Use of Meta-Analyses to Combine Multiple Results in Same Query

Christopher H Schmid, PhD
Professor of Medicine, Tufts University
Director, Biostatistics Research Center,Tufts Medical Center

Statistical and Epidemiological Issues in Active Medical Product Surveillance

The Brookings Institution • Washington, DC

February 16, 2011

Drug Safety Meta-Analysis

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2011; **20**: 119–130
Published online 7 December 2010 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.2046

ORIGINAL REPORT

Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data

Johan Askling[1]*, Kyle Fahrbach[2], Beth Nordstrom[2], Susan Ross[2], Christopher H. Schmid[3] and Deborah Symmons[4]

[1]*Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden*
[2]*United BioSource Corporation, Lexington, MA, USA*
[3]*Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, MA, USA*
[4]*ARC Epidemiology Unit, University of Manchester, UK*

Drug Safety MA: Eligibility

- All placebo or standard-care controlled trials of TNF-α inhibitors
  - Adalimumab
  - Etanercept
  - infliximab
- Sponsored by Abbott, Amgen/Wyeth, Centocor/Schering-Plough, or other corporate sponsors of same products

Drug Safety MA: Data

- For each trial, sponsor created patient-level dataset including
  - ***Study data***
    - condition, agent, control, location, exclusion, pre-trial work-up
  - ***Patient data***
    - gender, age, disease duration, prior and concomitant therapy
  - ***Treatment data***
    - time and doses of study drug, duration of intended and actual treatment, date and reasons for withdrawal, and date of last patient contact
  - ***Outcomes***
    - adjudicated events with person-time and narratives

Drug Safety MA: Statistical Analysis

- Hazard ratios from piecewise exponential Bayesian model
- Models for class effects and drug-specific effects
- Assessed differences in baseline risk stratified by type of drug trial
- Models adjusted for age, gender, concurrent treatment, condition and disease duration
- Stratification by trial not possible because of rare events

Drug Safety MA: Follow-Up

Table 1. Number of patients and person-years of follow-up in the meta-analysis, by drug, by treatment (Tx) and control (cont) arm, and by time since trial start

	Adalimumab		Etanercept		Infliximab		All Anti-TNF	
	Tx	Cont	Tx	Cont	Tx	Cont	Tx	Con
All trials								
N patients	4709	2646	6153	3063	4544	1769	15 406	7478
N person-years	2861	1466	4404	2073	2431	862	9696	4401
N patients at risk by time since trial start (months)								
0	4709 (100%)	2646 (100%)	6153 (100%)	3063 (100%)	4544 100%)	1769 (100%)	15406 (100%)	7478 (100%)
1	4703 (100%)	2644 (100%)	5920 (96%)	2946 (96%)	4249 (94%)	1611 (91%)	14872 (97%)	7201 (96%)
3	4085 (87%)	2173 (82%)	4962 (81%)	2659 (87%)	3969 (87%)	1422 (80%)	13016 (84%)	6254 (84%)
6	2300 (49%)	1095 (41%)	2230 (36%)	1102 (36%)	2195 (48%)	745 (42%)	6725 (44%)	2942 (39%)
12	818 (20%)	384 (15%)	1352 (22%)	575 (19%)	312 (7%)	67 (4%)	2482 (16%)	1026 (14%)
18	393 (17%)	183 (6.9%)	958 (16%)	396 (13%)	0 (0%)	1 (0.06%)	1351 (8.8%)	580 (8%)
Primary use conditions								
N patients	4709	2646	4570	2248	3576	1289	12 855	6183
N person-years	2859	1465	3275	1494	1953	650	8088	3608

Primary use conditions were defined as rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, and Crohn's disease.

