Evidence-Based Decision Making In Healthcare

Rating Up the Quality of Evidence

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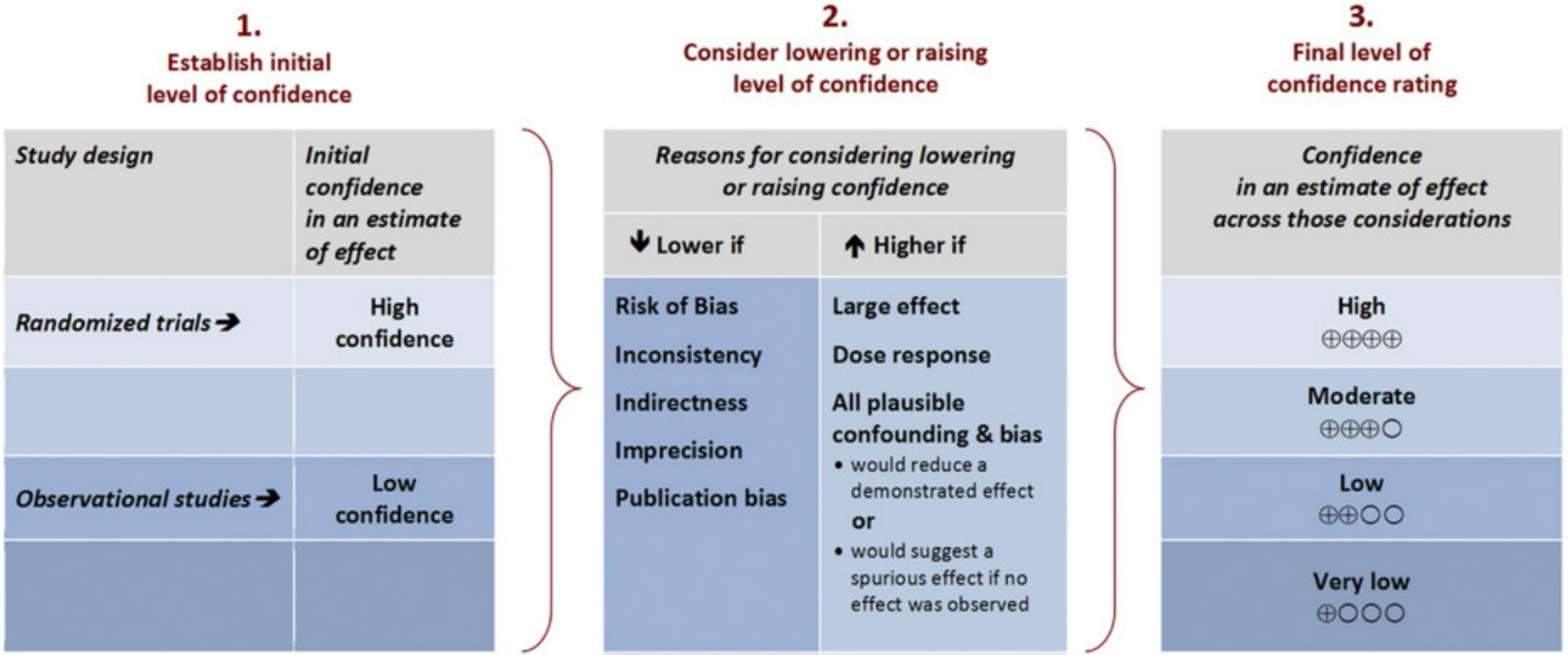
GRADE

