META-ANALYSIS OF OBSERVATIONAL STUDIES

Olaf Dekkers/Sønderborg/2016

Observational studies

- > 90% of all studies are observational

- Scope:
  - Study of risk factors
  - Rare side effects
  - Genetic factors
  - Prognosis
  - Therapeutic effects

Issues to consider

- Research question
- Study search/study inclusion
- Data extraction
- Risk of bias
  - SR of side effects
- To pool or not to pool
- (Data synthesis)

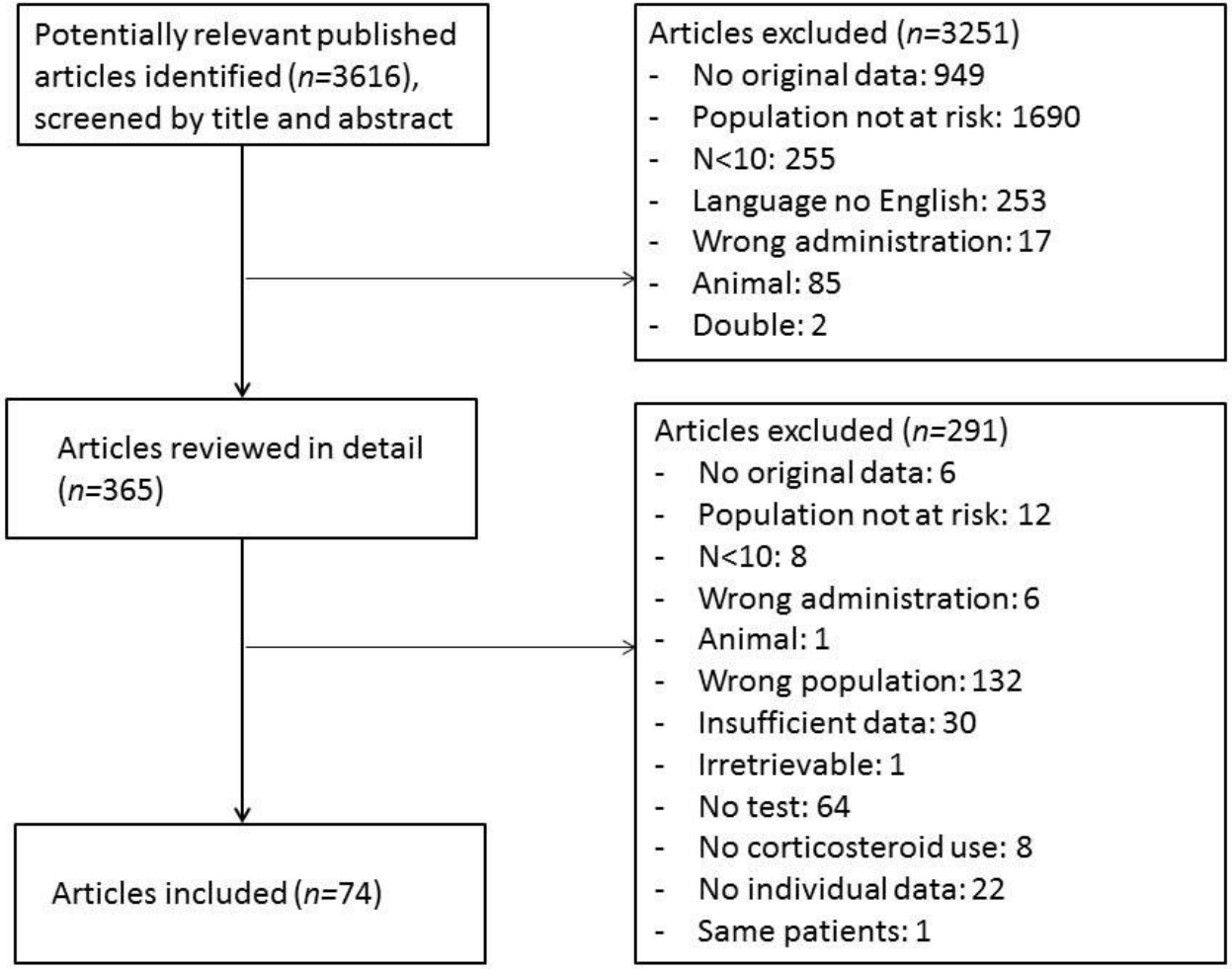
Research question

- Generally more broad (population broadly defined)
  - Relationship IGF-1 and mortality
  - Alcohol consumption and breast cancer risk
  - Obesity and cancer risk
  - Association between genetic factor X and outcome Y

Study search

- Signal to noise ratio unfavourable
  - Research question rather broad
  - No well-working index terms for observational studies
  - Observational studies often incorrectly indexed

Results: Flow chart



Indexing observational studies

- Case control studies are mislabeled in 20-30%
- Unstandardized labeling:
  - Retrospective noncomparative interventional case series
  - Prospective consecutive case series
- ***Study structure is more important than the labeling***

An example

- Aim: SR and MA
- Research question: how often does adenomyosis recur after treatment?
- Studies to be included: cohort studies

- Question: would you include case series?
  - What about a case series of 5 patients?
  - What about a case series of 104 patients?

Dekkers, Ann Int Med, Jan 2012

Data extraction

- 1. Which estimate to extract?
- 2. What to do with multiple categories?

