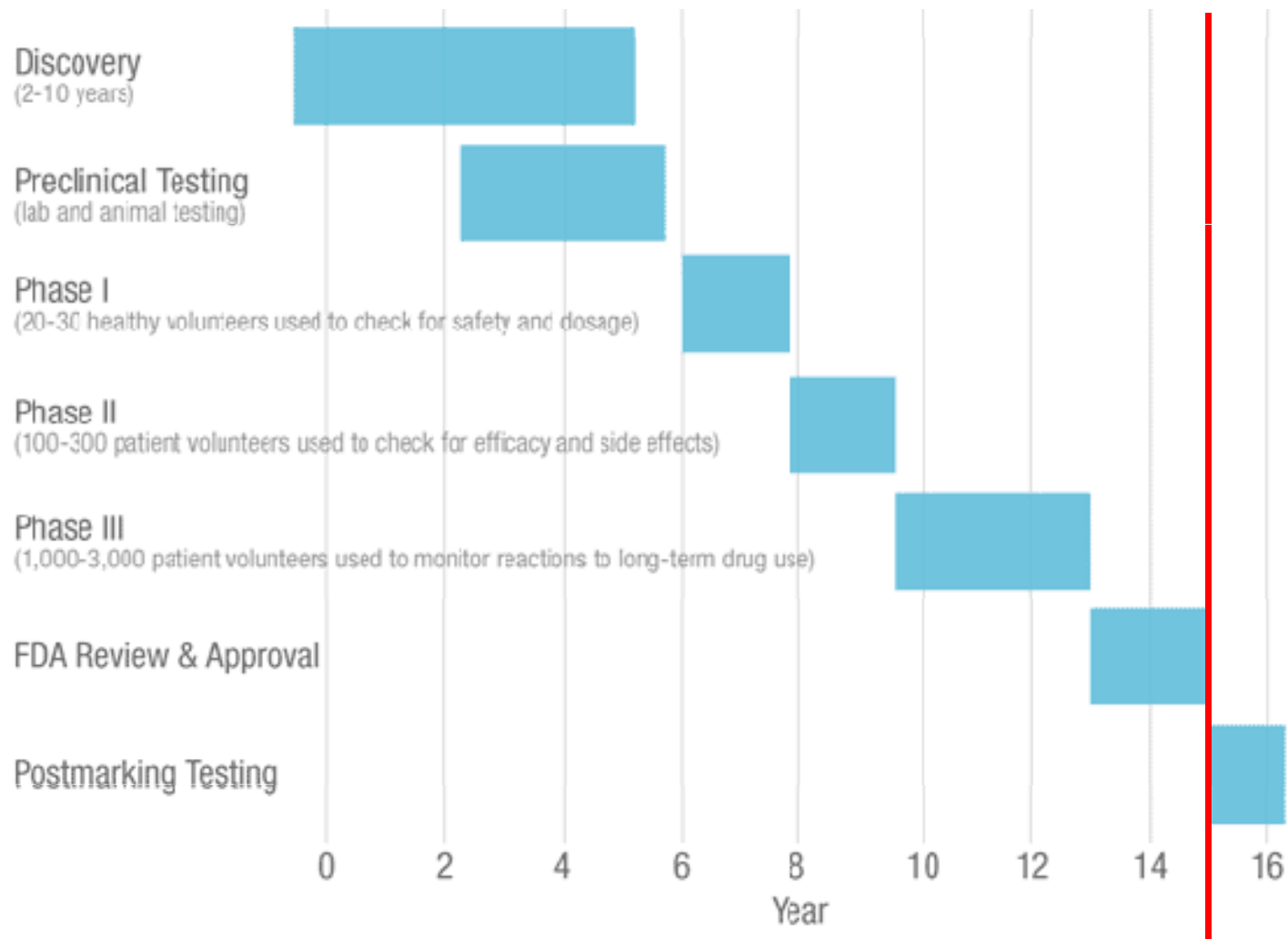


# Case Studies and Other Issues

David Madigan  
Columbia University



# Safety in Lifecycle of a Drug/Biologic product



# Drug Safety

## Pre-Approval:

- **High quality data (but small)**
- **No "data mining"**

## Post-Approval:

- **Low quality data (but lots of it)**
- **Extensive use of "data mining"**

# MEDWATCH

For VOLUNTARY reporting of  
adverse events, product problems and  
product use errors

The FDA Safety Information and  
Adverse Event Reporting Program

Page \_\_\_\_ of \_\_\_\_

FDA USE ONLY	
Triage unit sequence #	

A. PATIENT INFORMATION			
1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex <input type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight ____ lb or ____ kg
In confidence			

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR	
Check all that apply:	
<input type="checkbox"/> Adverse Event	<input type="checkbox"/> Product Problem (e.g., defects/malfunctions)
<input type="checkbox"/> Product Use Error	<input type="checkbox"/> Problem with Different Manufacturer of Same Medicine
2. Outcomes Attributed to Adverse Event (Check all that apply)	
<input type="checkbox"/> Death: _____ (mm/dd/yyyy)	<input type="checkbox"/> Disability or Permanent Damage
<input type="checkbox"/> Life-threatening	<input type="checkbox"/> Congenital Anomaly/Birth Defect
<input type="checkbox"/> Hospitalization - initial or prolonged	<input type="checkbox"/> Other Serious (Important Medical Events)
<input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)	
3. Date of Event (mm/dd/yyyy)	4. Date of this Report (mm/dd/yyyy)

5. Describe Event, Problem or Product Use Error
6. Relevant Tests/Laboratory Data, including Dates
7. Other Relevant History, including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)

C. PRODUCT AVAILABILITY	
Product Available for Evaluation? (Do not send product to FDA)	
<input type="checkbox"/> Yes	<input type="checkbox"/> No
<input type="checkbox"/> Returned to Manufacturer on: _____ (mm/dd/yyyy)	

D. SUSPECT PRODUCT(S)		
1. Name, Strength, Manufacturer (from product label)		
#1		
#2		
2. Dose or Amount		Frequency
#1		
#2		
3. Dates of Use (If unknown, give duration) from/to (or best estimate)		5. Event Abated After Use Stopped or Dose Reduced?
#1		#1 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply
#2		#2 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply
4. Diagnosis or Reason for Use (Indication)		8. Event Reappeared After Reintroduction?
#1		#1 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply
#2		#2 <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply
6. Lot #	7. Expiration Date	9. NDC # or Unique ID
#1		
#2		

E. SUSPECT MEDICAL DEVICE		
1. Brand Name		
2. Common Device Name		
3. Manufacturer Name, City and State		
4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date (mm/dd/yyyy)	<input type="checkbox"/> Health Professional
Serial #	Other #	<input type="checkbox"/> Lay User/Patient
<input type="checkbox"/> Other: _____		
6. If Implanted, Give Date (mm/dd/yyyy)	7. If Explanted, Give Date (mm/dd/yyyy)	
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?		
<input type="checkbox"/> Yes <input type="checkbox"/> No		
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor		

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS
Product names and therapy dates (exclude treatment of event)

G. REPORTER (See confidentiality section on back)	
1. Name and Address	
Phone #	E-mail

2. Health Professional? <input type="checkbox"/> Yes <input type="checkbox"/> No	3. Occupation	4. Also Reported to:
		<input type="checkbox"/> Manufacturer
		<input type="checkbox"/> User/Facility
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: <input type="checkbox"/>		<input type="checkbox"/> Distributor/Importer

PLEASE TYPE OR USE BLACK INK

# Problems with Spontaneous Reports

- Under-reporting
- Duplicate reports
- No temporal information
- No denominator
  
- But, at least a suspicion of causation

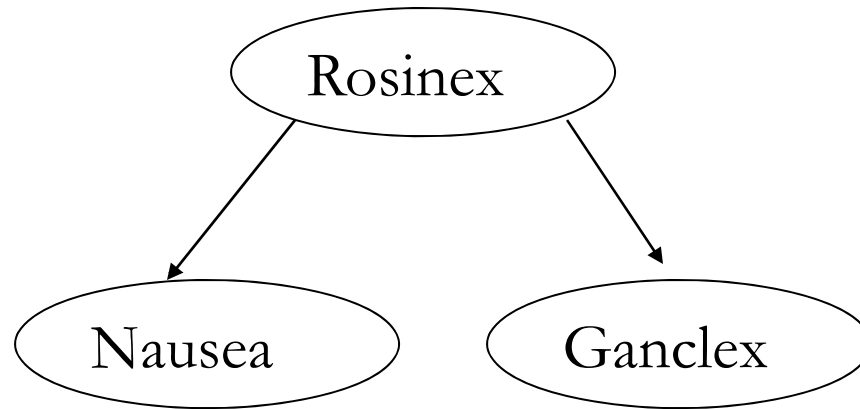
## Monitoring Spontaneous Drug Safety Reports

- Most reports contain several drugs and several AEs
- FDA, vendors, PhRMA, focus on 2X2 contingency table projections

	<i>AE j = Yes</i>	<i>AE j = No</i>	<i>Total</i>
<i>Drug i = Yes</i>	<i>a=20</i>	<i>b=100</i>	<i>120</i>
<i>Drug i = No</i>	<i>c=100</i>	<i>d=980</i>	<i>1080</i>
<i>Total</i>	<i>120</i>	<i>1080</i>	<i>1200</i>

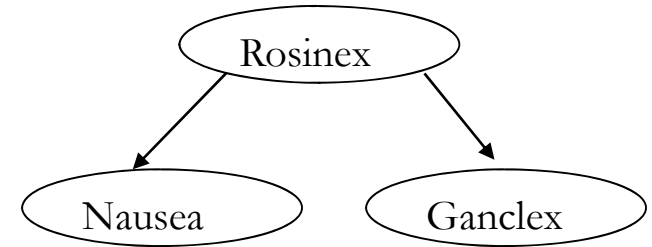
– 15,000 drugs \* 16,000 AEs = 240 million tables

Think about this...