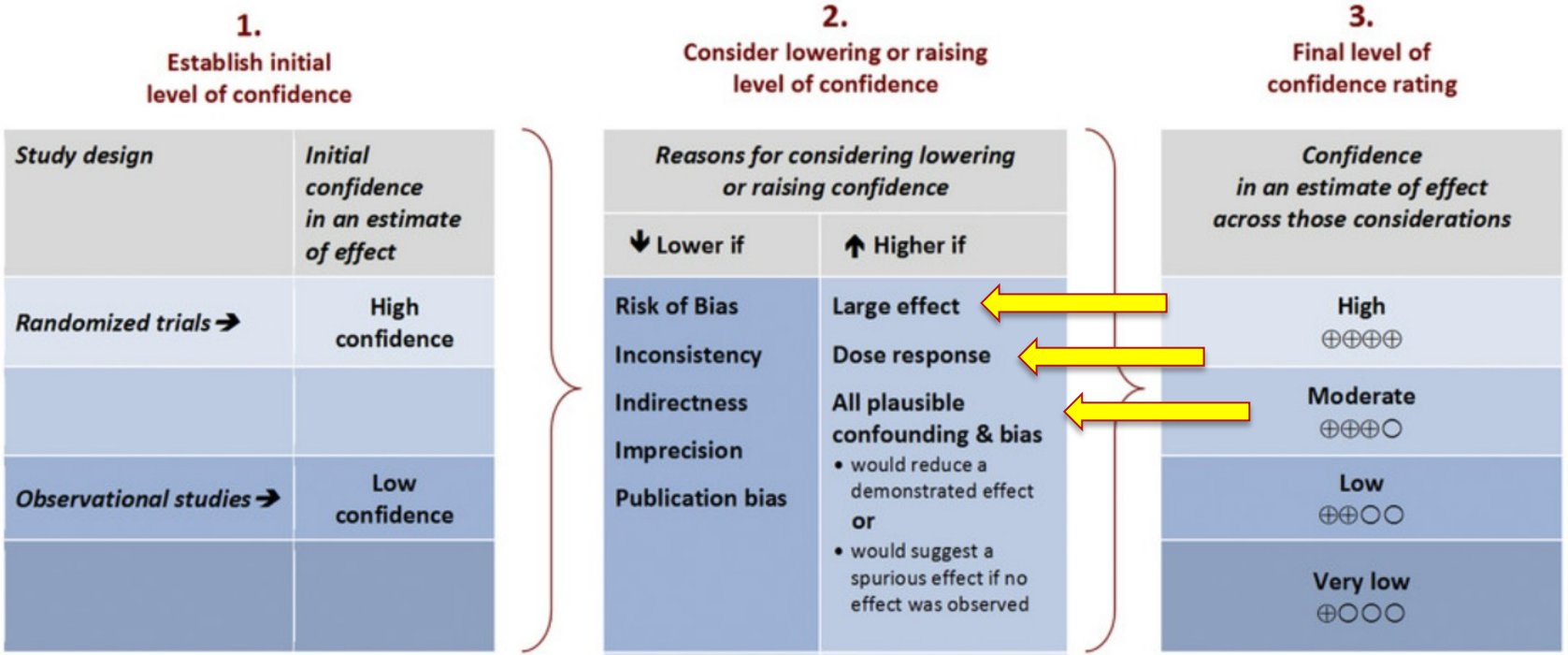
- Summary of evidence and systematic approach to make recommendations
- Reviews quality of evidence with the study design
  - 5 reasons to rate down, 3 reasons to rate up

Rating Quality of Evidence



Source: Environment International 2016

Rating Quality of Evidence



Source: Environment International 2016

Grading Quality of Evidence

Grade	Definition
High 	We are **very confident** that the true effect lies close to that of the estimate of the effect
Moderate 	We are **moderately confident** in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low 	Our **confidence** in the effect estimate **is limited**: the true effect may be substantially different from the estimate of the effect
Very Low 	We have **very little confidence** in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

LARGE EFFECT

What is an Effect Size?

- Impact of an intervention
- Standardized mean difference
- Compare interventions of different size and setting
- Not the same as statistical significance
- Large effect sizes means the difference is important; small effect sizes mean the difference is unimportant

$$\text{Effect Size} = \frac{\text{[Mean of experimental group]} - \text{[Mean of control group]}}{\text{Standard Deviation}}$$

What is an Effect Size?

Size	Effect size	Example
Small	0.2 (20%)	Height difference in 15 vs.16 yr old girls in USA
Moderate	0.5 (50%)	Sleeping on back to reduce SIDS – reduced 50-70%
Large	0.8 (80%)	Bicycle helmets to reduce injury – 85-88%

SIDS Example

- “Back to sleep”
- Sleeping on belly with odds ratio 4.1 (3.1,5.5)
- Sleeping on back associated with 50-70% decrease in SIDS in numerous countries

Bicycle Helmets

- Systematic review: Fewer head, brain, face injuries
- Five published studies, all cas—control, no RCTs
- Results – 63-88% reduction in risk of head, brain, and severe brain injury for all ages of bicyclists.

What helped strengthen this review despite the nonexperimental study designs?

