# A new instrument for assessing the credibility of effect modifiers

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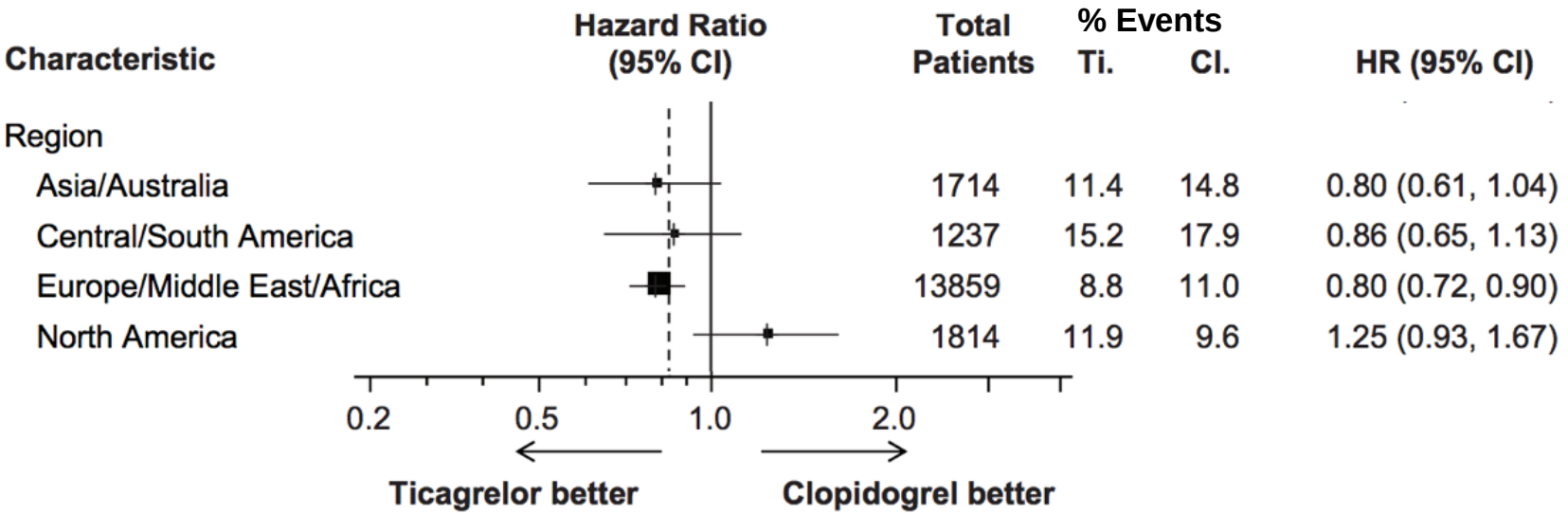
# PLATO trial

N Engl J Med. 2009
AstraZeneca

Ticagrelor versus Clopidogrel
>18000 Patients with acute coronary syndrome
Cardiovascular events: HR 0.84 (0.77 to 0.92)




Low risk of bias
Interaction test P=0.045

No a priori hypothesis
33 subgroup analysis (3 P≤0.05)

| | | |
|---|---|---|
| <1980 | Rothman, Greenland, Walter, et al. | **Concept** of effect modification |
| 1987 | Pocock et al. | Statistical problems |
| 1991 | Yusuf et al. | **Criteria** for critical appraisal |
| 1992 | Guyatt, Oxman | **Criteria** for critical appraisal |
| 2002 | Higgins, Thompson | Limitations of **meta-regression** |
| 2005 | Rothman et al. | Series in Lancet |
| 2010 | Kent, Rothwell, Ioannidis, Altman, et al. | Framework **reporting** and analysis |
| 2010 | Sun et al. | More criteria |
| 2011 | Guyatt, Oxman, Schünemann et al. | **GRADE** guidance subgroup analysis |
| 2014 | Koch, Keene, Wang et al. | Series in J Biopharm Stat |
| 2015 | VanderWeele et al. | **Causal** interaction |
| 2015 | Burke et al. | **Bayesian** credibility assessment |
| 2016 | Wallach et al. | **Empirical evidence** of spurious findings |