		<i>Nausea</i>	<i>No Nausea</i>
Rosinex	Ganclex	81	9
Rosinex	No Ganclex	9	1
No Rosinex	Ganclex	1	9
No Rosinex	No Ganclex	90	810

**Both RR' s are big!**



	<i>Nausea</i>	<i>No Nausea</i>
Rosinex	90	10
No Rosinex	91	819

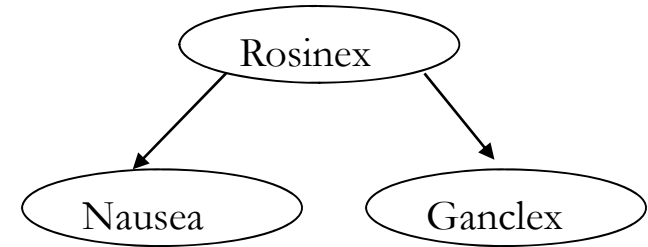
$$RR = (90/100)/(181/1010) = 5.0$$

	<i>Nausea</i>	<i>No Nausea</i>
Ganclex	82	18
No Ganclex	99	811

$$RR = (82/100)/(181/1010) = 4.6$$

		<i>Nausea</i>	<i>No Nausea</i>
Rosinex	Ganclex	81	9
Rosinex	No Ganclex	9	1
No Rosinex	Ganclex	1	9
No Rosinex	No Ganclex	90	810

# Need a conditional analysis



Rosinex users...

	<i>Nausea</i>	<i>No Nausea</i>
Ganclex	81	9
No Ganclex	9	1

$$RR = (81/90)/(90/100) = 1.0$$

Rosinex non-users...

	<i>Nausea</i>	<i>No Nausea</i>
Ganclex	1	9
No Ganclex	90	810

$$RR = (1/10)/(91/910) = 1.0$$

“Holding Rosinex constant, the RR for Ganclex and Nausea is 1”

		<i>Nausea</i>	<i>No Nausea</i>
Rosinex	Ganclex	81	9
Rosinex	No Ganclex	9	1
No Rosinex	Ganclex	1	9
No Rosinex	No Ganclex	90	810

# Another perspective

"bad drug" dose

# Another perspective

"bad drug" dose

more drug...less chance of MI. Bad drug is good???

# Another perspective

aspirin

"bad drug" dose

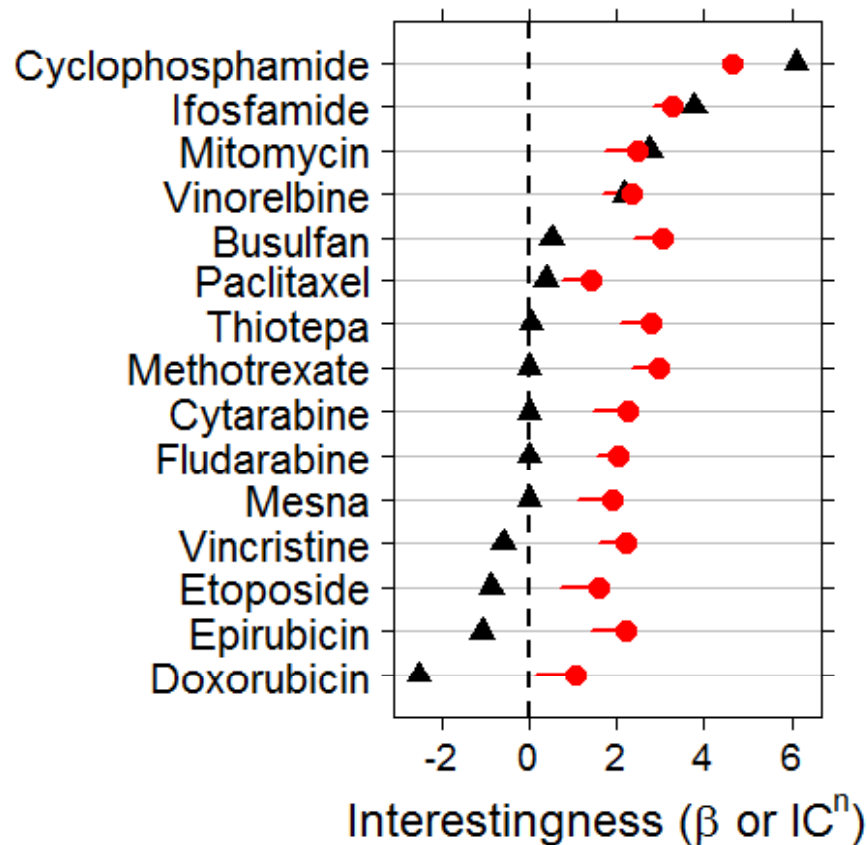
bad for aspirin users, bad for non-users!

Need a conditional analysis

# Logistic Regression

- $\log [P/(1-P)] = \text{intercept} + \beta$  (each drug effect )
  - $P = \text{Pr}(\text{report with these drugs will have the AE})$
- **Maximum likelihood logistic regression unstable**
  - 10,000+ predictors (drugs)
- **Bayesian/Regularized Logistic Regression**
  - Put a prior on coefficients  $(\beta_1, \dots, \beta_p)$ , and shrink their estimates towards zero
    - Stabilize the estimation when there are many predictors
    - Efficient coordinate-wise algorithms for finding posterior modes
    - Interactions?

# Benefits of Regression: Confounding



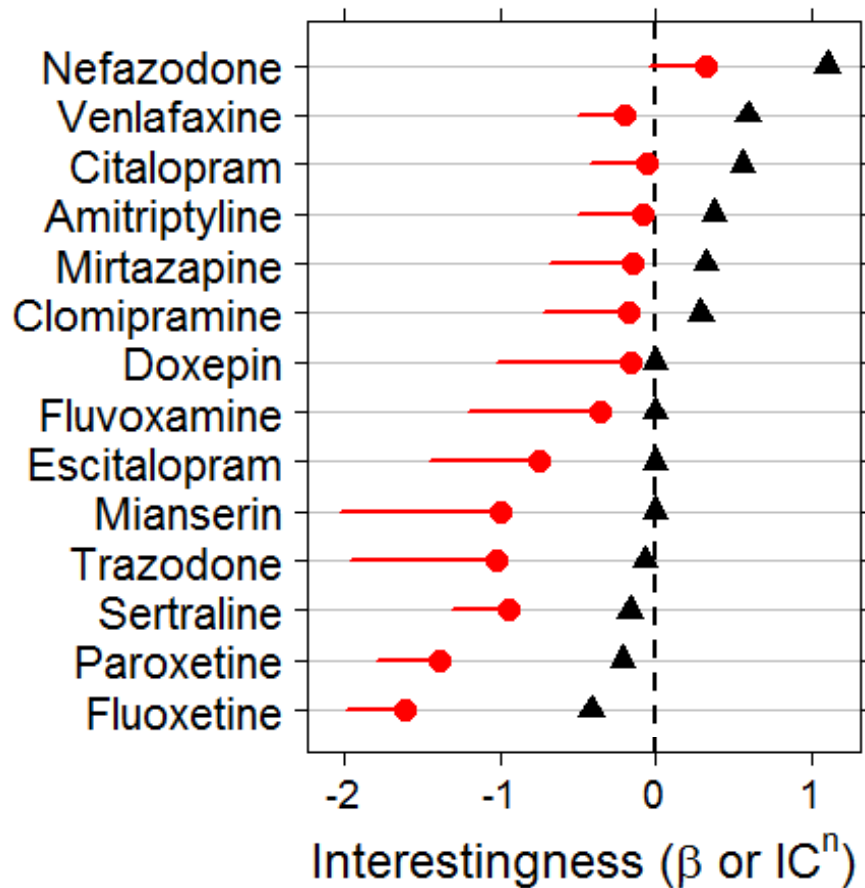
- LLR (□) and IC (•) results for hemorrhagic cystitis paired with anticancer drugs and mesna
- Agreement only for top drugs
  - Suspect confounding for the rest
- Consider mesna:
  - Only used with ifosfamide and cyclophosphamides to prevent this AE

# Benefits of Regression: Masking

Typical 2 X 2 measures based on:  $\frac{\text{Pr}(\text{AE}|\text{Drug})}{\text{Pr}(\text{AE})}$

- Masking means that the **background rate** is distorted (too high) due to massive reporting on AE with one drug or drug group
- Example: Rhabdomyolysis and cerivastatin
  - Background rate distorted because of media attention