An example

Tertiles	Difference in cIMT (μm)[a]			
	Crude (95% CI)	Model 1 (95% CI)	Model 2a/b/c (95% CI)	Model 3a/b (95% CI)
FPG (mmol/L)			Model 2a	Model 3a
<5.1 (reference)	–	–	–	–
5.1–5.5	26 (17, 35)	18 (10, 27)	17 (8, 25)	13 (4, 21)
>5.5	43 (35, 51)	24 (16, 32)	19 (11, 28)	11 (3, 19)
HbA_{1c} (%Hb)			Model 2a	Model 3a
<5.2 (reference)	–	–	–	–
5.2–5.4	16 (7, 25)	8 (0, 17)	7 (−1, 15)	5 (−3, 13)
>5.4	31 (22, 39)	16 (8, 24)	12 (3, 20)	4 (−4, 13)

Model 1: Adjusted for age, sex, ethnicity, education, and tobacco smoking.
Model 2a: Adjusted for model 1 plus HOMA-IR.
Model 2b: Adjusted for model 1 plus HbA_{1c} and FPG.
Model 2c: Adjusted for model 1 plus HOMA-IR, HbA_{1c}, and FPG.
Model 3a: Adjusted for model 2a plus waist circumference and BMI.

Gast, Atherosclerosis 2013;229

Risk of bias in RCT's vs observational studies

Scope for observational studies

Observational 'questions'

- Study of risk factors
- Rare side effects
- Genetic factors
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Risk of bias in RCTs

- Sequence generation
- Allocation concealment
- Blinding
- Incomplete outcome data
- Selective outcome reporting

Risk of bias in observational studies

Observational studies

Risk of bias in RCTs

confounding

- Sequence generation
- Allocation concealment

bias

- Blinding
- Incomplete outcome data
- Selective outcome reporting

Risk of bias in observational studies

=

Assessment of risk of bias and confounding of included studies

Risk of bias in observational studies

Assessment of risk of bias and confounding

However:

1. There is few empirical evidence for design elements causing risk of bias in observational studies
2. There is no generally accepted way to do it for etiologic research
3. There is recently published guidance on how to do a risk of bias analysis for interventions (ROBINS-I)
4. Risk of bias assessment should be tailor made

Assessment of risk of bias

Risk of bias assessment

- ***Domain based approach:***

- Incomparable groups
  - Confounding
- Inadequate exposure and outcome measurement
  - Information bias
- Inadequate selection of participants
  - Selection bias (Immortal time, Incidence-pervalence bias)
- Bias due to missing data
- Reporting bias
  - Selective reporting

IGF-1 and mortality: meta-analysis

- Association IGF-1 and mortality
- Restriction: population based cohort studies

- What design elements could cause bias?