# What's new?

Formal instrument

- Items, response options, overall
- RCTs and MAs
- Compatible with GRADE

Systematic survey of credibility criteria

Expert consensus

User testing, reliability study

# Systematic survey

1730 journal articles + 56 text book chapters

150 reviewed in detail

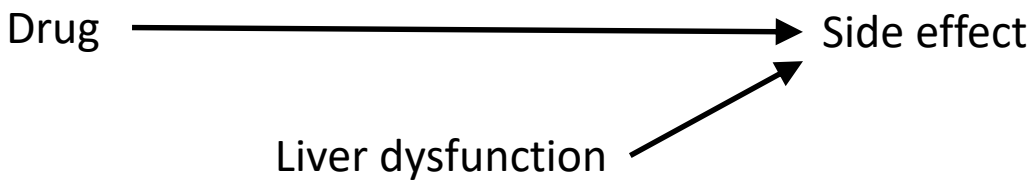
55 articles reporting 35 candidate items

- Chance
- Bias
- Rationale

# Chance (random error)

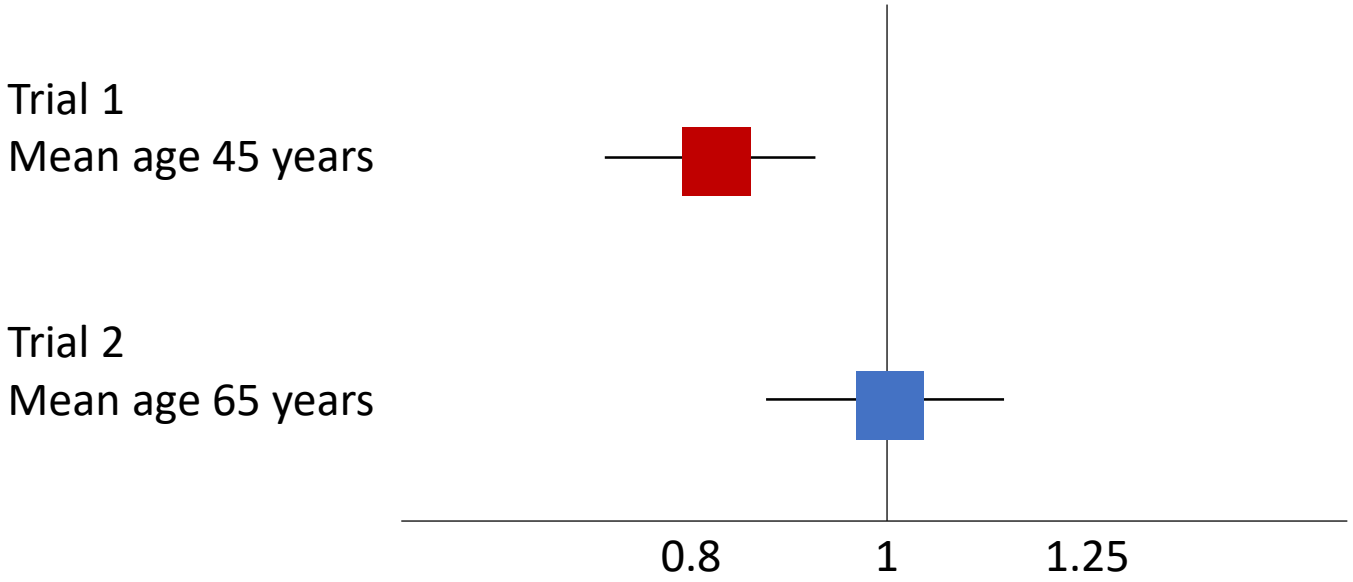
| | |
|---|---|
| Replication across studies | 13 (of 55) |
| Significant interaction test | 15 |
| Small number of subgroup analyses | 17 |
| Pre-specified analytic details | 15 |
| Adjustment for multiplicity | 8 |
| Reporting of all analysis | 6 |

# Bias (is it what we think it is?)




Baseline characteristic 7

Within vs between 7



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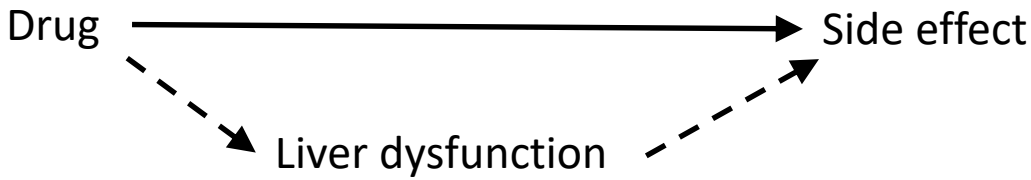