- Most follow-up short-term

Drug Safety MA: Counts

Table 2. Counts (numbers and %) of cancer events including non-melanoma skin cancer by outcome definition, by drug, by treatment (Tx) and control (cont) arm for all trials

	Adalimumab		Etanercept		Infliximab		All Anti-TNF	
	Tx	Cont	Tx	Cont	Tx	Cont	Tx	Cont
Patients	4709 (100%)	2646 (100%)	6156 (100%)	3069 (100%)	4553 (100%)	1771 (100%)	15 418 (100%)	7486 (100%)
Flagged events	270 (5.73)	127 (4.80)	306 (4.97)	158 (5.15)	196 (4.30)	48 (2.71)	772 (5.01)	333 (4.45)
Adjudicated events	97 (2.06)	30 (1.13)	130 (2.11)	63 (2.05)	57 (1.25)	13 (0.73)	284 (1.84)	106 (1.42)
Outcome A*	41 (0.87)	15 (0.57)	57 (0.93)	25 (0.81)	32 (0.70)	8 (0.45)	130 (0.84)	48 (0.64)
Outcome B†	29 (0.62)	12 (0.45)	45 (0.73)	24 (0.78)	20 (0.44)	6 (0.34)	94 (0.61)	42 (0.56)
Outcome C‡	17 (0.36)	2 (0.08)	29 (0.47)	16 (0.52)	13 (0.28)	2 (0.11)	59 (0.38)	20 (0.27)

*Outcome A was defined as all cancer events (definite or probable cancers) diagnosed during the study period, using the date of diagnosis as the event date, irrespective of judgments on pre-trial prevalence.
†Outcome B was defined as all cancer events (definite or probable cancers) diagnosed during the study period, but excluding events in retrospect judged definitely prevalent on the basis of a first reported date of sign or symptom pre-dating the trial.
‡Outcome C was defined as all cancer events (definite or probable cancers) diagnosed during the study period, excluding both events with a first reported date of sign or symptom before the study period, *and* events which for other reasons were judged by the oncologists to be *probably* prevalent at trial start.

- Number of events sensitive to definitions
- Small once strict criteria applied

Drug Safety MA: Choice of Priors

- Initial vague priors on model parameters
- Because several control arms had < 3 events, data did not provide sufficient information to accurately estimate posterior distributions with no prior information
- Three weakly informative priors imposed weak restrictions on size of treatment effect
- Because this is a safety study, priors 1 and 3 conservatively assumed prior increased risk in treatment compared with control

	Mean HR	95% PI	Risk Increase with Tx	Precise
1	2.0	0.04-110	Yes	No
2	1.0	0.02-55	No	No
3	2.0	0.5-8.2	Yes	Somewhat