# Other Benefits of Regression: Masking

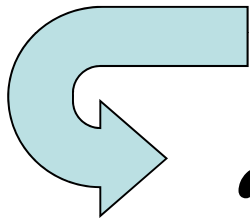


**Lasso logistic regression (▴) and IC (•) results for rhabdomyolysis paired with antidepressants**

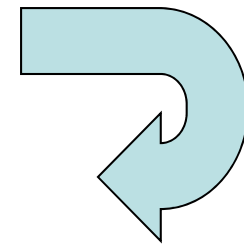
**Clear masking effect visible**

**Vioxx, Baycol, etc.** 

**IOM**

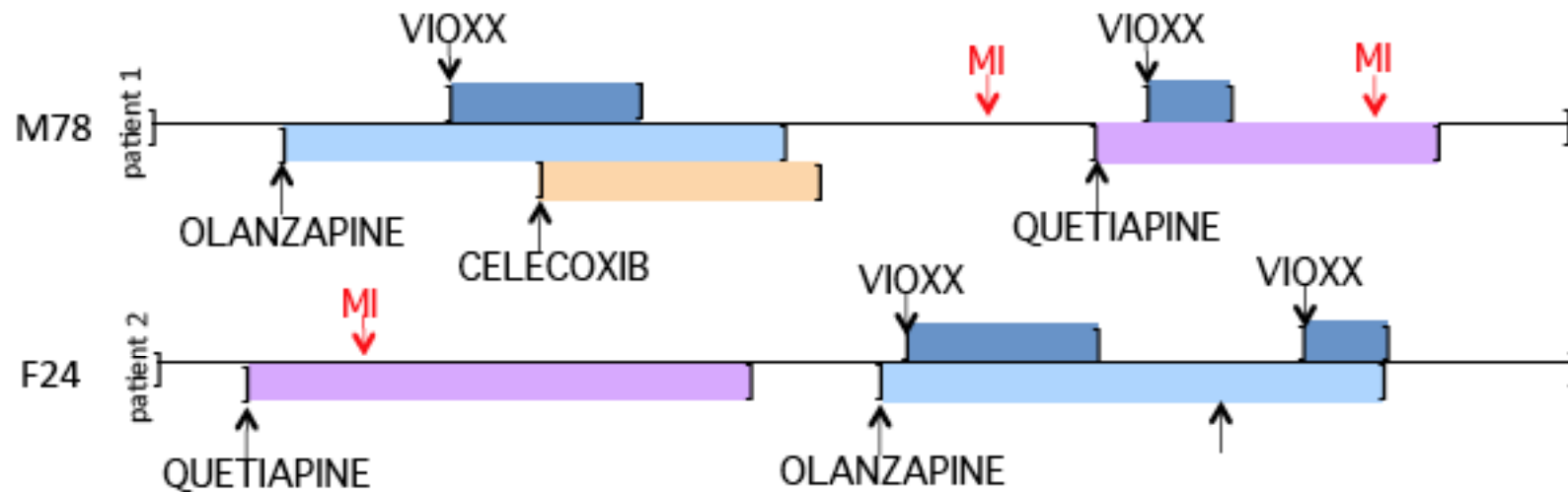


**2007 FDAAA**

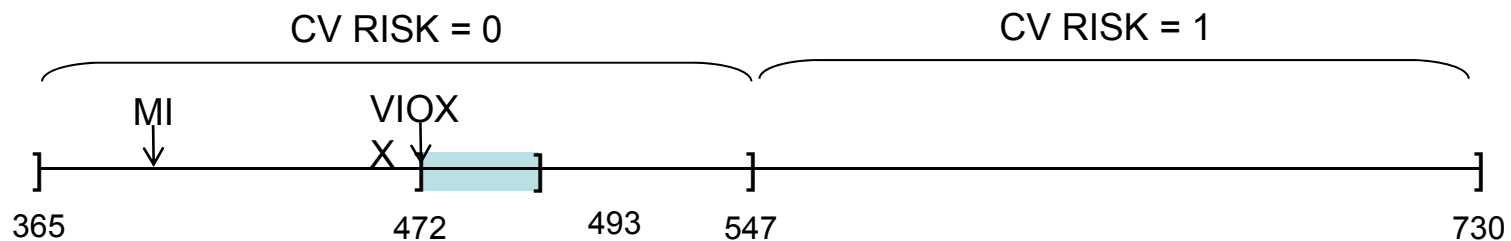


**Sentinel, OMOP, EU-ADR**

# Longitudinal Observational Databases



# Self Controlled Case Series



- assume diagnoses arise according to a non-homogeneous Poisson process

$e^{\phi_i}$  baseline incidence for subject  $i$

$e^{\alpha_1}$  relative incidence associated with CV risk group 1

$e^{\beta_1}$  relative incidence associated with Vioxx risk level 1

$\lambda_1 = 107 e^{\phi_1}$  Poisson rate for subject 1, period 1

overall Poisson rate for subject 1:

$$\Lambda = 107e^{\phi_1} + 21e^{\phi_1}e^{\beta_1} + 54e^{\phi_1} + 183e^{\phi_1}e^{\alpha_1}$$

cohort study contribution to the likelihood:

$$(\lambda_1 e^{-\lambda_1}) \times e^{-\lambda_2} \times e^{-\lambda_3} \times e^{-\lambda_4} = \lambda_1 e^{-\Lambda}$$

conditional likelihood:

$$\begin{aligned} \frac{\lambda_1 e^{-\Lambda}}{\Lambda e^{-\Lambda}} &= \frac{\lambda_1}{\Lambda} \\ &= \frac{107e^{\phi_1}}{107e^{\phi_1} + 21e^{\phi_1}e^{\beta_1} + 54e^{\phi_1} + 183e^{\phi_1}e^{\alpha_1}} \\ &= \frac{107}{107 + 21e^{\beta_1} + 54 + 183e^{\alpha_1}} \end{aligned}$$

# Self-Controlled Case Series Method

Farrington et al.

equivalent multinomial likelihood:

$$l(\alpha_1, \beta_1) = \left( \frac{107}{107 + 21e^{\beta_1} + 54 + 183e^{\alpha_1}} \right)^1 \times \left( \frac{21e^{\beta_1}}{107 + 21e^{\beta_1} + 54 + 183e^{\alpha_1}} \right)^0 \times \left( \frac{54}{107 + 21e^{\beta_1} + 54 + 183e^{\alpha_1}} \right)^0 \times \left( \frac{183e^{\alpha_1}}{107 + 21e^{\beta_1} + 54 + 183e^{\alpha_1}} \right)^0$$

regularization => Bayesian approach

scale to full database?

# Vioxx: A Case Study

# COX-2: The Promise

- COX-2 inhibitors were designed to minimize GI complications of traditional NSAIDs — adverse effects attributed to suppression of COX-1
- COX-2 inhibitors include rofecoxib (Vioxx), celecoxib (Celebrex), and etoricoxib (Arcoxia)



Time to Event in Days

withdrawn by Merck in Sept. 2004 because of this graph

\$2.5billion in annual sales (> 10% of 2004 revenues)

# Serious Consequences

- 88,000-139,000 excess myocardial infarctions in US
- 27,000-55,000 excess deaths

David Graham, FDA

# CVT potential suggested early on

December 1997, International Consensus Meeting on the Mode of Action of COX-2 Inhibition

“although gastric intolerance was the most obvious [adverse event], renal and cardiac toxicity were important and a probable link between these two phenomena had been established. It is therefore important to monitor cardiac side effects with selective COX-2 inhibitors.”



## MEMORANDUM

**DATE:** November 21, 1996

**TO:** B. Friedman, A. Nies, R. Spector

**CC:** B. Gertz, J. Bolognese, B. Daniels, E. Ehrich, H. Guess, D. Khanna, J. McIntyre, B. Morrison, R. Silverman, S. Simpson, T. Simon, D. Watson

**FROM:** T. Musliner

**SUBJECT:** Anticipated consequences of NSAID antiplatelet effects on cardiovascular events and effects of excluding low-dose aspirin use in the Cox-2 GI Outcomes Megatrial

### 1. Background -- prophylactic use of low-dose aspirin and risk of cardiovascular events

The largest clinical trial testing aspirin for cardiovascular (CV) primary prevention was the U.S. Physician's Health Study, in which 22,071 men 40 to 84 years of age were randomized to 325 mg aspirin q.o.d. vs. placebo<sup>1</sup>. The aspirin arm was terminated prematurely after ~5 years of follow-up, upon recommendation of the Data Monitoring Board. There was a 44% reduction in the risk of first myocardial infarction (MI) (RR=0.56, 95% CI 0.45-0.70;  $p < 0.00001$ ). A slightly increased risk of stroke in the aspirin group did not achieve statistical significance, although for hemorrhagic stroke alone the RR was 2.14 (95% CI 0.96-4.77,  $p = 0.06$ ). There was no significant difference in total CV mortality (RR=0.96, 95% CI 0.60-1.54;  $p = 0.87$ ). A reduction in risk for fatal MI (10 vs. 28, RR=0.31, 95% CI 0.14-0.68,  $p = 0.004$ ) was balanced by trends toward increased risk of sudden death (22 vs. 12, RR=1.96, 95% CI 0.91-4.22,  $p = 0.09$ ), stroke and other CV death. Fifty nine percent of the participants were  $\geq 50$  years of age at baseline and reduction in risk for MI in association with aspirin use was only apparent in patients above this age cut-off ( $p$  value in trend in RR with increasing age = 0.02; RR for participants  $< 50$  was 1.12).

The only other large randomized trial of aspirin in primary prevention of CV disease was the 6-year British Doctor's Trial in 5139 men 50 to 79 years of age<sup>2</sup>. The dose of aspirin was 500 mg/day. No significant reductions in total mortality, MIs or strokes were observed, however, the confidence intervals were wide. There was a trend towards greater numbers of disabling strokes in the aspirin-treated patients. There were significantly fewer TIAs in the aspirin-treated group. A meta-analysis of the U.S. and British studies<sup>3</sup> concluded that a 33% reduction in the risk of a first nonfatal MI ( $p < 0.0002$ ) could be anticipated with low-dose aspirin prophylaxis. The role of aspirin in primary prevention of stroke and death from vascular causes was considered inconclusive. There are no good clinical trial data on the use of still lower doses of aspirin for primary prevention, which might have a more favorable risk-