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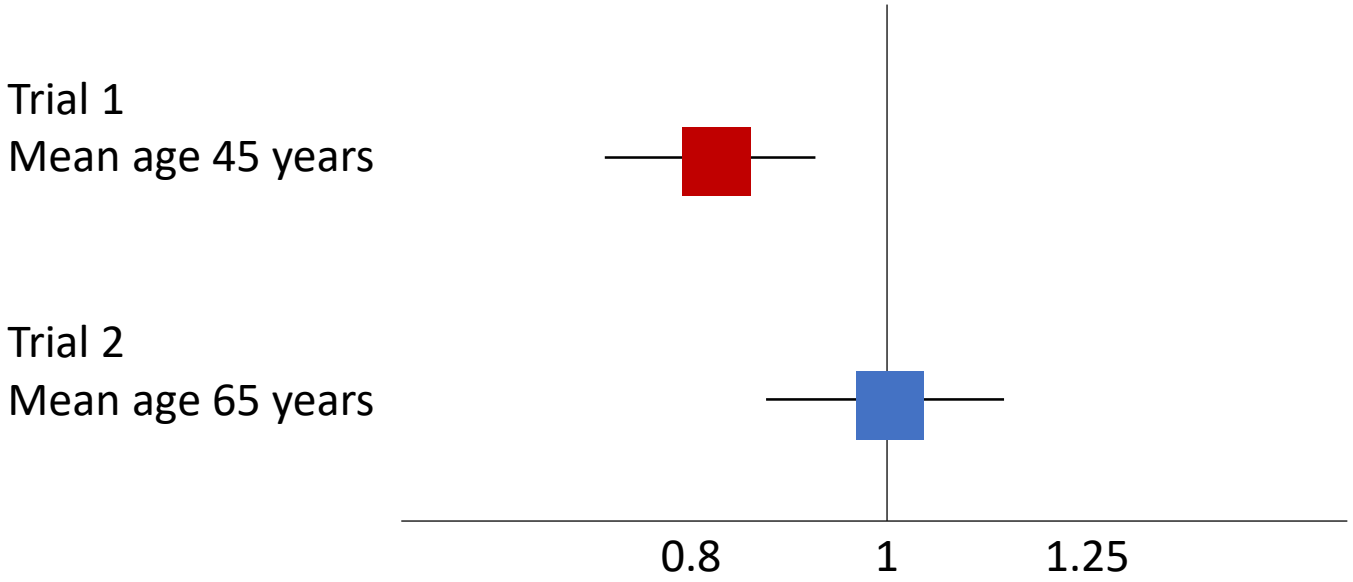

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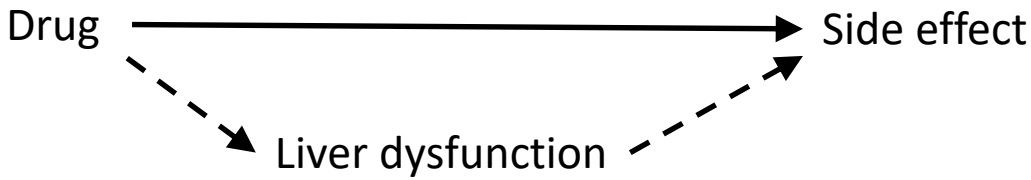


