

Evaluating the Potential Teratogenicity of an Exposure

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Animal Teratology Studies

- Usually performed in rats, mice and/or rabbits with rigorous standardized methodology
- Basis for almost all initial regulatory classification of teratogenic risk

Animal Teratology Studies

May identify teratogenic exposures before any children are harmed

BUT

Cannot prove whether or not an exposure is teratogenic in human pregnancy

We Are In Bed With The Devil

- The only way we can ever know that an exposure is teratogenic in humans is to recognize that it causes birth defects in babies.

We Are In Bed With The Devil

- Clinical teratology research is all about recognizing when we have harmed babies as quickly and as effectively as possible.

Kinds of Human Data

- Case reports
- Case series
- Pregnancy registries
- Cohort studies
- Case-control studies
- Ecological studies
- Record linkage studies

Case Reports

- Useful for raising causal hypotheses, but most are wrong
- Coincidental occurrence of congenital anomalies and exposures common
- Cannot be used to provide quantitative estimate of risk

Case Series

- Permit recognition of characteristic patterns of anomalies (syndromes)
- How most major human teratogens have been recognized



Case Series

- *Anathema to epidemiologists:* Biased ascertainment, multiple confounding, no controls, no statistical assessment
- Cannot be used to provide quantitative risk estimates

Pregnancy Registries

- Pregnancy outcomes among women who have taken a particular drug or drugs
- Most useful if prospective
- Usually no control group: statistical comparisons problematic

Pregnancy Registries

- In most instances:
 - Case series with less consistent data collection
 - Data quality limited
 - Can only detect large effects
- Can be used in exposure cohort studies

Randomized Controlled Trials

- Provide most reliable risk estimates
- Findings applicable only to comparable patients and exposures
- Rarely used in clinical teratology

Cohort Studies

- Compare frequency of birth defects among children born to women treated with an agent or not during pregnancy

Cohort Studies

- Large, very expensive population-based studies
- Exposure cohort (TIS) studies

Cohort Studies

- Can be used to estimate risk and statistical significance
- May be subject to serious biases and confounding
- Limited (or insufficient) power is often a concern

Case-Control Studies

- Compare frequency of maternal treatment during pregnancy among children with or without birth defects

Case-Control Studies

- Can be used to estimate risk and statistical significance
- Can only be used to look for association with birth defects present in cases
- May be subject to serious biases and confounding

Record Linkage Studies

- Cost effective
- Limited information on potential confounders
- Quality of exposure and/or outcome data may be poor

Record Linkage Studies

- Use existing records or databases to identify both exposures and outcomes
- May be analyzed as cohort studies or case-control studies (or both)

Ecological Studies

- Unit of analysis: groups of people rather than individuals
- Information collected on the group as a whole
- Used most often for studies of environmental exposures (e.g., pollutants, radiation)

Ecological Studies

- Test for association between summary measure of exposure (e.g., average concentration of a particular chemical in drinking water) and a summary measure of disease (e.g., frequency of miscarriage) in a group

Ecological Studies

- Cost effective
- Often can be done with data collected for other purposes
- ***Ecological fallacy***: attributing correlations observed in groups to individual members of those groups

Assessing Associations

- Significance
 - Statistical
 - Clinical
- Effect size
 - Relative risk (odds ratio)
 - Absolute risk