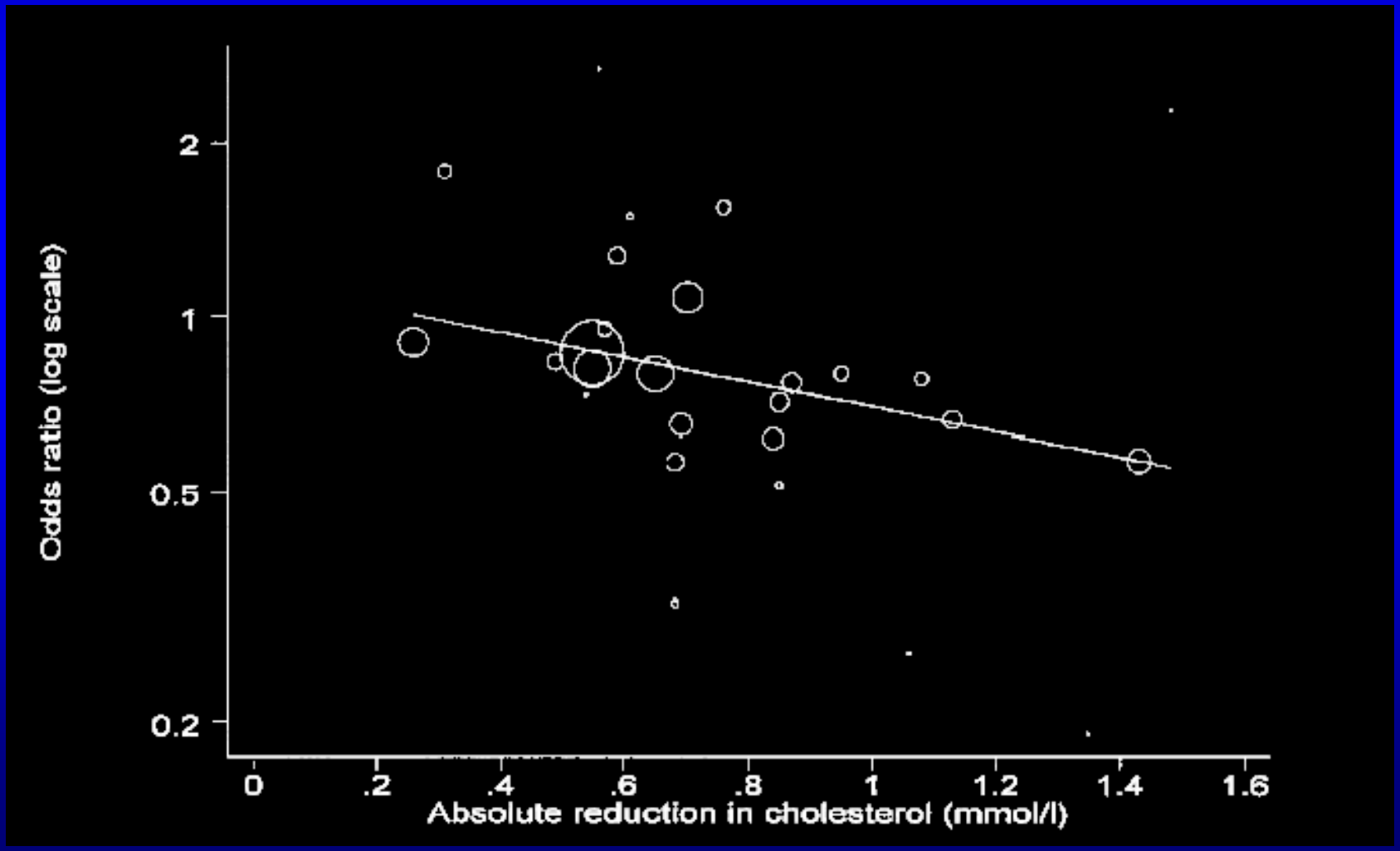
Meta-Regression

- Regression analysis to identify correlations between treatment effects (outcomes) and covariates of interest (predictors)
- Unit of analysis is the individual study
- Correlation implies treatment interaction
- Factors may be study-level or subject-level
- Study-level factors: blinding, randomization, dosage, protocol
- Subject-level factors: age, gender, race, blood pressure