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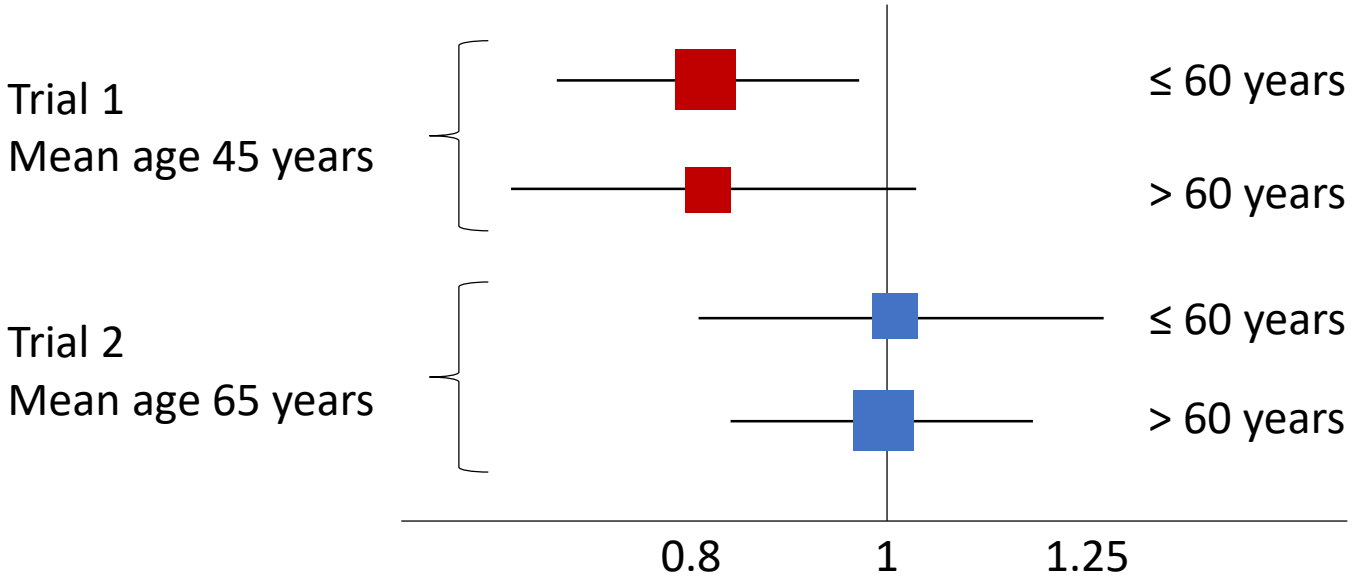
Within vs between 7



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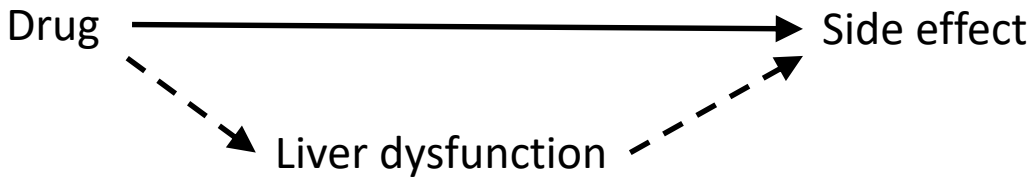


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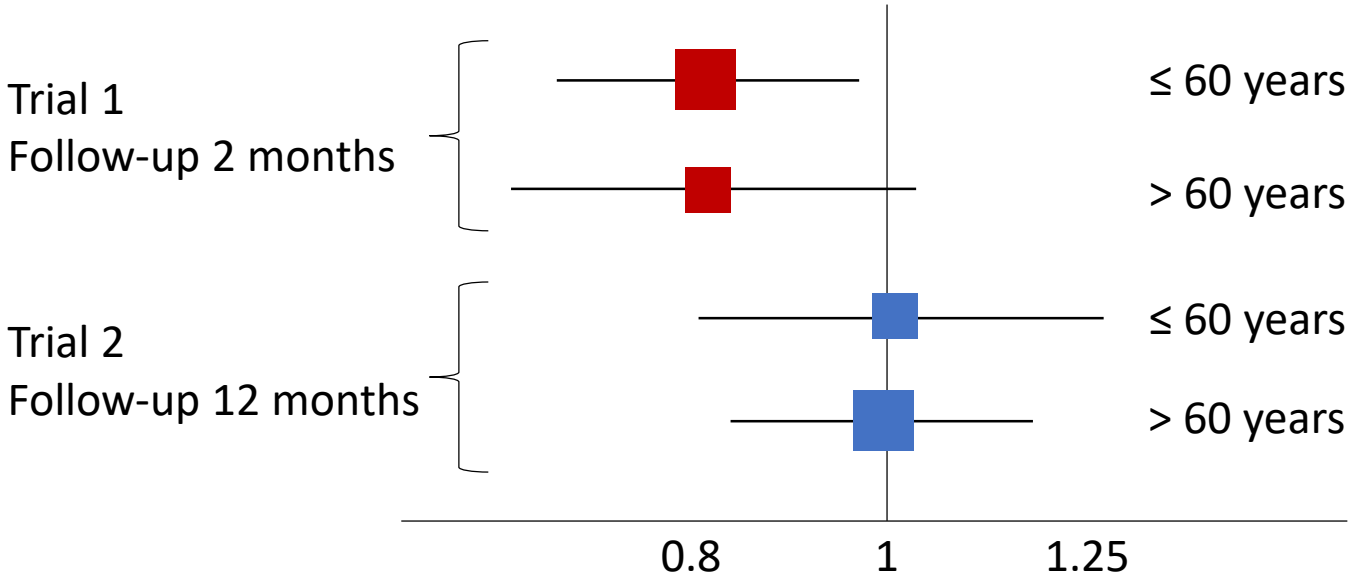
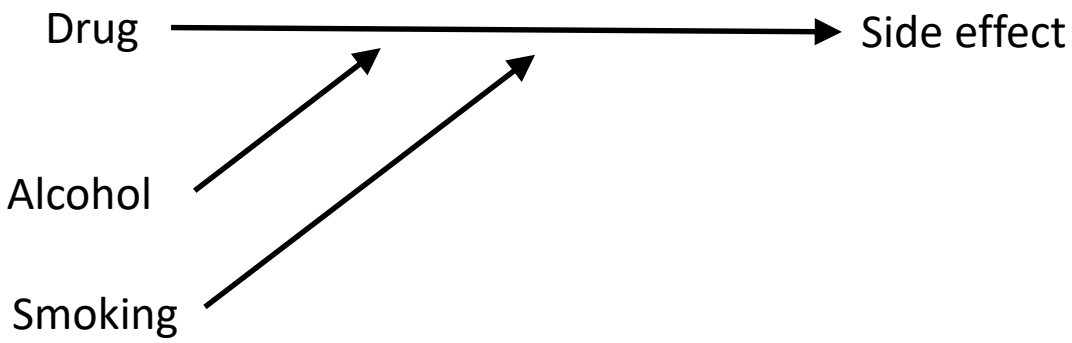