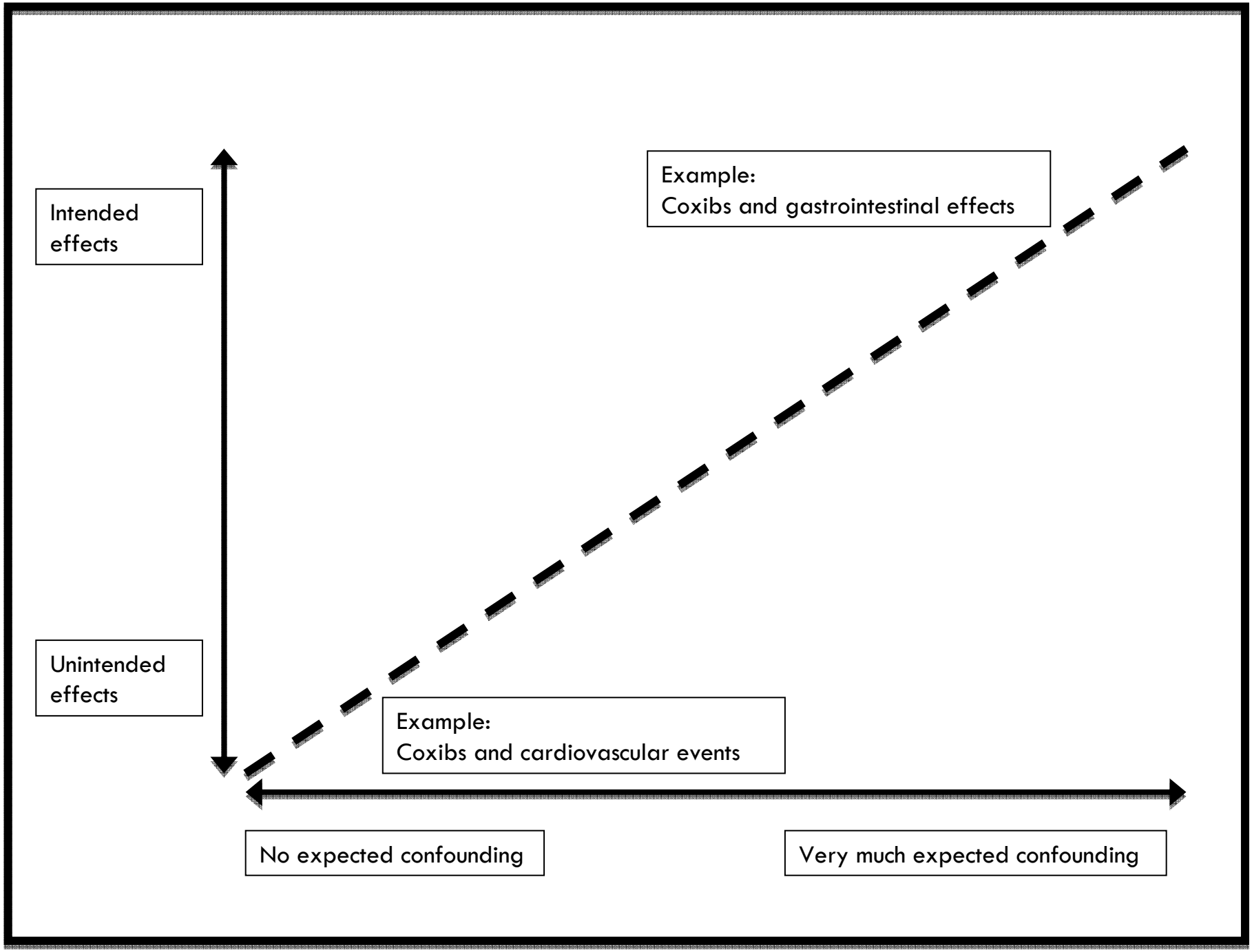
Risk of bias table

TABLE 2. Exposure measurement, follow-up, and endpoint ascertainment

First author, year	IGF-I assay (company)	Follow up	Endpoint ascertainment	Adjustments in analyses
Friedrich, 2009	CIA (Nichols)	Complete	Local health authority	Waist circumference
Arai, 2008	RIA (SRL Ltd.)	2.3% missing	Telephone contact	BMI, smoking, comorbidities
Andreassen, 2009	ELISA (R&D Systems)	Complete	NDI	Smoking, diabetes, AF
Brugts, 2008	RIA (Mediagnost)	Complete	Contact GP	BMI, smoking, diabetes
Kaplan, 2008	ELISA (DSL)	Complete	NDI	BMI, smoking
Maggio, 2007	IRMA (DSL)	Complete	Mortality registry	BMI, smoking, comorbidities
Cappola, 2003	RIA (Nichols)	Complete	NDI	BMI, smoking, comorbidities
Saydah, 2007	ELISA (DSL)	5 persons missing	NDI	BMI, smoking
Kaplan, 2007	ELISA (DSL)	2% missing	NDI	Smoking
Major, 2010	RIA (Nichols)	Complete	Mailed questionnaires	Waist-hip ratio, smoking
Van Bunderen, 2010	IRMA (DSL)	Complete	NDI, death certificates	BMI, smoking, diabetes
Pham, 2010	IRMA (Daiichi)	Complete	Death certificates	BMI, smoking

Risk of bias: confounding

- Crucial in observational studies
- Confounding can be a matter of degree
  - Examples
    - Vegetarian diet and mortality
    - Gene polymorphism and mortality
- Judgement requires subject-matter knowledge


Intended effects
Unintended effects
Example:
Coxibs and gastrointestinal effects
Example:
Coxibs and cardiovascular events
No expected confounding
Very much expected confounding

EuroIntervention

Favourable effect of statin therapy on early survival at the time of percutaneous coronary intervention for ST-elevation myocardial infarction and shock

Garot EuroIntervention 2010;6:350-355

Confounding

- Identification of confounding factors requires subject matter knowledge
- Defining confounders differs per research question

- This determines which effect-estimate is to be extracted
- This determines whether confounding is adequately dealt with

Confounding

" There is a scientific consequence to the potential confounding in observational studies. Suppose you conducted an observational study to identify the effect of heart transplant on death and that you assumed no unmeasured confounding given disease severity. A critic of your study says "the inferences from this observational study may be incorrect because of potential confounding." The critic is not making a scientific statement, but a logical one. Since the findings from any observational study may be confounded, it is obviously true that those of your study can be confounded. If the critic's intent was to provide evidence about the shortcomings of your particular study, he failed. His criticism is completely noninformative because he simply restated a characteristic of observational research that you (and apparently he) already knew before the study was conducted.

To appropriately criticize your study, the critic needs to work harder and engage in a truly scientific conversation."

Cf: Hernan and Robins *Causal Inference*

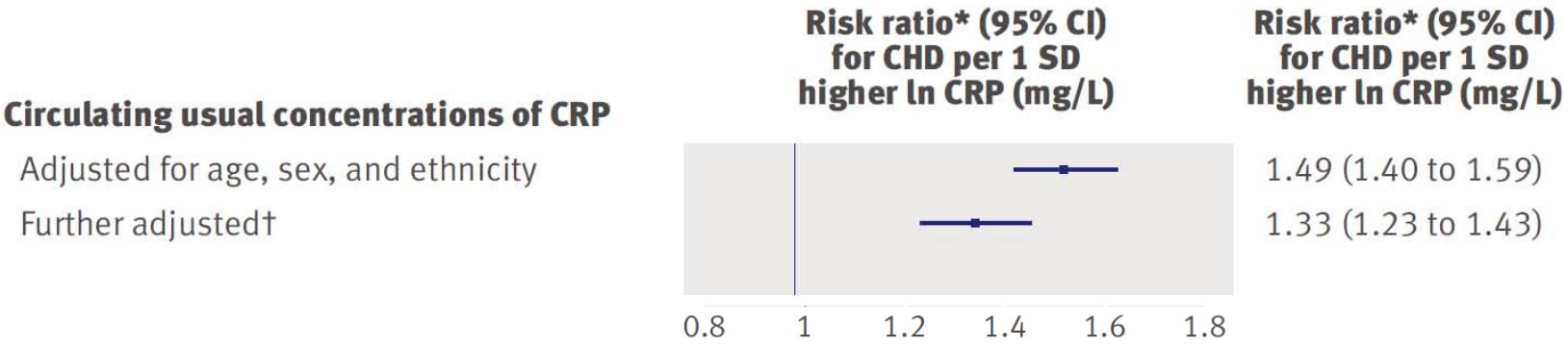
Risk of bias: confounding

- Think about the ideal adjusted effect estimate from an ideal study (target trial)

