One database – two answers
Ten databases – million answers

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Two GPRD Studies Evaluating Statins and Fractures (both JAMA)

	Selected population Adjusted OR (95% CI) Meier et al	Entire population Adjusted OR (95% CI) van Staa et al
Any fracture	0.55 (0.44-0.69)	1.01 (0.88-1.16)
Femur/hip	0.12 (0.04-0.41)	0.59 (0.31-1.13)
Vertebral	0.14 (0.02-0.88)	1.15 (0.62-2.14)

Main Differences in Methods in the Two GPRD Studies

- Nested within cohort – entire population case-control
- Definition of fractures
- Time-window of exposure (30 days – 6 months)
- Use of case exclusions
- Variables in adjustment

Re-analysis of two studies with contrasting results on the association between statin use and fracture risk: the GPRD [Int J Epidemiol 2006]

- Frank de Vries [1,2]
- Corinne de Vries [2]
- Hubert Leufkens [1]
- Cyrus Cooper [3]
- Tjeerd van Staa [1,2,3]

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Baseline Characteristics

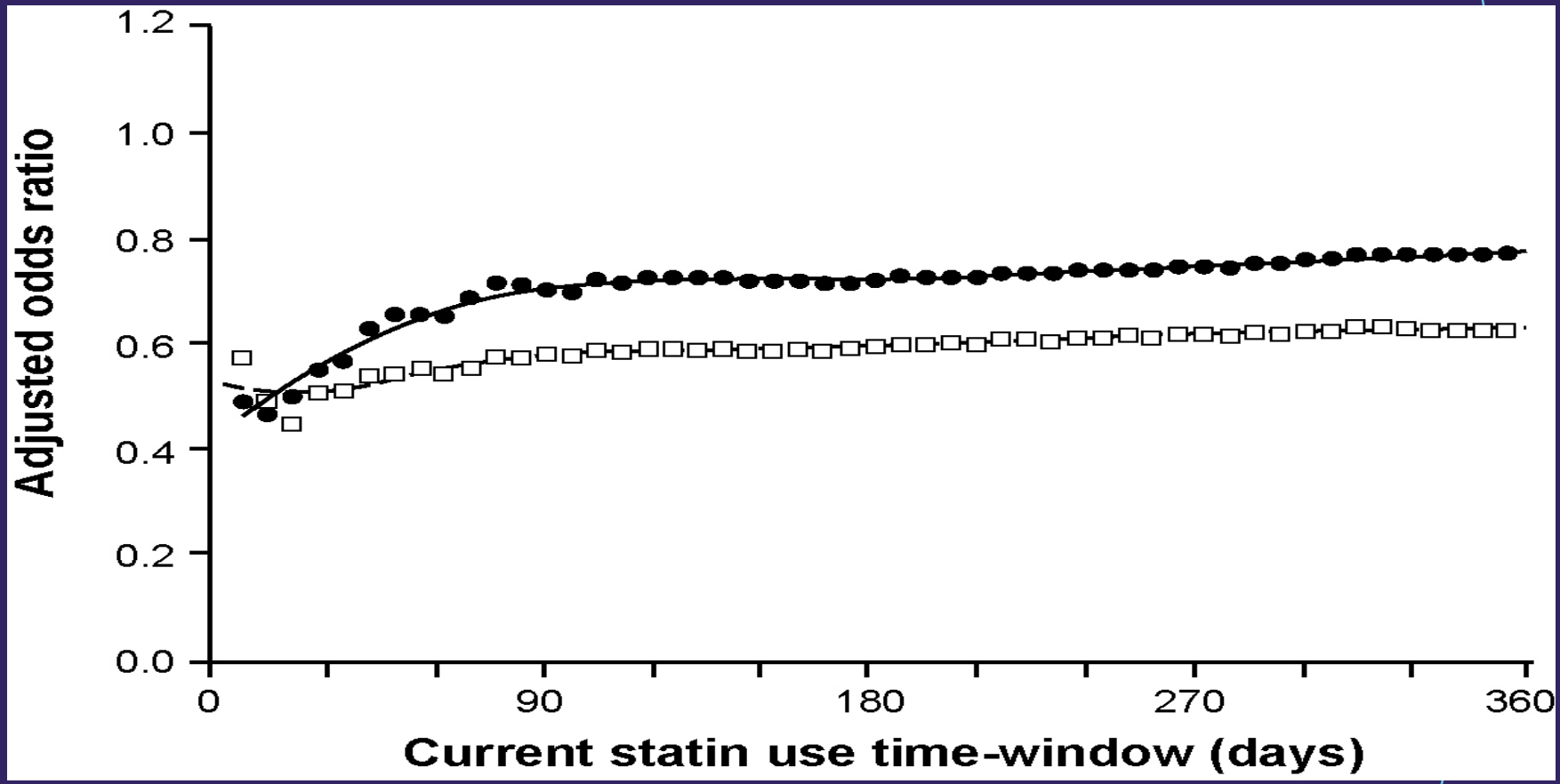
	Selected population		Entire population	
	Cases	Control	Case	Control
N	17,948	95,468	131,838	131,838
Mean age	72.0	71.1	71.6	71.6
Degree matching by YOB		37%		99%
Women	76%	76%	75%	75%