Bicycle Helmets

- Case-controls studies with low risk of bias
  - Controls selected from same population as cases
  - Injuries verified by medical records
  - Ascertainment of exposure was equivalent for case and control groups
- Consistent benefit for head injury in all studies
- Large magnitude of effect, precise estimate in all studies: protective effect for head, brain, face 64-88%

Inference of Strong Association

Table 1. Key Question 1: Overall Summary of Impact of Screening vs No Screening on Colorectal Cancer Incidence and Mortality

Screening test (sample No.)	No. of studies (participants)	Rounds (intervals)	Follow-up, y	CRC incidence	CRC mortality
Colonoscopy[37,47]	2 cohort studies[a] (n = 436 927)	1	8-24[b]	With polypectomy: HR, 0.53 (95% CI, 0.40 to 0.71)[c] Negative colonoscopy result: HR, 0.47 (95% CI, 0.39 to 0.57)[c] Age 70-74 y: RD, −0.42% (95% CI, −0.24% to −0.63%)[d] Age 75-79 y: RD, −0.14% (95% CI, −0.41% to −0.16%)[d]	HR, 0.32 (95% CI, 0.24 to 0.45)[c]
Flexible sigmoidoscopy[19,24,29,35]	4 RCTs[a] (n = 458 002)	1-2 (every 3-5 y)	11-17	IRR, 0.78 (95% CI, 0.74 to 0.83)	IRR, 0.74 (95% CI, 0.68 to 0.80)
Hemoccult II[20,21,27,36,39]	5 RCTs[e] (n = 419 966)	2-9 (every 2 y)	11-30	RR range, 0.90 (95% CI, 0.77 to 1.04) to 1.02 (95% CI, 0.93 to 1.12)	RR range, 0.78 (95% CI, 0.65 to 0.93) to 0.91 (95% CI, 0.84 to 0.98)[f]
FIT[46]	1 cohort study[a] (n = 5.4 million)	Every 2 y	6 (mean, 3)	NR	RR, 0.90 (95% CI, 0.84 to 0.95)

Abbreviations: CRC, colorectal cancer; FIT, fecal immunochemical test; HR, hazard ratio; IRR, incidence rate ratio; NR, not reported; RCT, randomized clinical trial; RD, risk difference; RR, relative risk.

[a] Includes newly identified studies or newly identified articles with additional follow-up to a previously included study.

[b] Twenty-two–year follow-up for incidence; 24-year follow-up for mortality.

[c] Adjusted for age, body mass index, family history, smoking status, physical activity, diet, vitamin use, aspirin use, nonsteroidal anti-inflammatory drug use, cholesterol-lowering drug use, hormone replacement therapy.

[d] Standardized 8-year risk.

[e] One RCT in Finland that only has interim follow-up is not represented in this table (n = 360 492).

[f] Annual RR from 1 trial only, 0.68 (95% CI, 0.56-0.82); 11 rounds every 1 year, 30-year follow-up.