- Think about the ideal study

  - CRP and myocardial infarction
  - Sport and venous thrombosis
  - Flu vaccination

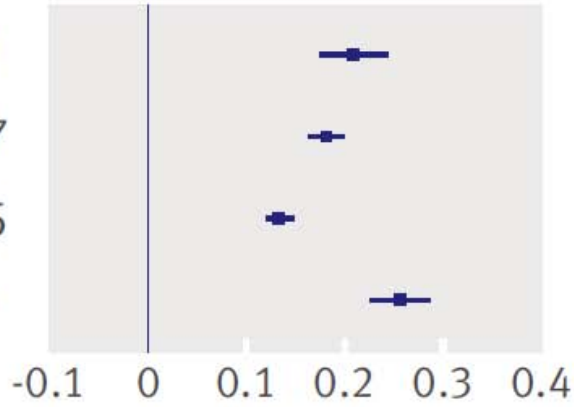
CRP and CV disease



BMJ 2011

Polymorphisms affecting CRP

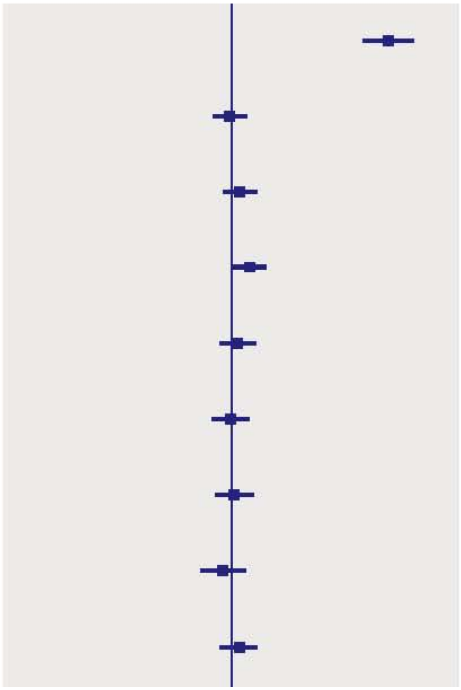
Single nucleotide polymorphism	Allele frequency*	No of studies/cases /participants†	Per allele higher mean ln CRP (95% CI), mg/L
rs3093077	0.06	19/15 133/96 807	
rs1205	0.67	43/40 527/172 567	
rs1130864	0.30	41/37 145/157 905	
rs1800947	0.94	31/31 636/93 507	



BMJ 2011

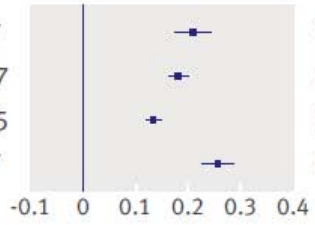
Polymorphism (rs3093077) and other CV risk factors

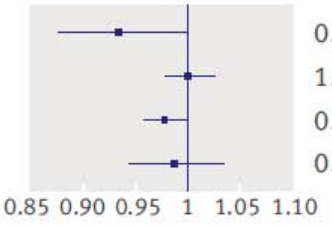
Variable	No of studies/ participants	P value	SD (95% CI) change in biomarker per allele change in SNP
Ln C reactive protein (mg/L)	15/70 117	5.44×10^{-35}	
Age at survey (years)	18/81 648	0.83	
BMI (kg/m^2)	16/73 663	0.34	
Systolic BP (mm Hg)	16/74 309	0.04	
Diastolic BP (mm Hg)	16/74 292	0.46	
Total cholesterol (mmol/L)	16/72 938	0.91	
Non-HDL cholesterol (mmol/L)	16/70 969	0.71	
HDL cholesterol (mmol/L)	16/70 971	0.44	
Ln triglycerides (mmol/L)	16/70 476	0.42	