Statins and Risk of Hip/Femur Fracture (matching by age)

	Selected population		Entire Population	
	OR (within 5 years)	OR (by YOB)	OR (within 5 years)	OR (by YOB)
Original [1,2]	0.12 (0.04-0.41)			0.59 (0.31-1.13)
New study	0.37 (0.27-0.52)	0.58 (0.43-0.79)	0.54 (0.39-0.74)	0.61 (0.44-0.86)

[1] JAMA 2000; 283 (3205-10) [2] JAMA 2001; 285 (1850-55)

Statins and Risk of Hip/Femur Fracture (exposure time-window)



□=entire population ; •=selected population

Statins and Risk of Hip/Femur Fracture (design heterogeneity)

- **Different choices in exposure time-window (1-6 months), age matching (by 0-5 years) and confounder selection: range of ORs**
- **Selection population:**

  from 0.38 (0.27-0.53) to 0.82 (0.63-1.05)
- **Entire population:**

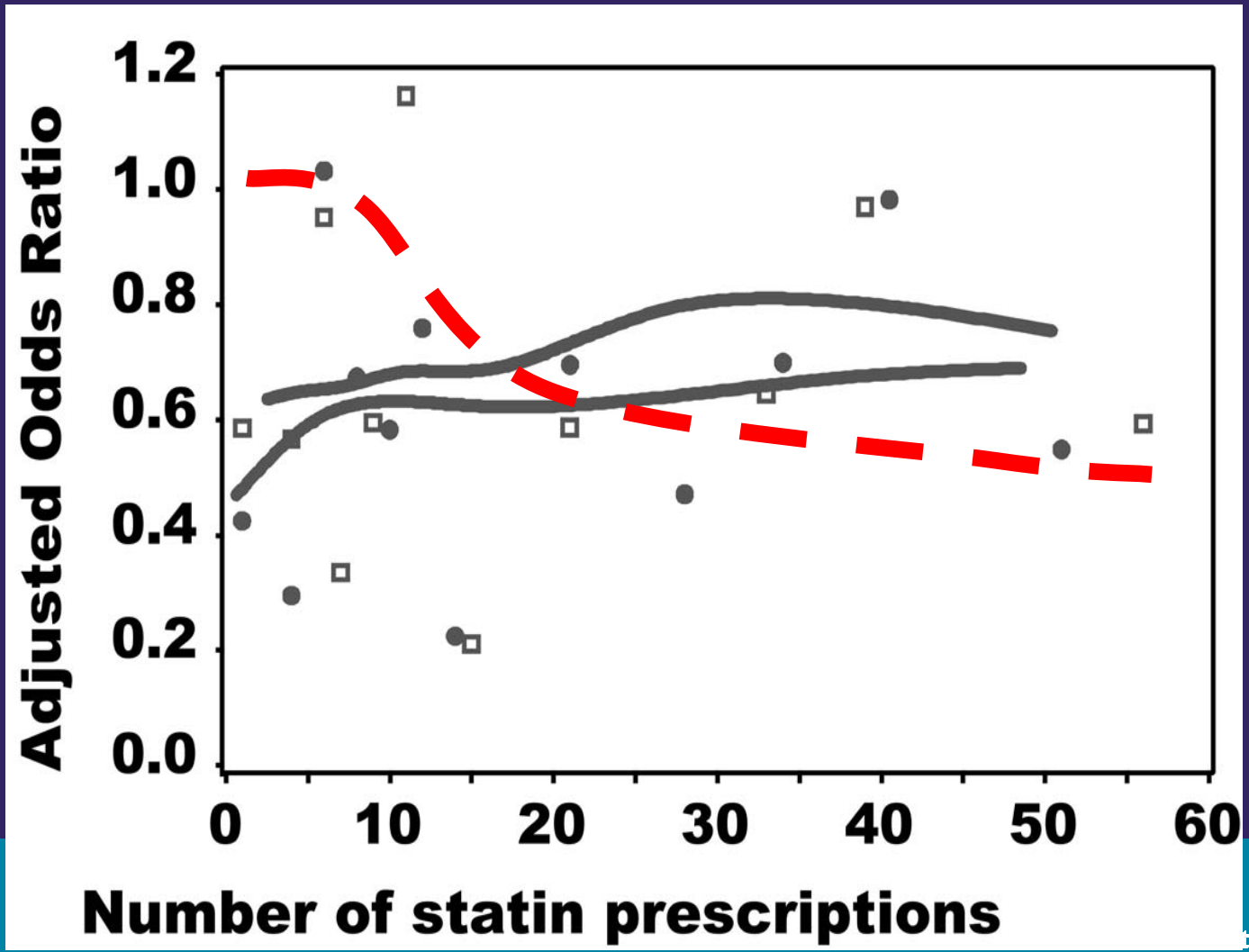
  from 0.48 (0.34-0.68) to 0.77 (0.58-1.02)