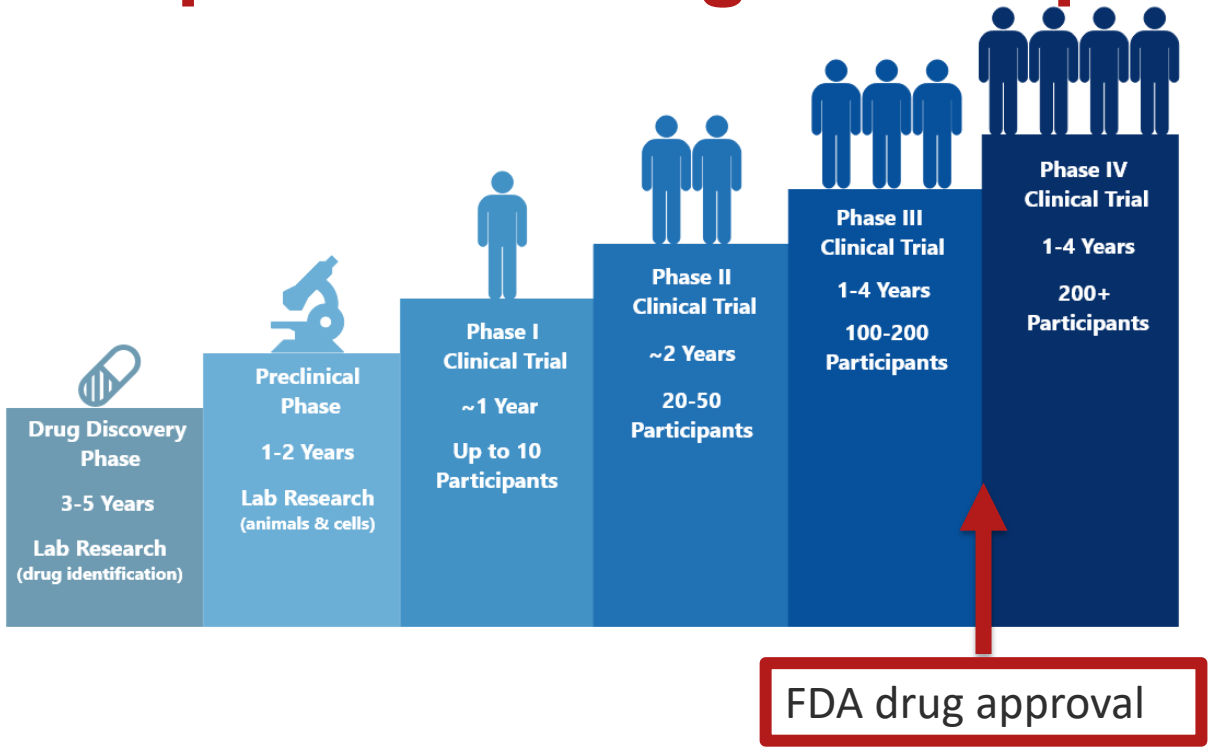
Reference: JAMA Network

DOSE-RESPONSE EFFECT

Dose-Response Gradient

- An important criterion for believing a putative cause-effect relationship
- Increases confidence in findings of observational studies

Dose-Response in Drug Development



The Drug-Dosing Conundrum in Oncology — When Less Is More

Examples of Drugs Whose Doses or Schedules Were Modified for Safety or Tolerability after Approval.*

Drug	Initial Dose and Trials	Modified or Added Dose and Trials	Reason for Modified or Added Dose
Small-molecule drugs			
Ceritinib (Zykadia)	750 mg PO daily fasted (ASCEND-1)	450 mg PO daily with food (ASCEND-8)	Reduce gastrointestinal toxic effects
Dasatinib (Sprycel)	70 mg PO twice daily (CA180013, CA180005, CA180006, and CA180015)	100 mg PO daily (CA180034)	Reduce hematologic toxic effects and fluid retention
Niraparib (Zejula)	300 mg PO daily (NOVA)	200 mg PO daily (PRIMA)	Reduce thrombocytopenia in patients with a lower platelet count or lower body weight
Ponatinib (Iclusig)	45 mg PO daily (PACE)	45 mg PO daily, then 15 mg PO daily once ≤1% *BCR-ABL* is achieved (OPTIC)	Reduce vascular occlusive events
Chemotherapy			
Cabazitaxel (Jevtana)	25 mg/m² IV every 3 wk (TROPIC)	20 mg/m² IV every 3 wk (PROSELICA)	Reduce hematologic toxic effects and infections
Antibody–drug conjugates			
Gemtuzumab ozogamicin (Mylotarg)	9 mg/m² IV on days 1 and 15 (Study 201, Study 202, and Study 203)	3 mg/m² IV on days 1, 4, and 7 (Mylofrance-1)	Reduce veno-occlusive disease and treatment-related mortality

* Adapted from the Food and Drug Administration.[2] IV denotes intravenous, and PO by mouth.