$$\theta_i = \beta_0 + \beta_i X_{i1} + \beta_2 X_{i2} + \ldots + u_i$$

Meta-Regression with Study-Level Summary of Patient Level Covariates

- Data points proportional to study size
- Line is meta-regression



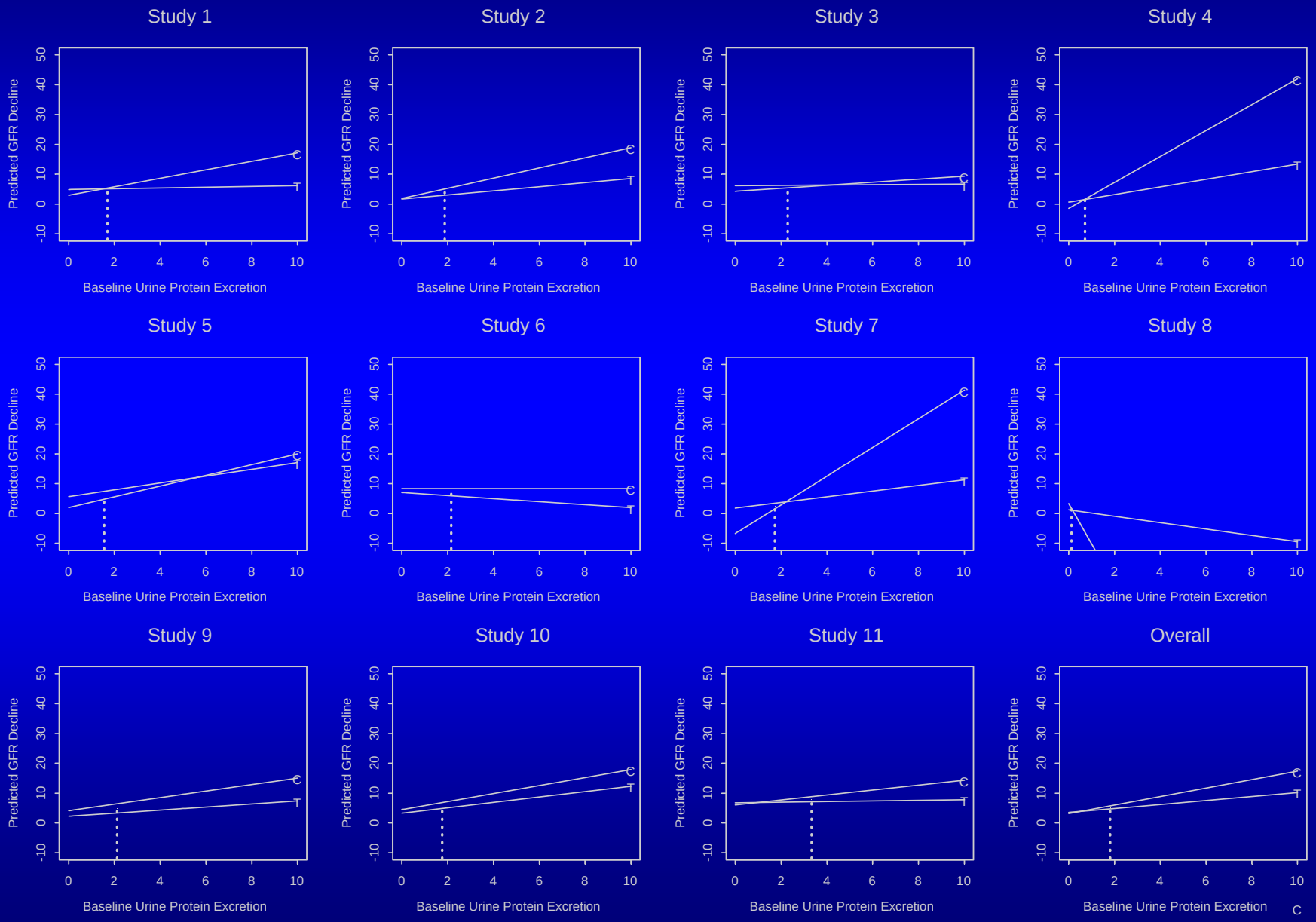
Problems with Meta-Regression

- Requires heterogeneity of treatment effects
- Number of studies usually small
- Data may be unavailable (not conceived or not reported)
- Covariates pre-selected (biased?)
- Little variation in range of mean predictor
- Subject-level factors can be affected by ecological bias
- Causality uncertain

Ecological Bias

- Group averages don't represent individuals well
  - Changes in male/female mixture proportions vs. comparing individual males and females
  - Low SES subjects might perform worse than high SES ones but clinics with low SES patients might do better because of targeted intervention experience with these patients
- Averages have little between-study variation
- Averages do not account for within-study variation, e.g., 40 year average age can mean different things
- Events concentrated in high-risk subgroup
  - May want to construct group-level variable to represent this
    E.g., percentage of elderly, rather than mean age

Within-Study Interaction



Conclusions

- Rare events are a major feature of safety data
- Bayesian models with informative priors may be needed to overcome lack of data
- In Phase IV type observational studies, need to carefully control for potential heterogeneity introduced by lack of experimental design
- Lack of explicit balancing mechanism between treatment and control groups requires adjustment for confounding
- Meta-regression may allow discovery of factors that change treatment effects
- When adjusting for group effects, beware of ecological bias