RISK OF FRACTURE AND STATINS

Systematic review [Toh S PDS 2007]

- Current evidence does not support an effect of statins in preventing fractures, due to
  - Lack of association in RCTs
  - Heterogeneity between epi studies
  - Potential residual confounding
  - Potential publication bias

Pattern of Hip fracture risk: Bias or Association?



- Squares: "selected" study design
- Dots: "entire population" study design
- Red line: expected shape

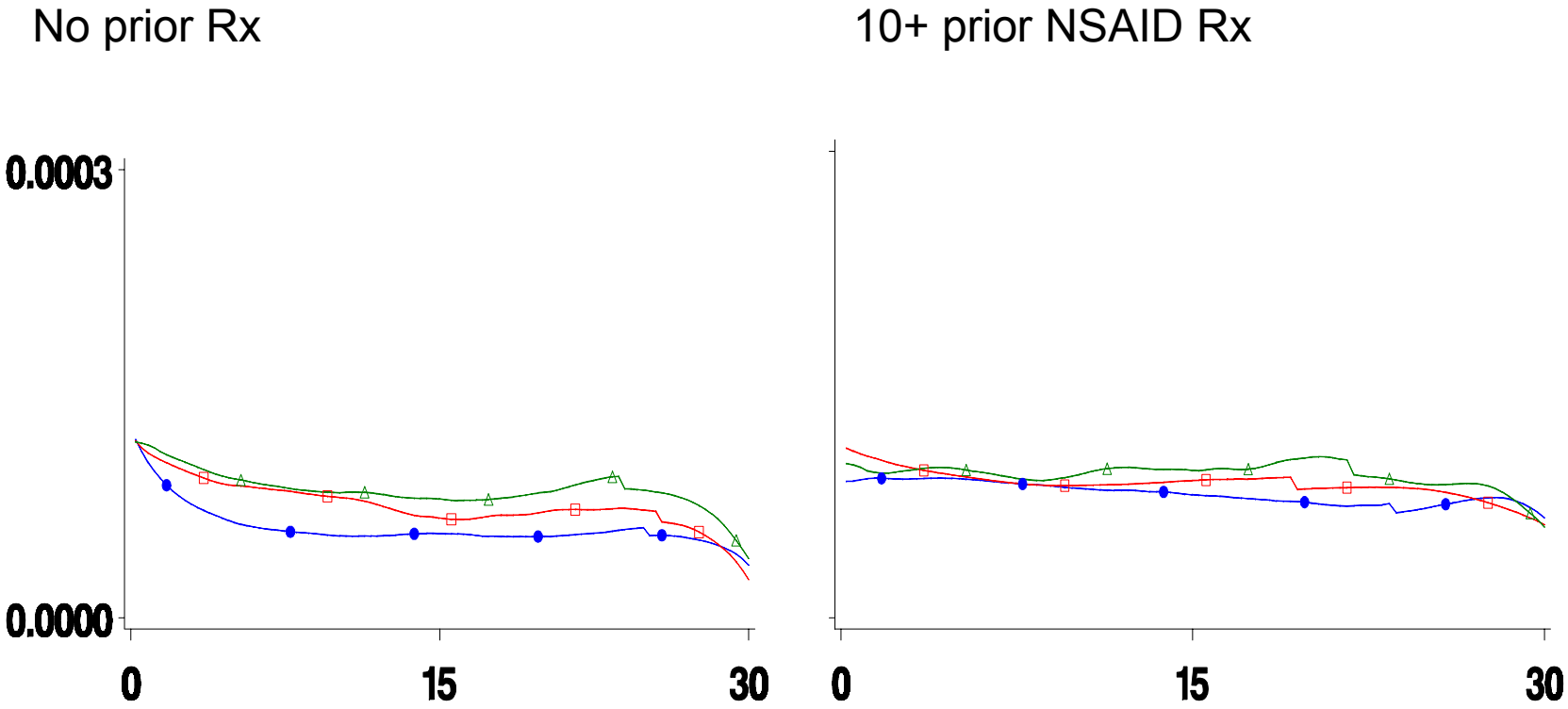
NSAIDs and Myocardial Infarction in GPRD