Polymorphisms affecting CRP

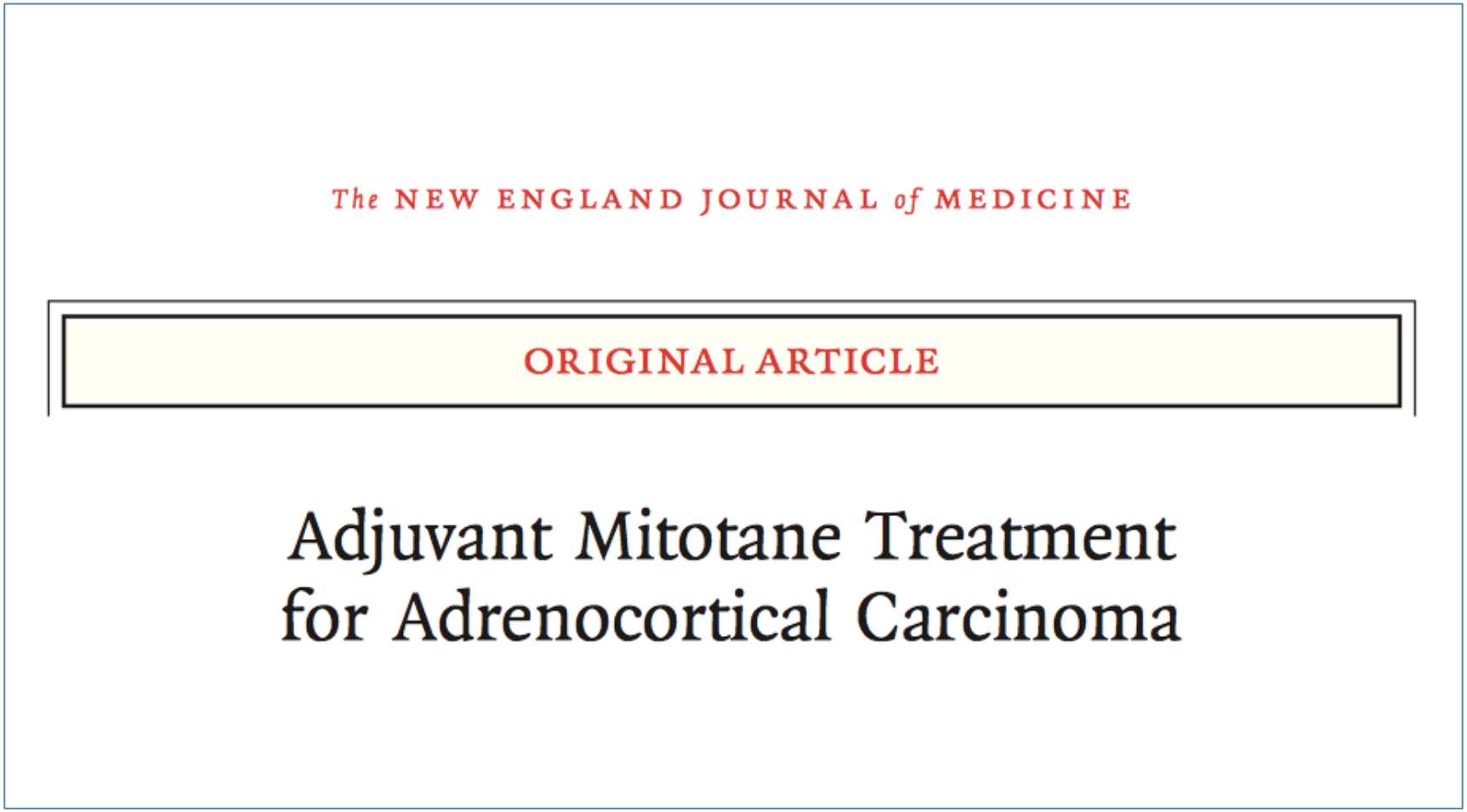
Single nucleotide polymorphism	Allele frequency*	No of studies/cases /participants†	Per allele higher mean ln CRP (95% CI), mg/L	Per allele higher mean ln CRP (95% CI), mg/L	Per allele risk ratio for CHD (95% CI)	Per allele risk ratio for CHD (95% CI)
rs3093077	0.06	19/15 133/96 807		0.21 (0.17 to 0.24)		0.93 (0.87 to 1.00)
rs1205	0.67	43/40 527/172 567		0.18 (0.16 to 0.20)		1.00 (0.98 to 1.02)
rs1130864	0.30	41/37 145/157 905		0.13 (0.12 to 0.15)		0.98 (0.96 to 1.00)
rs1800947	0.94	31/31 636/93 507		0.26 (0.23 to 0.29)		0.99 (0.94 to 1.03)





BMJ 2011

Risk of bias: example of selection bias



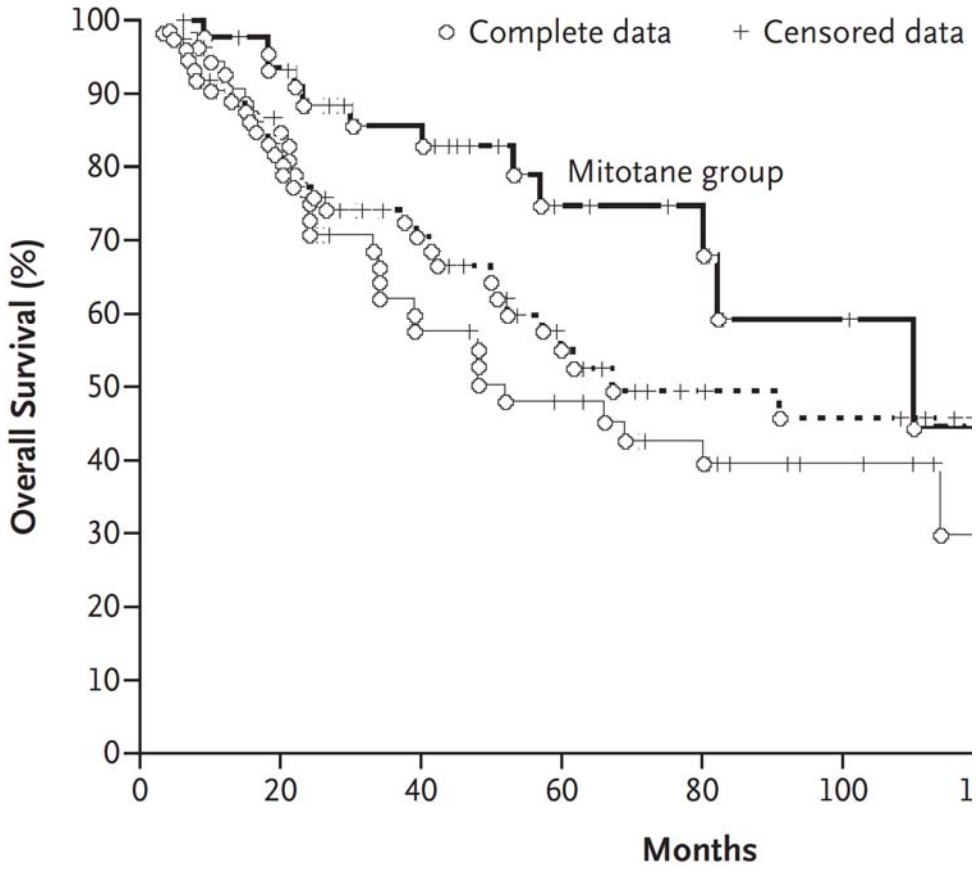
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Mitotane Treatment for Adrenocortical Carcinoma