N Engl J Med 2021; 385:1445-1447

Dose-Response Gradient of Drugs

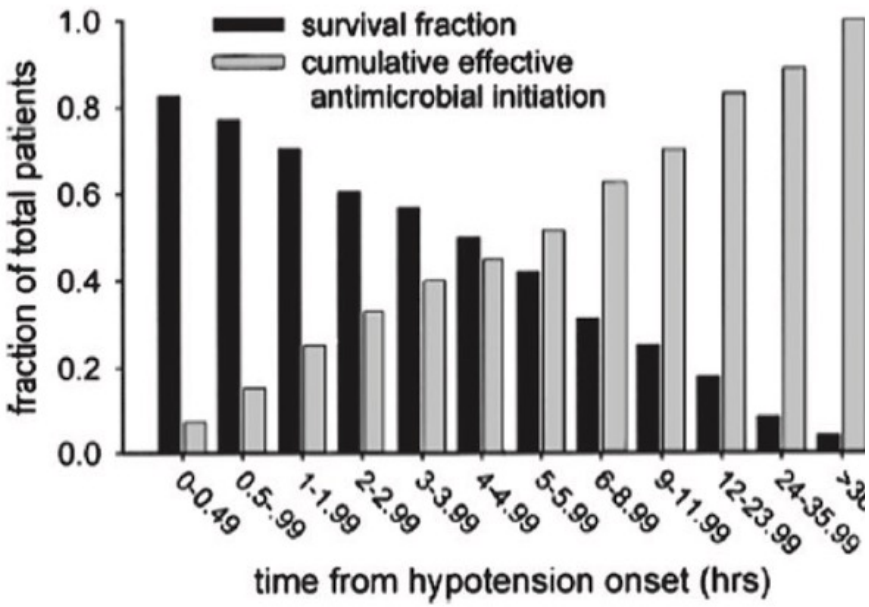
Table 3. Results of Case-Control and Cohort Studies Reporting on Cardiovascular Risks With Cyclooxygenase 2 Inhibitors

Source	Relative Risk (95% Confidence Interval)				
	All Celecoxib	All Rofecoxib	Rofecoxib ≤25 mg/d	Rofecoxib >25 mg/d	Meloxicam
Case-control studies that reported on COX-2 inhibitors					
Hippisley-Cox and Coupland,[2] 2005	1.21 (0.96-1.54)	1.32 (1.09-1.61)	NR	NR	NR
Graham et al,[3] 2005	0.84 (0.67-1.04)	1.34 (0.98-1.82)	1.23 (0.98-1.71)	3.00 (1.09-8.31)	NR
Solomon et al,[4] 2004	0.93 (0.84-1.02)	1.14 (1.00-1.31)	1.21 (1.01-1.44)*	1.70 (1.07-2.71)†	NR
McGettigan et al,[14] 2006	1.11 (0.59-2.11)	0.63 (0.31-1.28)	NR	NR	NR
Kimmel et al,[15,16] 2004/5	0.43 (0.23-0.79)	1.16 (0.70-1.93)	NR	NR	NR
Singh et al,[23] 2005‡	1.09 (1.02-1.15)	1.32 (1.22-1.42)	NR	NR	1.37 (1.05-1.78)
Sturkenboom et al,[24] 2005‡	NR	1.52 (1.08-2.15)	NR	2.32 (1.2-4.4)§	NR
Johnsen et al,[25] 2005	1.25 (0.97-1.62)	1.80 (1.47-2.21)	NR	NR	NR
Levesque et al,[26] 2005	0.99 (0.85-1.16)	1.24 (1.05-1.46)	1.2 (1.02-1.43)	1.73 (1.09-2.76)	1.06 (0.49-2.30)
Garcia Rodriguez et al,[28] 2004	NR	NR	NR	NR	0.97 (0.60-1.56)
Summary relative risk	1.01 (0.90-1.13)	1.31 (1.18-1.46)	1.21 (1.08-1.36)	1.89 (1.43-2.51)	1.25 (1.00-1.55)
Cohort studies that reported on COX-2 inhibitors					
Gíslason et al,[17] 2006‖	2.06 (1.73-2.45)	2.29 (1.99-2.65)	2.17 (1.86-2.54)	3.31 (2.37-4.61)	NR
Mamdani et al,[20] 2003	0.90 (0.70-1.20)	1.0 (0.80-1.40)	NR	NR	NR
Ray et al,[21] 2002	0.96 (0.76-1.21)	NR	1.03 (0.78-1.35)	1.70 (0.98-2.95)	NR
Summary relative risk	1.22 (0.69-2.16)	1.53 (0.68-3.44)	1.51 (0.73-3.13)	2.46 (1.29-4.71)	NR
Case-control and cohort studies combined risk estimates	1.06 (0.91-1.23)	1.35 (1.15-1.59)	1.33 (1.00-1.79)	2.19 (1.64-2.91)	1.25 (1.00-1.55)

JAMA, October 4, 2006—Vol 296, No. 13

Dose-Response Gradient an Intervention

- Observing effect of the intensity of an intervention
- Sepsis survival and timeliness of antibiotic administration