- Extensive use of rofecoxib, celecoxib, and diclofenac increases the risk of acute myocardial infarction, but similar use of ibuprofen and naproxen does not [Jick et al Pharmacotherapy 2006]
- The results suggest that the use of coxib and non-coxib COX-2 selective NSAIDs was associated with an elevated risk of AMI within the first month of exposure. [Hammad et al PDS 2008]
- Long-term users of traditional NSAIDs have an increased risk of MI that is probably explained by the underlying disease severity. Most of the differences in MI risk between diclofenac, ibuprofen or naproxen may be explained by their varied use [van Staa et al J Intern Med 2008]

NSAIDs and Myocardial Infarction in GPRD

[van Staa 2008]

Hazard rate

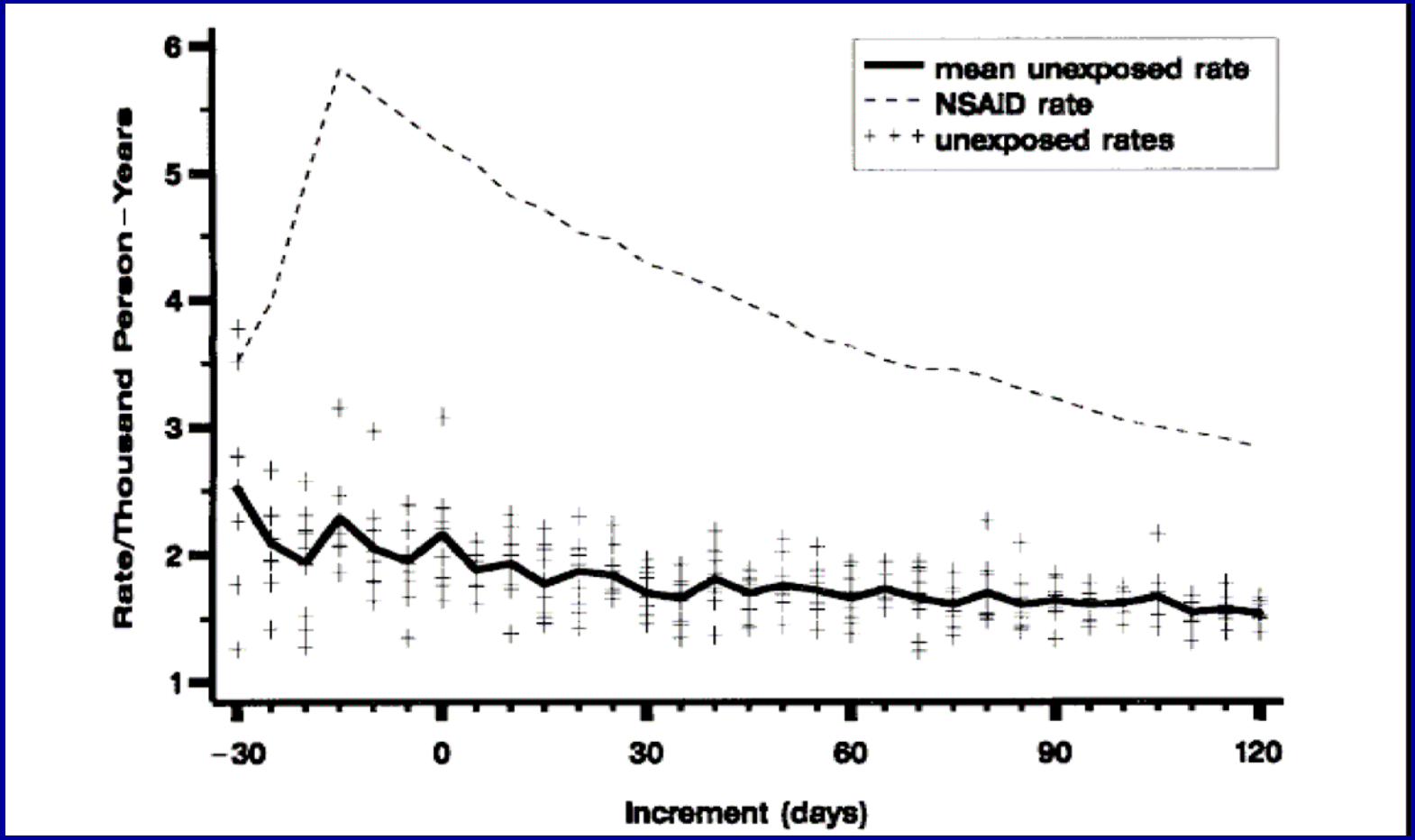


Patient exclusion in pharmacoepidemiology

- Important differences between investigators in application of exclusion criteria (Perrio et al 2006)
- Use of case validation procedure (range 7-74%) or disease-related exclusions (0-81%)

- Case-validation / confirmation (based on non-routine information): only for cases and not for controls => always correct?

Definition of time-window of exposure



McMahon Pharmacoepi 1998

The ‘highest’ level of evidence can surely not produce discrepant results….or can it?

- RCT – Women Health Initiative:
  - Conclusion [NEJM 2003]: hormone therapy may *increase* the risk of CHD
  - Conclusion [JAMA 2007]: women who initiated hormone therapy closer to menopause tended to have *reduced* CHD risk

- Meta-analysis of RCTs