Terzolo NEJM 2007

Risk of bias: example of selection bias



Terzolo NEJM 2007

Risk of bias: how to deal with it

- Overall judgement per study
  - The study is judged to be low/moderate/high/crucial risk of bias in at least one domain
- Restriction
  - Compare SR of interventions: often restricted to RCTs
- Use to explore heterogeneity in sensitivity analysis
- Meta-regression

Randomised vs non-randomised studies

What about side-effects?

Randomisation

- Randomisation
  - Treatment allocation based on prognosis
  - *Expected* exchangeability
  - Baseline differences due to chance

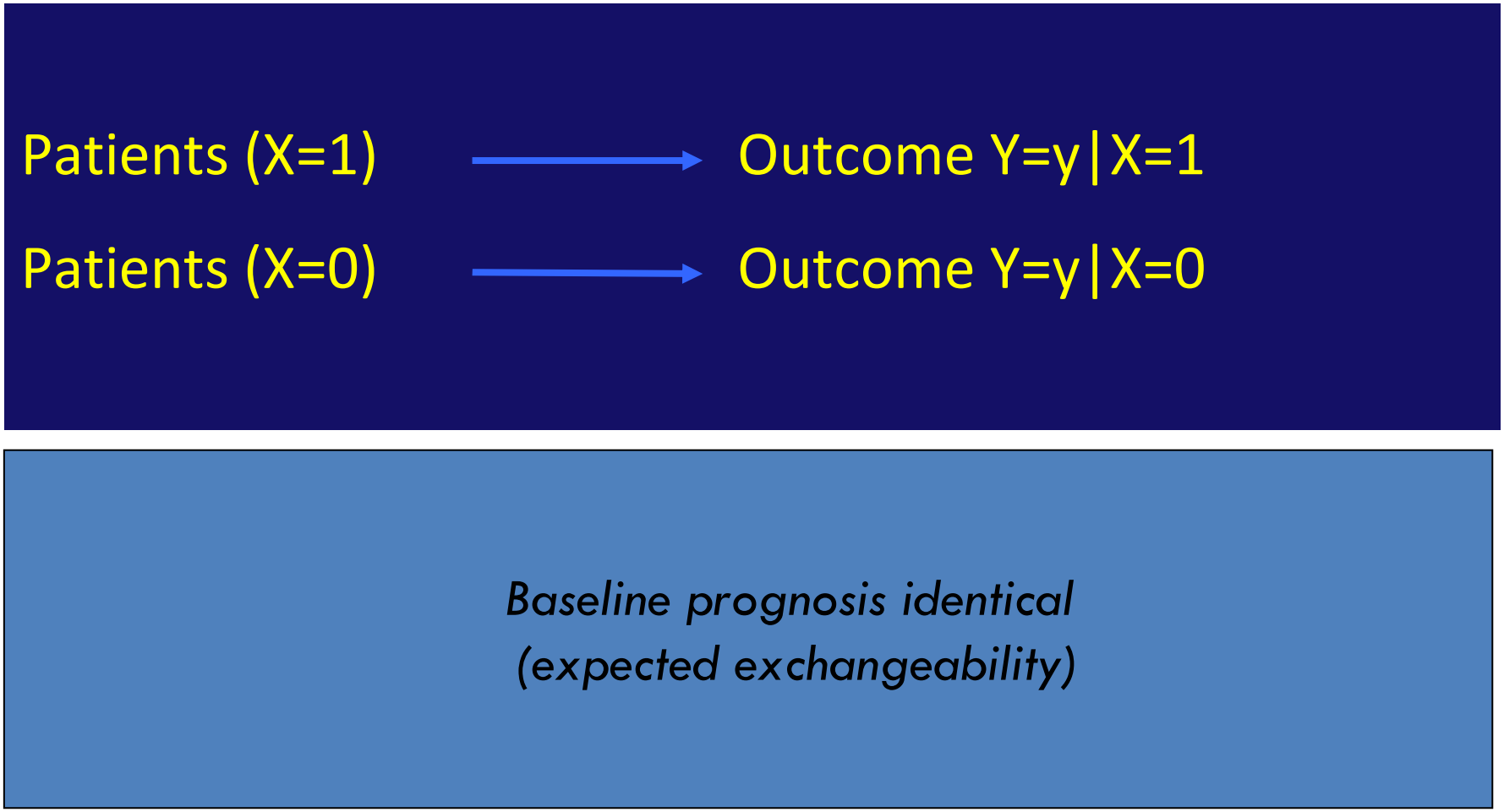
Randomisation

Randomisation

Lifestyle factors

Tooth decay

Randomisation



Dicing

- Two dices. ‘What is the probability of throwing ’11’?’
  - Determine the probability before the two dices are thrown
  - Determine the probability after the two dices have been thrown