Dose-Response in Psychotherapy

Study Data

- Dose for clinical improvement: 13-18 sessions
- Rate of improvement: 50%

Real-World Data

- Median dose of sessions in practice: 3
- Rate of improvement: 20%

Reference: https://onlinelibrary-wiley-com.ezproxy.med.cornell.edu/doi/pdf/10.1093/clipsy.9.3.329

PLAUSIBLE RESIDUAL CONFOUNDING

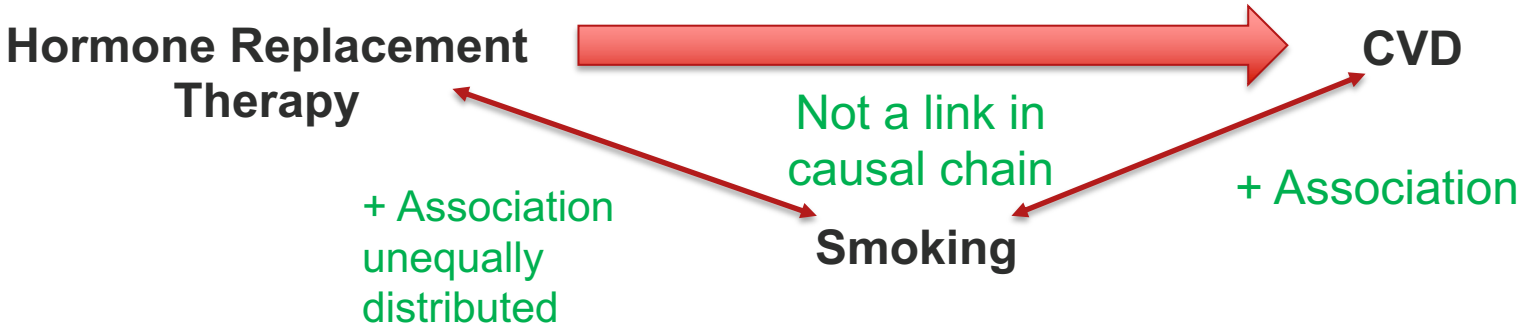
Effect of Plausible Residual Confounding

- Distortion of effect of exposure on disease by 3rd factor
- Can result in the overestimation or underestimation of the true effect of exposure on disease

Attributes of a Confounder

- It is associated with the outcome of interest and;
- Associated with exposure and unequally distributed between the exposed and unexposed cohorts
- Not just a link in the causal chain between exposure and outcomes

Confounding



Are These Confounders?

TABLE 1. AGE-STANDARDIZED DISTRIBUTION OF CHARACTERISTICS OF WOMEN PARTICIPATING IN THE NURSES' HEALTH STUDY IN 1990, ACCORDING TO THE USE OR NONUSE OF POSTMENOPAUSAL HORMONES.

CHARACTERISTIC	HORMONE USE	
	NEVER USED (N = 27,034)	CURRENTLY USED
		Estrogen with Progestin (N = 6224)
Parental MI before the age of 60 yr (%)*	29.6	20.6
Hypertension (%)	32.9	27.3
Diabetes mellitus (%)	5.8	2.7
High serum cholesterol level (%)	35.6	41.6
Moderate smoker (%)†	9.4	4.6
Bilateral oophorectomy (%)	4.2	8.9
Past use of oral contraceptives (%)	30.6	46.4

Residual Confounding

- Distortion that remains in exposure-outcome association due to **incompletely** controlling for confounding in the design or analysis of a study
- Confounding factors not considered, no attempt to adjust, because data on these factors was not collected.
- Control of confounding was not tight enough

Confounding Expected to Reduce Effect

- Comparing mortality rates of private for-profit and private not-for-profit hospitals
- Systematic review of observational studies including a total of 38M patients
- Private for-profit hospitals were associated with an increased risk of death
  - Relative Risk [RR] 1.020 (1.003-1.038; p = 0.02)

Confounding to Reduce Effect

- Are there any potential sources of bias in this study?
- Towards which hospital type are the results likely biased?