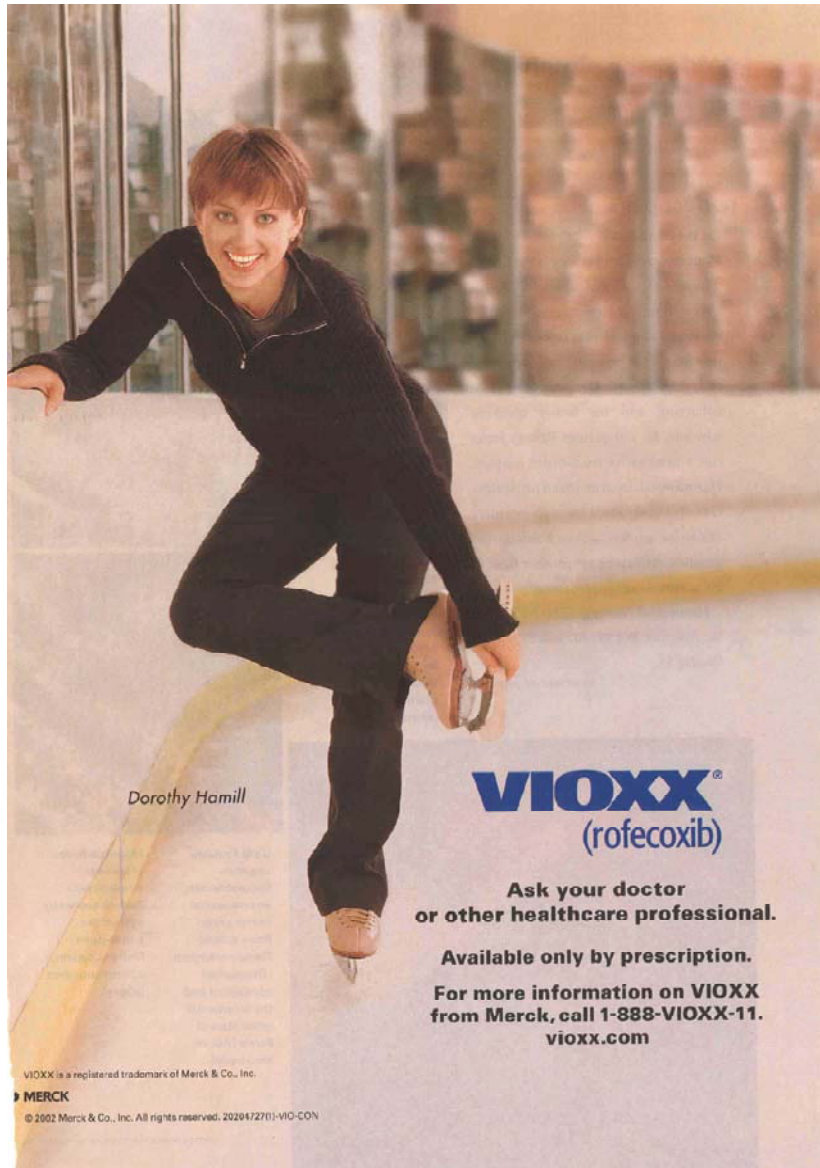
# In November 1996...

...Merck scientists feared that because selective COX-2 inhibitors like Vioxx did not inhibit COX-1, as did NSAIDs such as aspirin, if patients on COX-2 inhibitors [e.g., Vioxx] in clinical studies were not permitted to take aspirin...

“...there is a substantial chance that significantly higher rates of CV AE events (MIs, angina, strokes, TIAs, etc.) will be observed in” them.

# Against this backdrop...

- Vioxx received a 6-month priority review because the drug potentially provided a significant therapeutic advantage over existing approved drugs due to fewer gastrointestinal side effects
- Approved May 1999
- Evidence based on many short-term RCTs
- Large RCT of RA patients was on-going



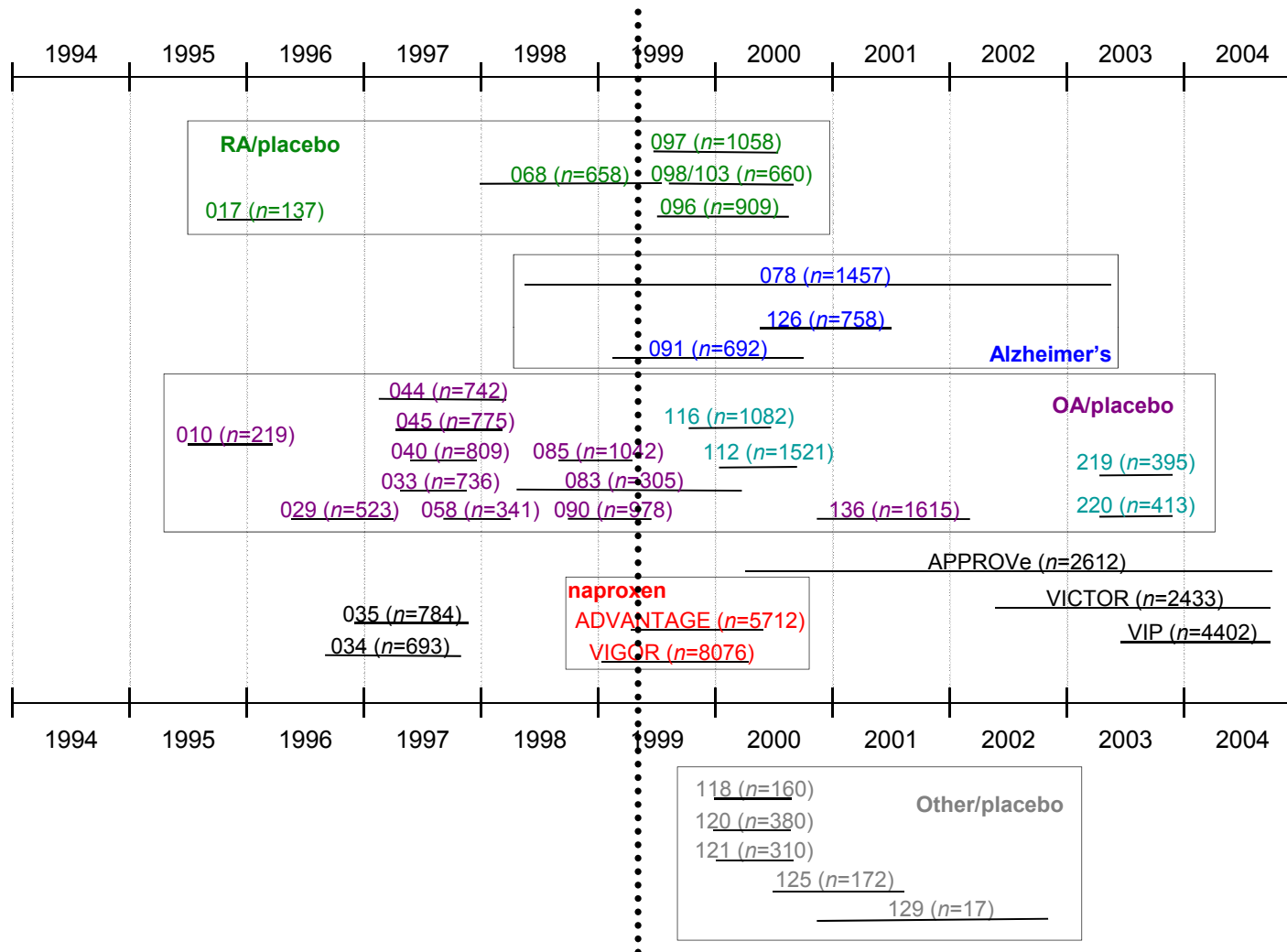
In 2000 Vioxx was the drug with the largest direct-to-consumer advertising campaign in the U.S. at ~\$160m.

More than Budweiser (\$146m) or Pepsi (\$125m).

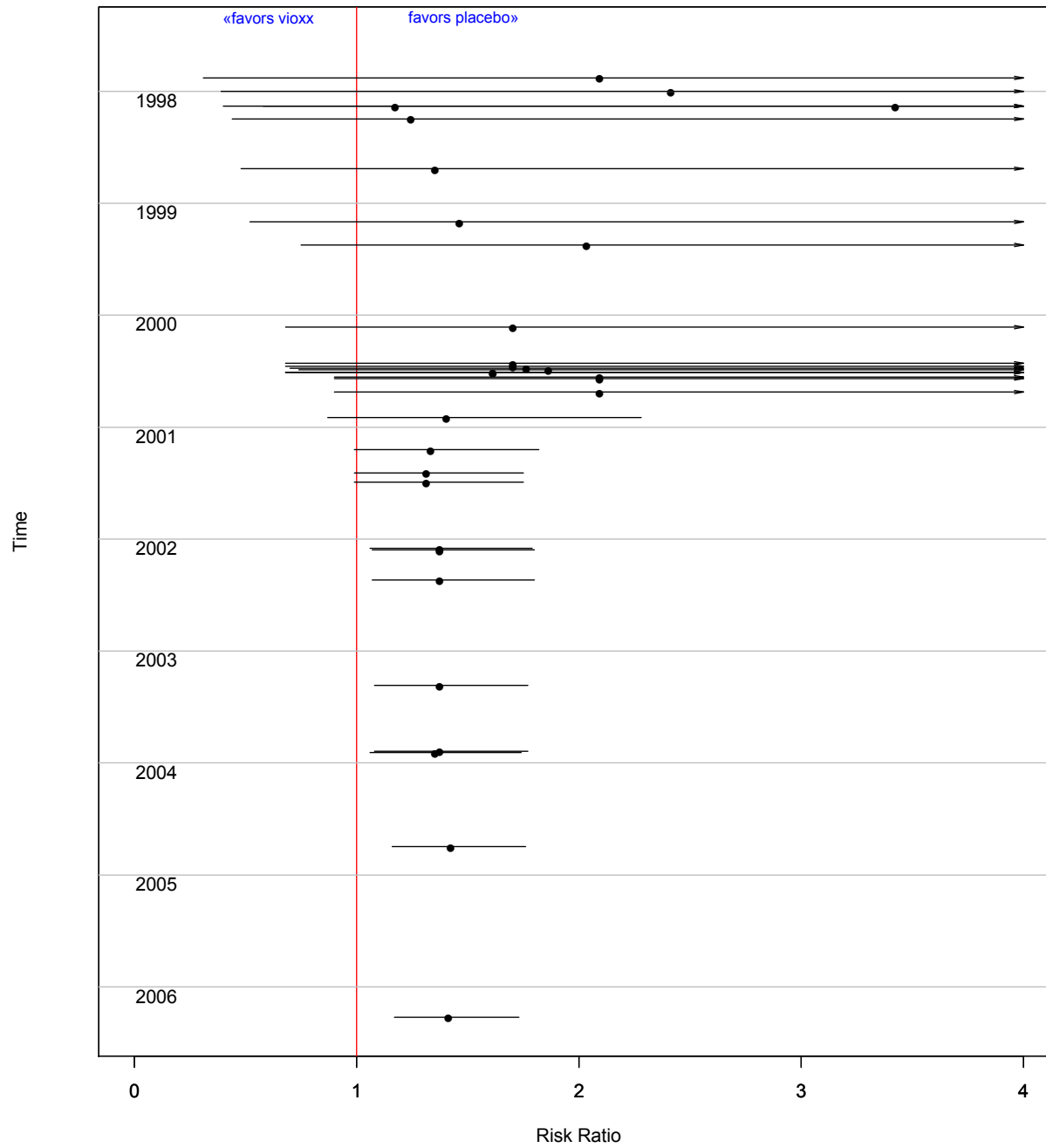
Nature 436, 910-911 (18 August 2005)