# Rationale



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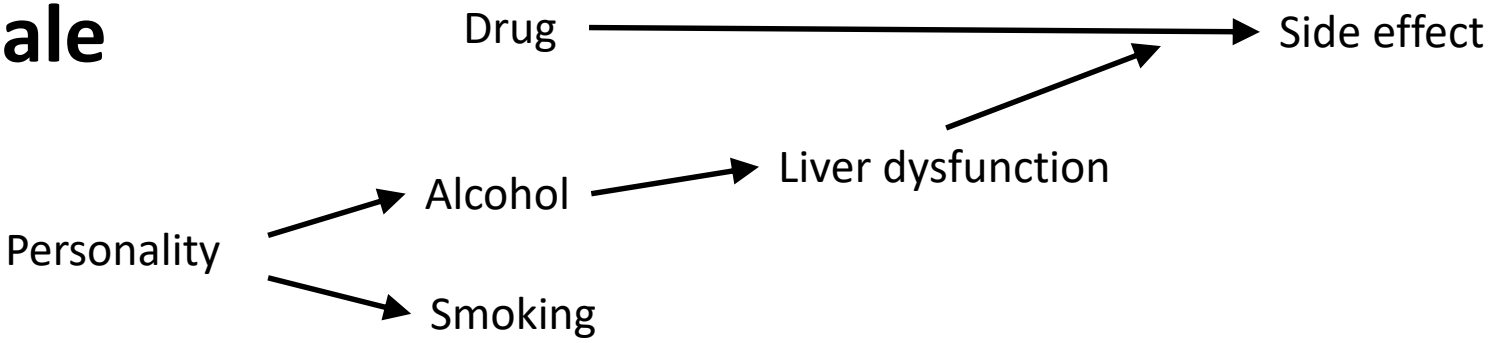
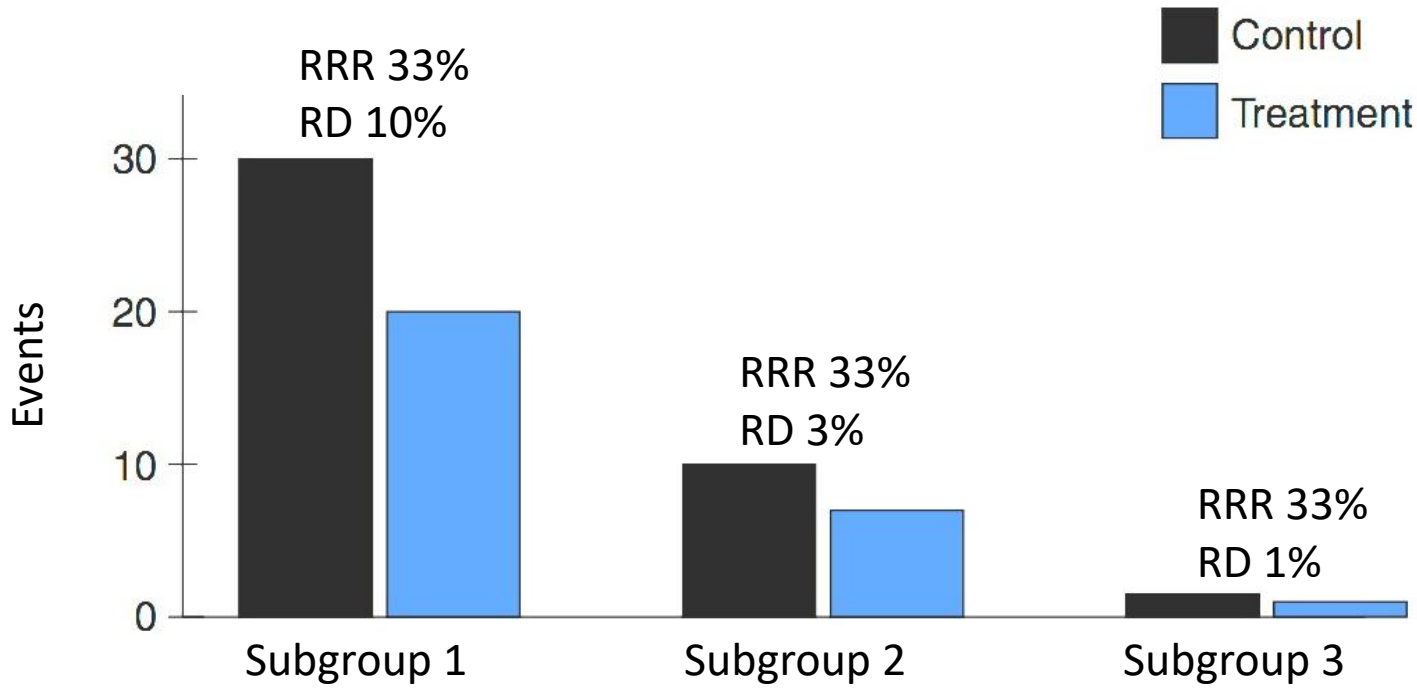