Chance: prior vs posterior probabilities

- Prior probability '11' = 1/18
- Posterior probability: 0 or 1

- Prior: there are different possibilities
- Posterior: one of the possibilities has become actual

- Analogous to randomisation and exchangeability:
  - Prior to randomisation you expect exchangeability
  - After randomisation: there or there is not exchangeability

Table 1

Table 1. Demographic and Clinical Characteristics of the Patients at Diagnosis and Randomization.*

Characteristic	Azathioprine Group (N=63)	Methotrexate Group (N=63)	P Value
Age at diagnosis — yr			
Mean	56.3±13.8	59.8±11.9	0.13
Range	21.6–79.2	25.2–78.6	
Sex — no. (%)			
Male	36 (57)	25 (40)	0.05
Female	27 (43)	38 (60)	0.05
Diagnosis — no. (%)			
Wegener's granulomatosis	48 (76)	48 (76)	1.00
Microscopic polyangiitis	15 (24)	15 (24)	1.00
Manifestations at diagnosis — no. (%)†			
Temperature >38.5°C (101.3°F)	40 (63)	33 (54)	0.29
Ear, nose, and throat involvement	47 (75)	47 (77)	0.75
Lung involvement	52 (83)	41 (67)	0.05
Alveolar hemorrhage	18 (29)	8 (13)	0.03

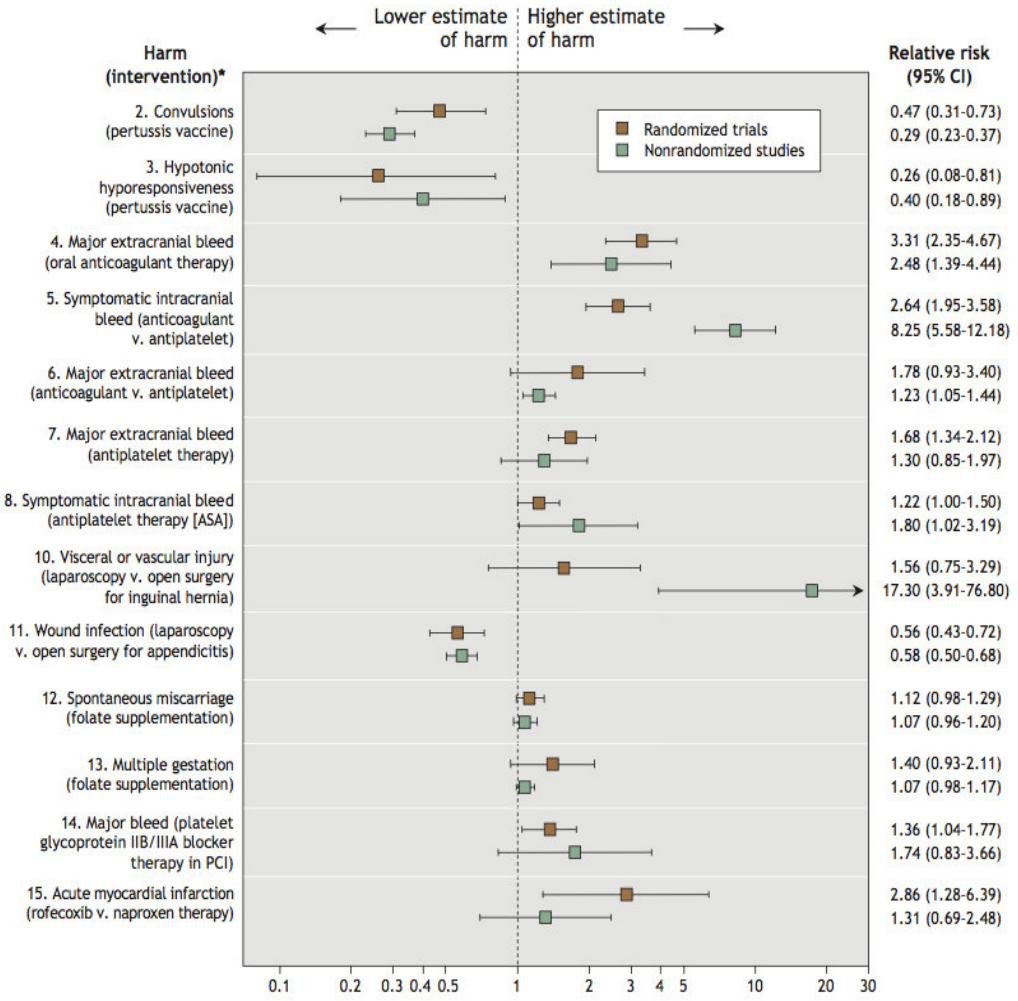
Randomisation

- Randomisation
  - Is about mechanism of allocation, not about the outcome of the allocation
  - Randomisation breaks the link between allocation and prognosis (*Ignorability*)
    - *Compare: observational studies*
  - Leads *in principle* to exchangeability
  - But differences at baseline can occur

Studies on side effects

- Studies on side-effects: ignorability?
- Groups to be compared are exchangeable in case of ignorability
- Examples:
  - Oral contraceptives and venous thrombosis
  - Antibiotics and rash