**What do the clinical trials show?**

# Vioxx Timeline

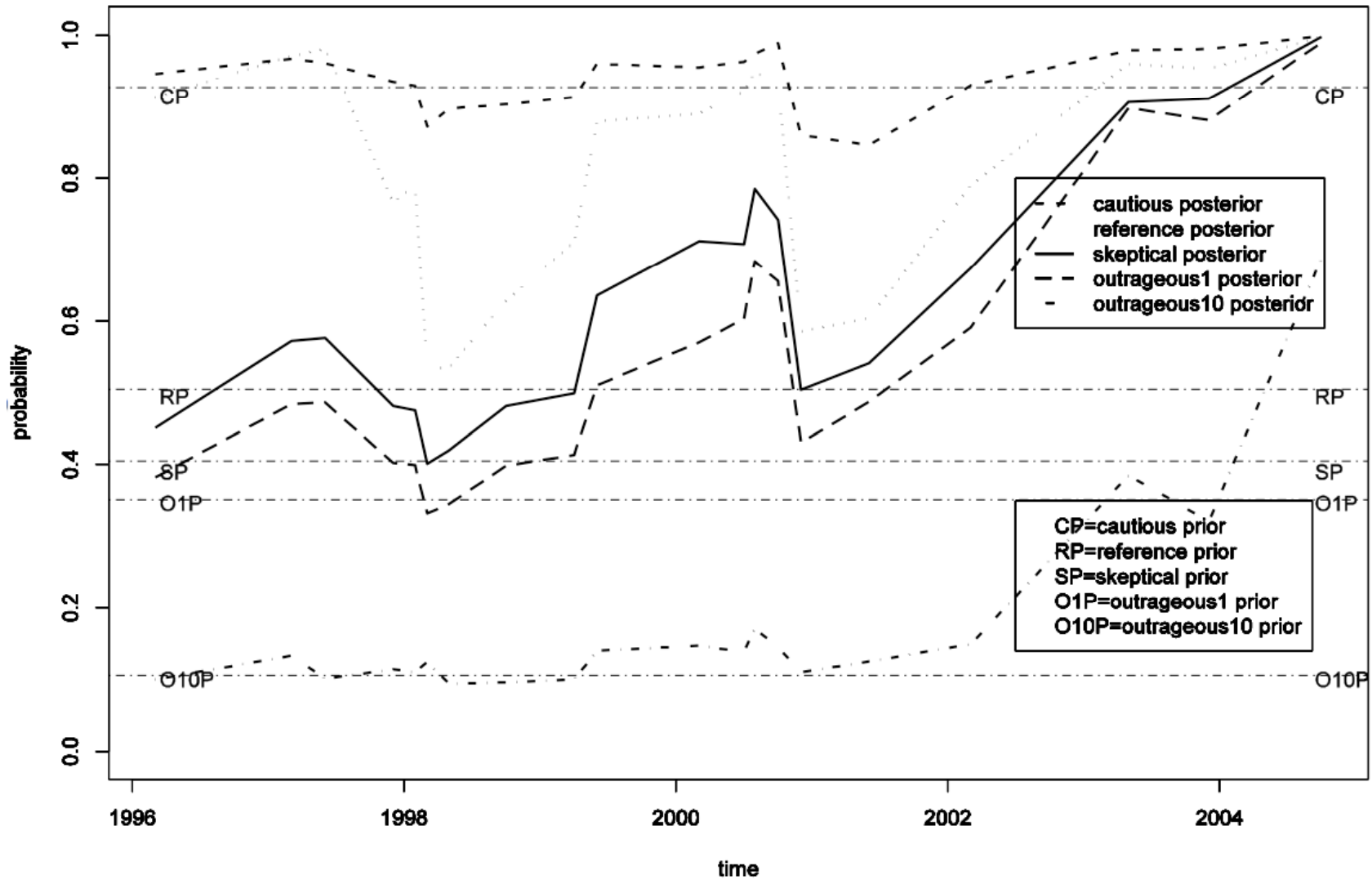


### CVT+Mortality Cumulative Risk Ratio, Vioxx versus Placebo

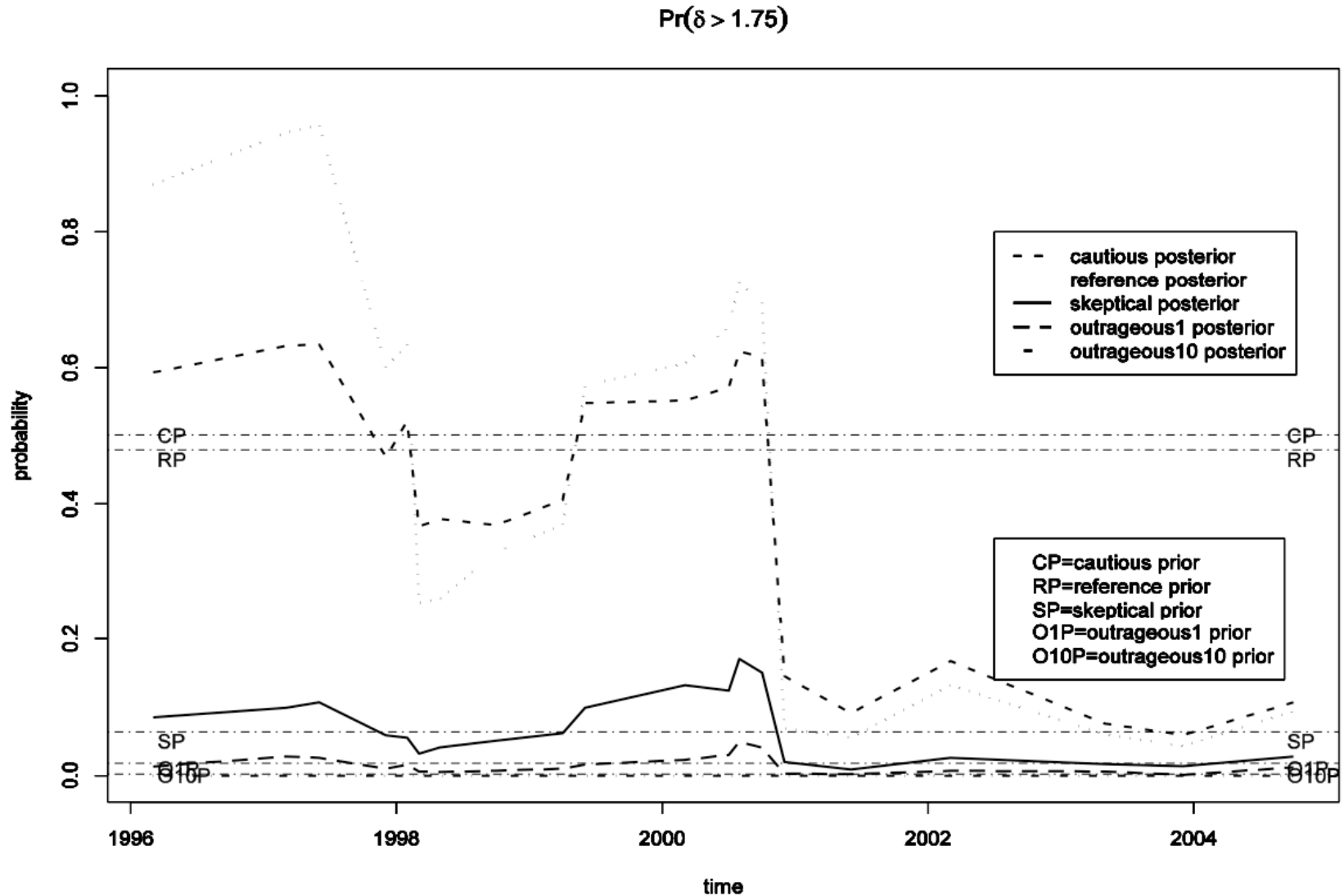


# Posterior Probability (1) – block effect model

$$\Pr(\delta > 1.1)$$



# Posterior Probability (2) – block effect model



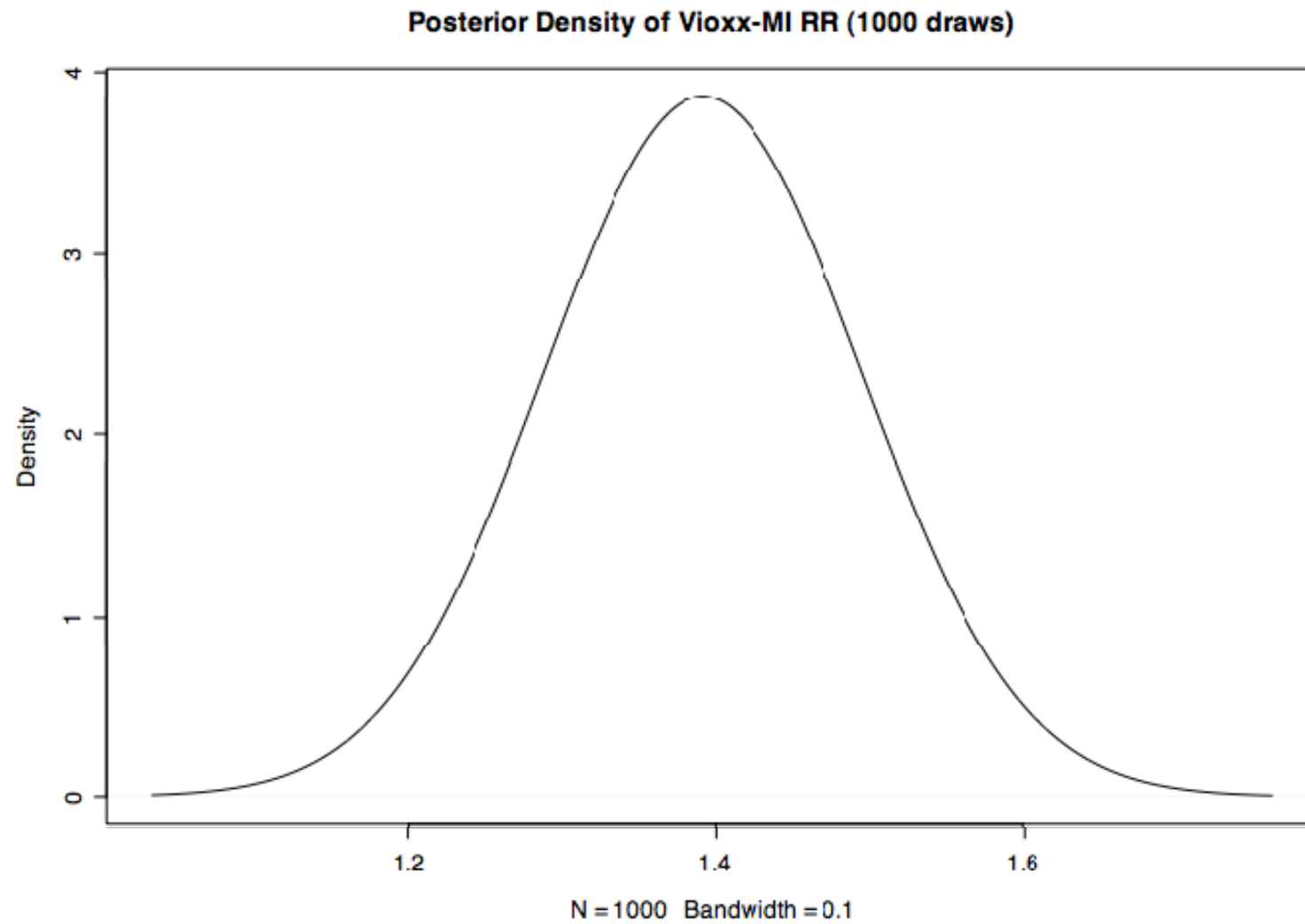