RCT population ≠ population in actual clinical practice [Setakis A&R 2008]

	RCT rofecoxib	GPRD rofecoxib (N=72,096)	RCT celecoxib	GPRD celecoxib (N=67,346)
Indication				
Osteoarthritis	0%	35.0%	72.7%	35.5%
Rheumatoid arthritis	100%	4.8%	27.3%	4.8%
Other	0%	61.8%	0%	61.4%
Daily dose (mean)	50 mg	22 mg	800 mg	224 mg
Percentage of patients with continuous Cox-2 use	71% (11 months)	17% (11 months)	57% (6 months)	24% (6 months)
Rate of upper GI events	2.1	0.7	2.2	0.5
Rate of MI	0.7	0.7	0.7	0.6

Possible reasons for discrepant results (in general)

- Competent versus incompetent researchers? NO!
- Weaker associations / heterogeneous populations in presence of confounding
- ‘Scratch the surface’ – partial picture
- Programming errors
- Investigator choices (e.g. case exclusions, exposure time-window, patient selection)
- Changes in database structure or population
- Differences in medical practice, coding etc

Conclusions

- More guidelines, forms, committees and SOPs? => NO!
- In analysis: '*peel an onion*' rather than '*bungee jump*'
- '*Torture-test*' analyses ('last is best' rather than 'first is best')
- '*Learn-retest*' approach across databases rather than rigid uniform protocol
- We should cherish replication and heterogeneity!

"The data are the object of inquiry rather than the character and intelligence of those who generate it……individuals of highest intelligence can generate flawed information and those of limited talent can stumble into trustworthy findings" (Savitz – epi evidence)