Side-effects



Papanikolau CMAJ 2006

Weights in meta-analysis of observational studies

Standard weights in meta-analysis

- According to precision
- $1/SE^2$

- Larger studies get more weight
  - Accounts for random error

Systematic error vs random error

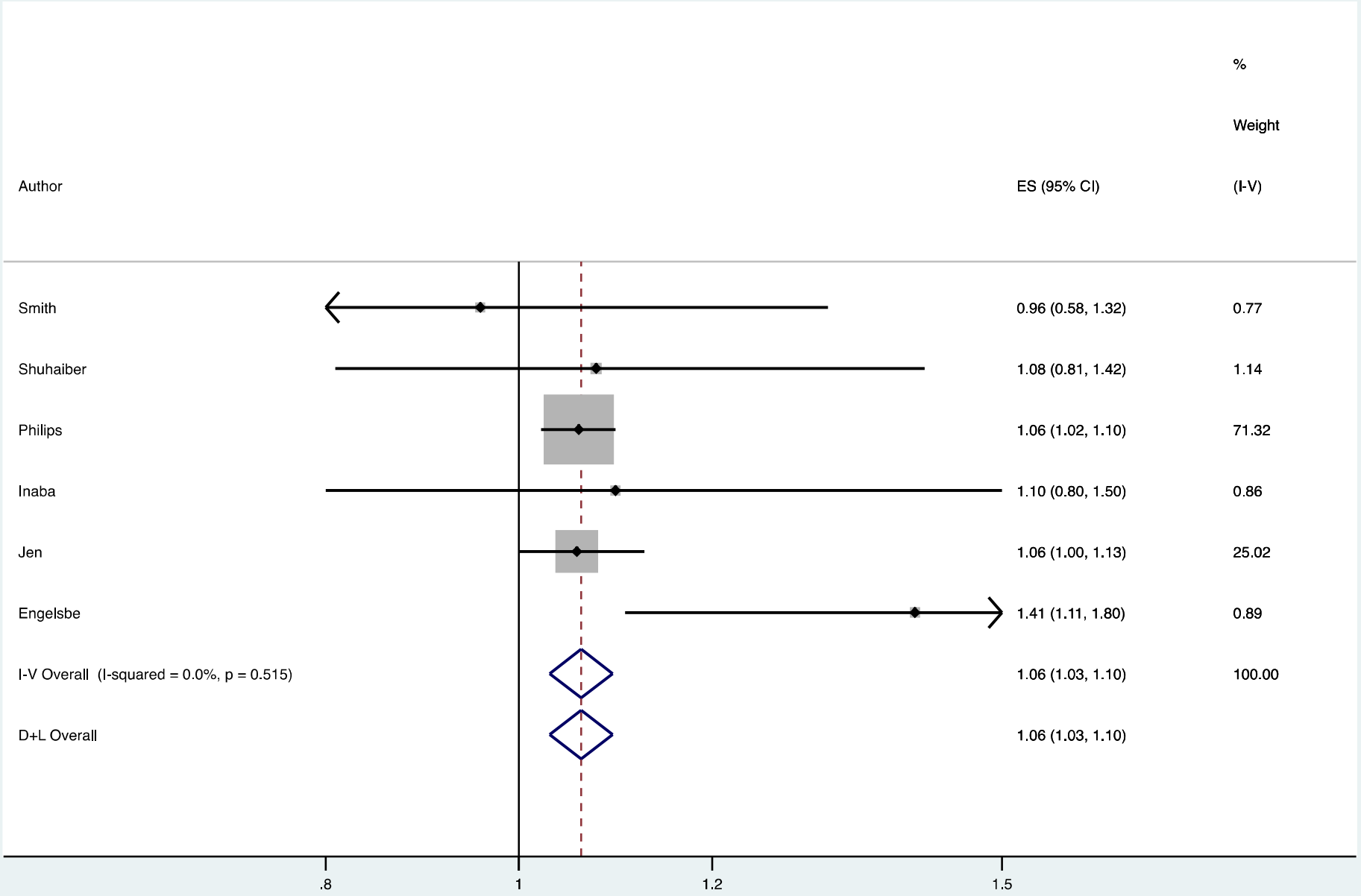
Annals of Internal Medicine | Review

"July Effect": Impact of the Academic Year-End Changeover on Patient Outcomes

A Systematic Review

John Q. Young, MD, MPP; Sumant R. Ranji, MD; Robert M. Wachter, MD; Connie M. Lee, MD; Brian Niehaus, MD; and Andrew D. Auerbach, MD, MPH

Young Ann int med 2011;155;5


Author
ES (95% CI)
%
Weight
(I-V)
Smith
0.96 (0.58, 1.32)
0.77
Shuhaiber
1.08 (0.81, 1.42)
1.14
Philips
1.06 (1.02, 1.10)
71.32
Inaba
1.10 (0.80, 1.50)
0.86
Jen
1.06 (1.00, 1.13)
25.02
Engelsbe
1.41 (1.11, 1.80)
0.89
I-V Overall (I-squared = 0.0%, p = 0.515)
1.06 (1.03, 1.10)
100.00
D+L Overall
1.06 (1.03, 1.10)
.8
1
1.2
1.5

Standard weighing in meta-analysis

- According to precision ($1/SE^2$)
- Larger studies get more weight
  - Accounts for random error
  - Clear rationale for RCTs
- But: this might introduce bias if larger studies are more biased
- No generally accepted solution

Conclusion

SR & MA of observational studies

I. Less standardized

II. Searches are less efficient

III. Assessment of risk of bias in observational studies depends on research questions and study design

IV. One study(design) might circumvent bias

V. Inverse variance weighing in observational meta-analysis can be questioned