What about observational data?

# Vioxx & MI: SCCS RRs

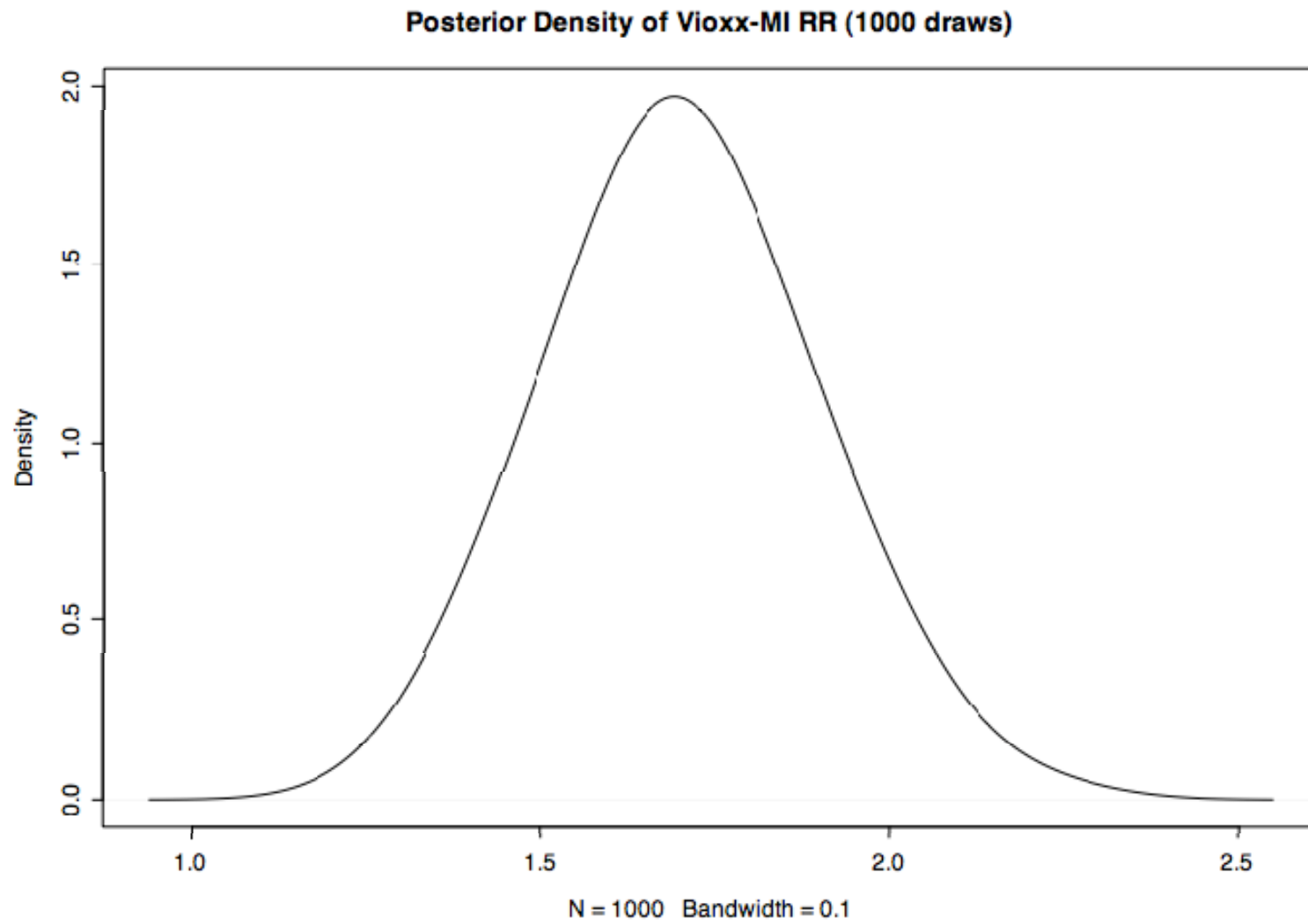
i3 claims database

- Bayesian analysis  $N(0,10)$  prior + MCMC
- Overall: 1.38 (n=11,581)
- Male: 1.41    Female: 1.36
- Age  $\geq 80$ : 1.48
- Male + Age  $\geq 80$ : 1.68

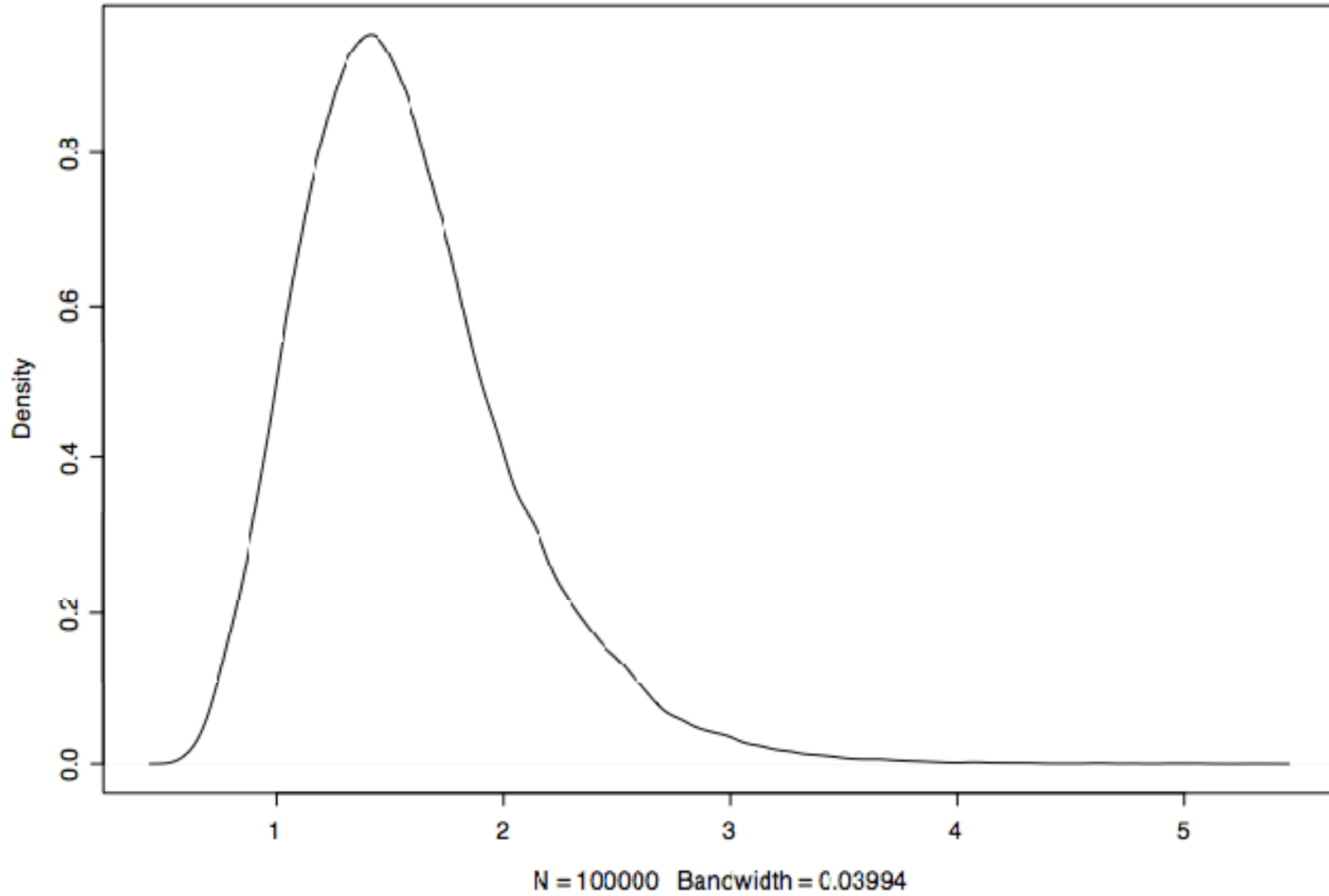
overall (n=11,581)



males 80 and over (n=440)