Confounding Expected to Reduce Effect

- Possible source of bias: Disease severity between patients in the two hospital types
- Residual confounding: Biases results against non-for-profit hospitals (sicker patients)
- As residual confounding reduced the demonstrated effect (higher risk of death at private for-profit hospitals) => UPGRADE

Confounding Expected to Increase Effect, but No Effect Observed

- Example: Metformin under suspicion of causing lactic acidosis
- Approved by FDA in 1995
- First line therapy for newly diagnosed type 2 diabetes
- Most commonly prescribed oral antihyperglycemic in the world

Metformin and Lactic Acidosis

- Related drug phenformin caused lactic acidosis
- Metformin-associated lactic acidosis n extremely rare condition
  - ≤10 events per 100,000 patient-years of exposure
  - Mortality rates of 30 to 50%

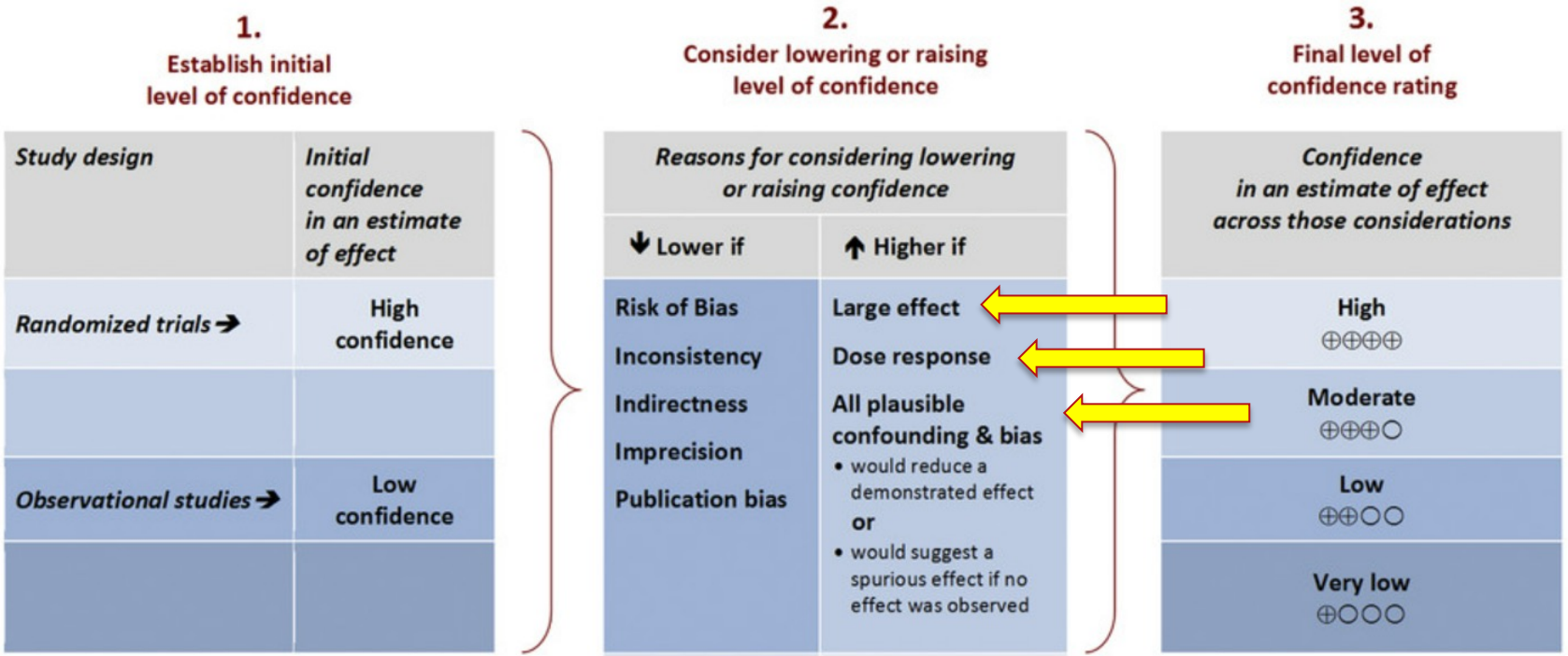
Metformin and Lactic Acidosis

- Large observational studies failed to demonstrate
- Systematic review with 347 comparative trials and cohort studies found no cases of lactic acidosis, no difference in plasma lactate levels
- Case–control study compared lactic acidosis between metformin and sulfonylurea users
  - In 50,048 patients, no significant difference

Metformin and Lactic Acidosis

- Clinicians likely have been more alert to lactic acidosis with metformin due to phenformin
- Clinicians likely over-reported occurrence of lactic acidosis with metformin
- Upgrade the evidence for ***no association between metformin and lactic acidosis***

Rating Quality of Evidence



Source: Environment International 2016