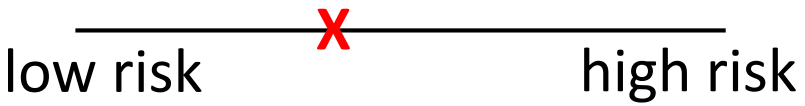

| | |
|---|---|
| Rationale preceded analysis | 15 |
| Specified direction | 15 |
| Expert input | 4 |
| Indirect evidence | 4 |
| Causal factor not proxy | 6 |

# Effect modification is scale-dependent

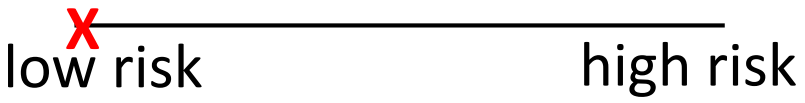


**Scale of interest:**

**Chance**




**Bias**

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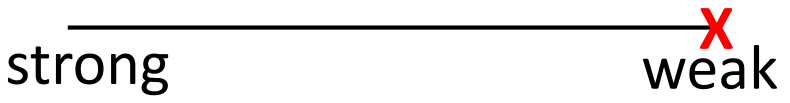
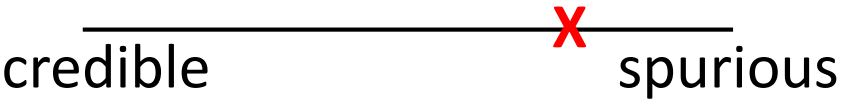



**Overall, how credible is the effect modifier?**



# Strengths and limitations

✓ Systematic survey

✓ Expert consensus

✓ Reliability

Validity

✓ Presence

Absence

( ) Relevance

# Bottom line

- Credibility of subgroup analyses has taken up a lot of intellectual energy
- No single criterion will be sufficient to establish credibility
- Formal instrument for overall credibility