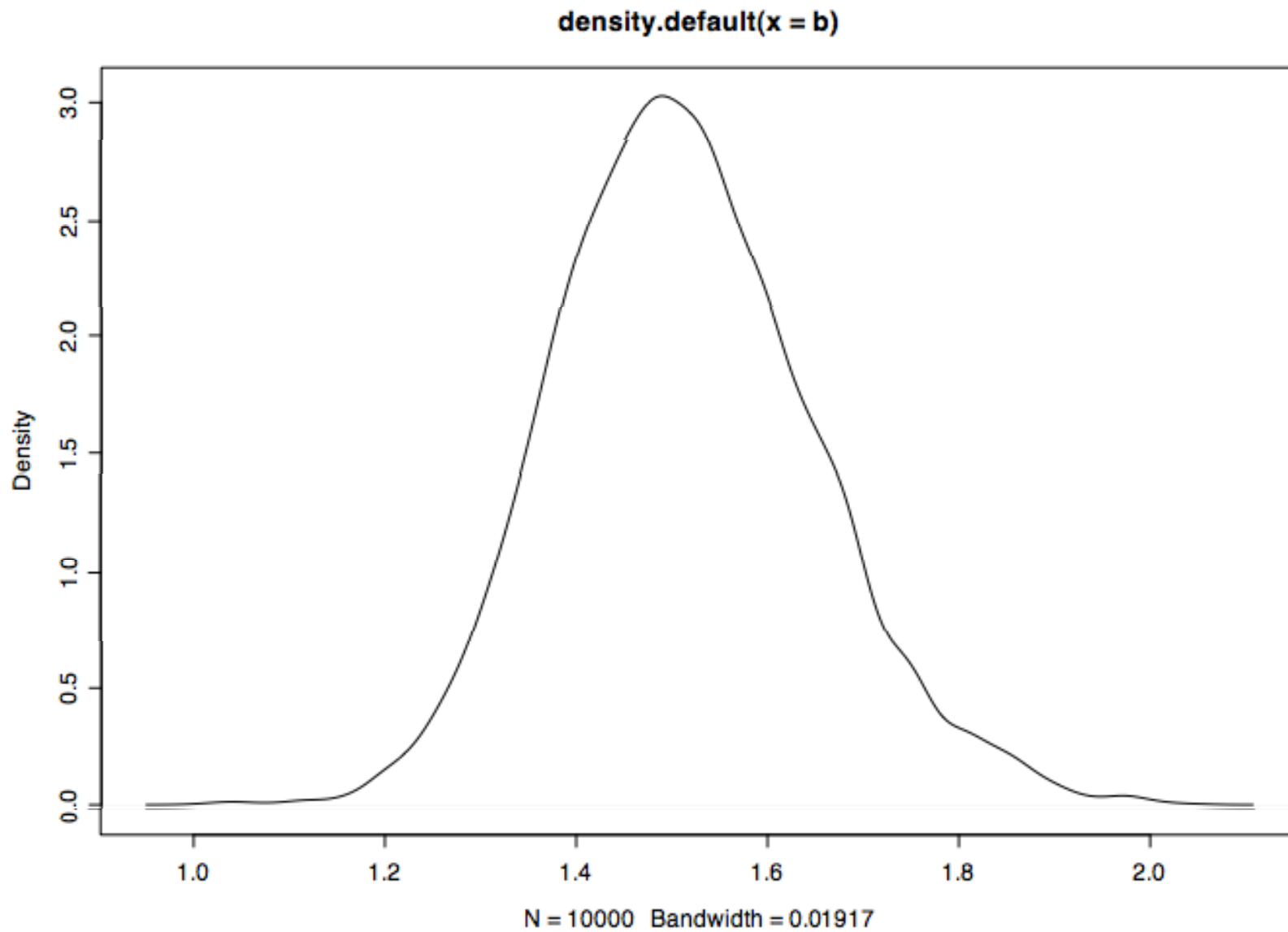


density.default(x = b)



June 30, 2000

RR=1.53 Pr(RR>1)=0.92

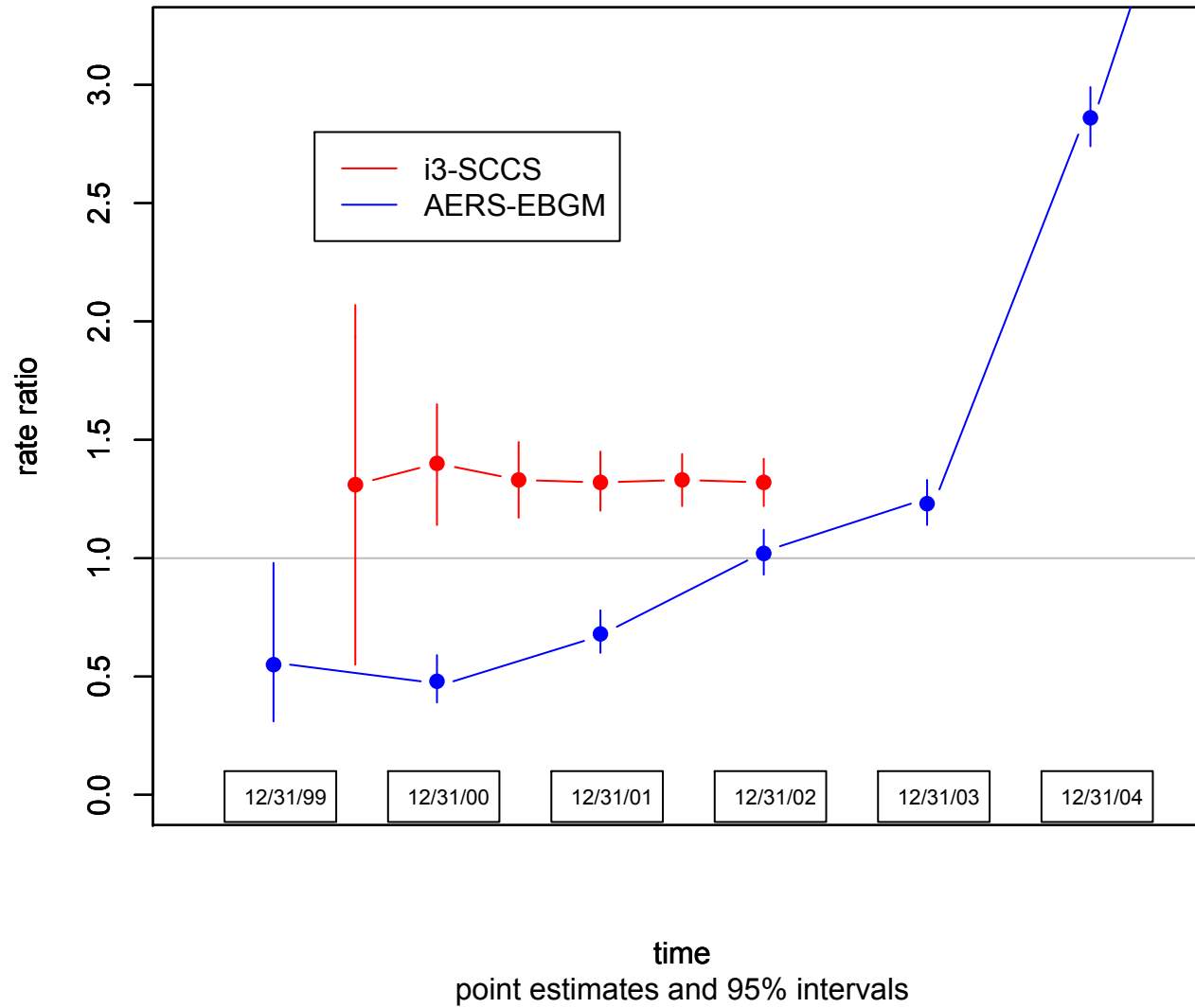


Dec 31, 2000

RR=1.51 Pr(RR>1)=1.0

What about spontaneous reports?

# Vioxx and MI



# Byetta (exenatide) and Acute Pancreatitis

- Label was changed in October 2007
- FDA alert issued in August 2008



# The New York Times

## Diabetes Drug Tied to New Deaths

By BLOOMBERG NEWS  
Published: August 26, 2008

The [diabetes](#) drug Byetta, marketed by [Eli Lilly & Company](#) and [Amylin Pharmaceuticals](#), was linked to four more deaths in patients with [pancreatitis](#), adding to two deaths announced by federal regulators last week.

---

### Add to Portfolio

 [Amylin Pharmaceuticals Incorporated](#)

[Go to your Portfolio »](#)


No definite relationship between Byetta and the deaths has been proved, and the [Food and Drug Administration](#) was aware of the additional deaths when it made its announcement last week, Amylin's chief executive, Dan Bradbury, said on Tuesday. The company is talking with the F.D.A. about adding warnings on the drug's prescribing information.


Byetta is Amylin's leading product.

 E-MAIL

 PRINT

 REPRINTS

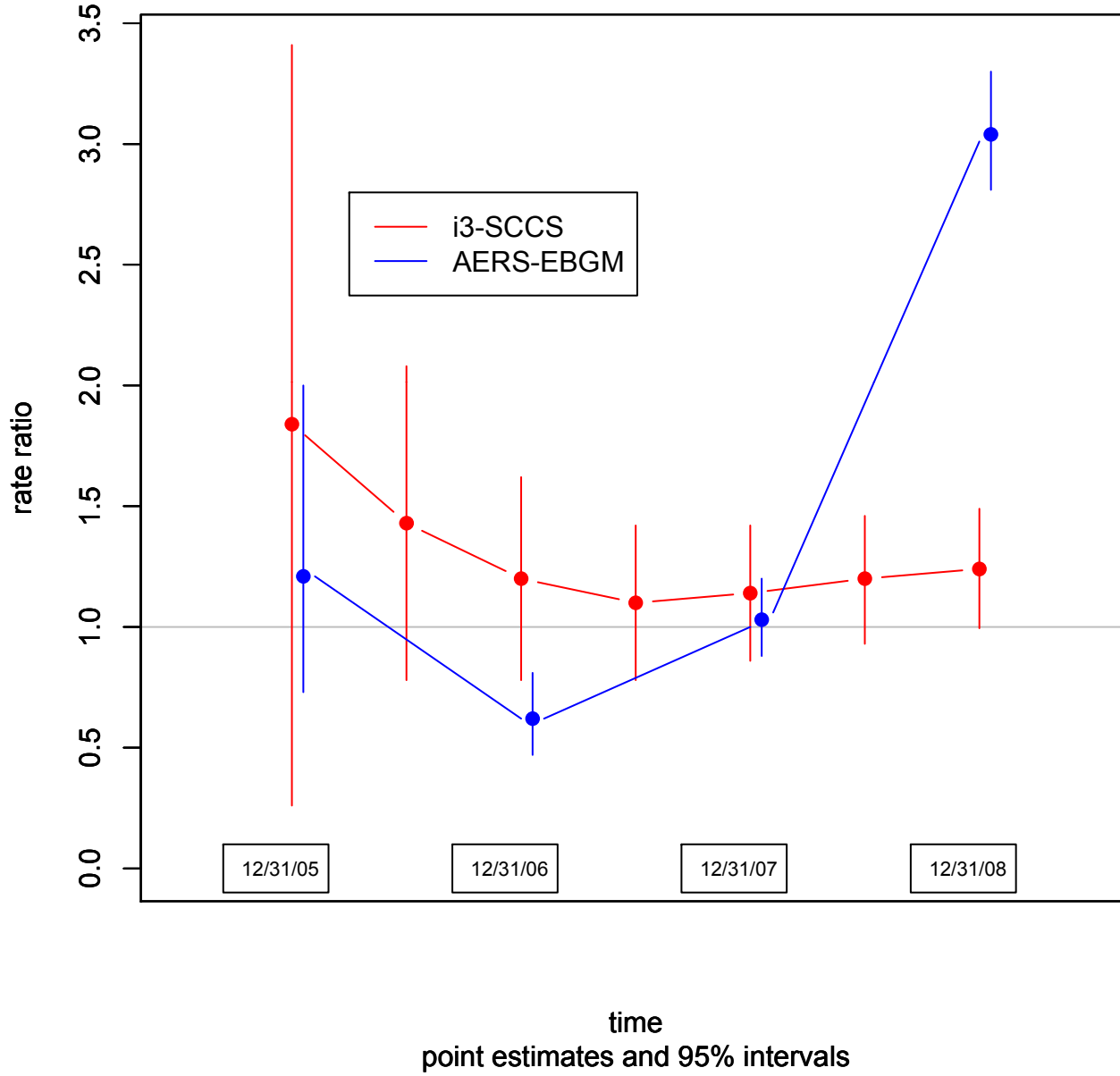
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# Exenatide and Pancreatitis



# Estrogen and MI

Initially thought to be cardioprotective...

IJE vol.33 no.3 © International Epidemiological Association 2004; all rights reserved.  
Advance Access publication 27 May 2004

*International Journal of Epidemiology* 2004;33:445–453  
DOI: 10.1093/ije/dyh125

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## REPRINTS AND REFLECTIONS

### **Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence<sup>1,2</sup>**

By Meir J Stampfer, M.D.\*†,<sup>3</sup> and Graham A Colditz, M.D.\*‡

#### **Discussion**

Although the findings from the epidemiologic studies are not completely consistent, the preponderance of the evidence strongly suggests that women taking postmenopausal estrogen therapy are at decreased risk for CHD. The consistency of the findings is more apparent in the better designed and analyzed studies.

Then the women's health initiative RCT...

The NEW ENGLAND  
JOURNAL of MEDICINE

ESTABLISHED IN 1812

AUGUST 7, 2003

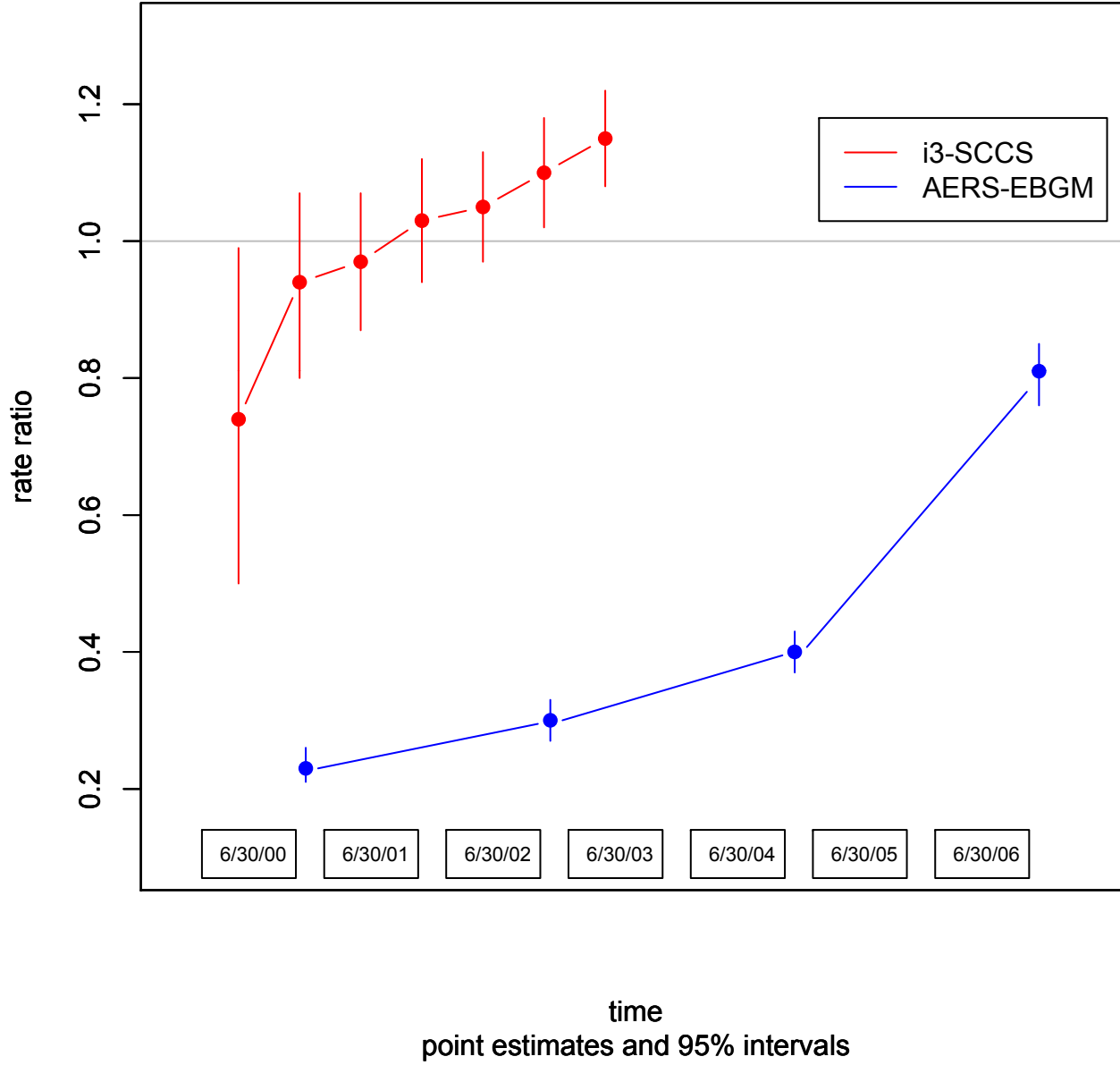
VOL. 349 NO. 6

## Estrogen plus Progestin and the Risk of Coronary Heart Disease

### CONCLUSIONS

Estrogen plus progestin does not confer cardiac protection and may increase the risk of CHD among generally healthy postmenopausal women, especially during the first year after the initiation of hormone use. This treatment should not be prescribed for the prevention of cardiovascular disease.

# Estrogen and MI



# Discussion

- Spontaneous reports and observational studies can differ substantially
- A reasonable strategy considers all possible sources of evidence
- Clinical trials (or meta-analyses of clinical trials) provide the strongest source
- Ideally, formally combine all sources in a Bayesian framework