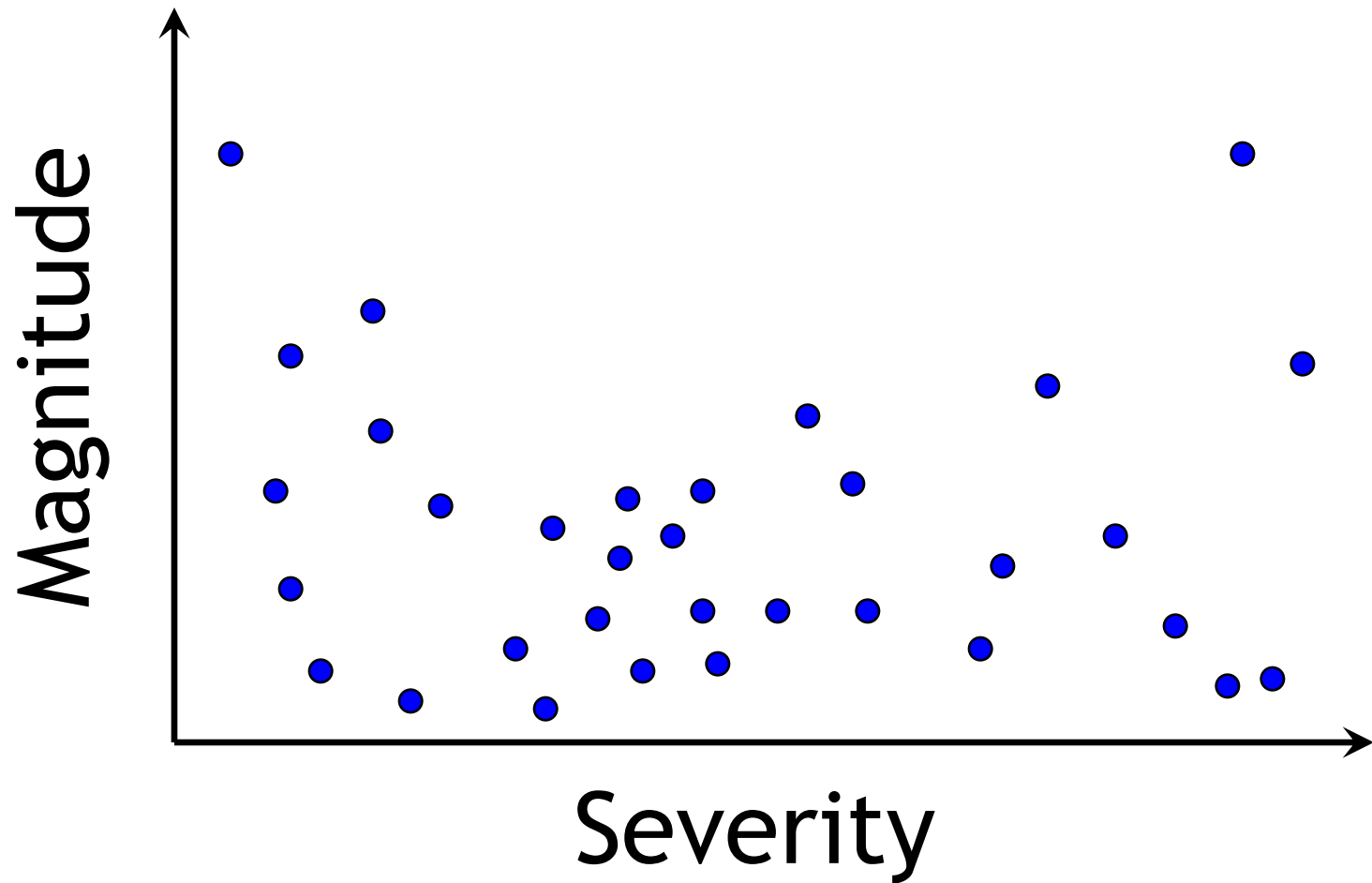
Statistical Significance

- An expression of how likely an association is to have occurred by chance alone
- Usually a relative risk
- What gets a paper published in the *New England Journal of Medicine*

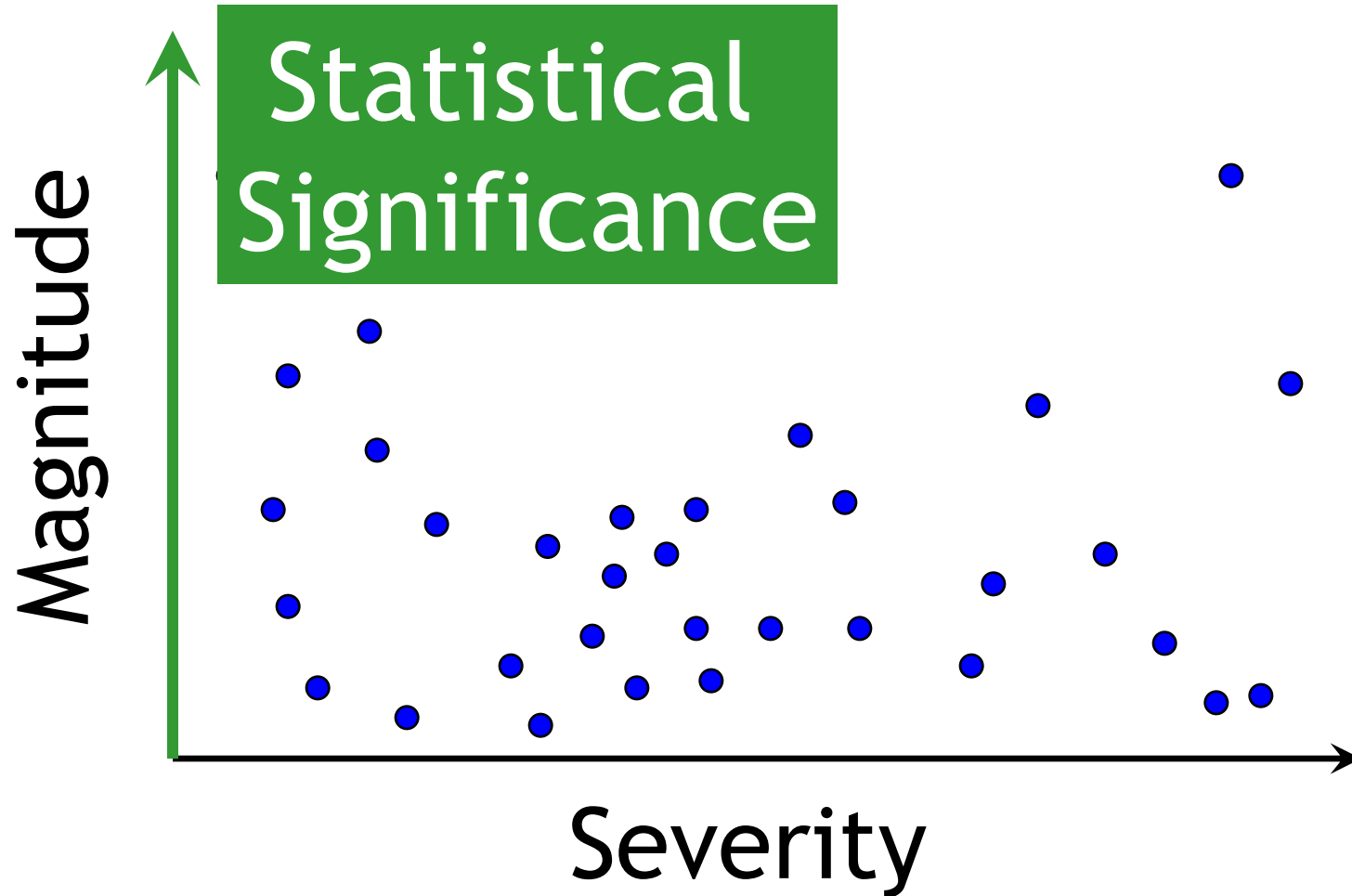
Clinical Significance

- What matters to a pregnant woman and her physician.
- Usually an absolute risk.

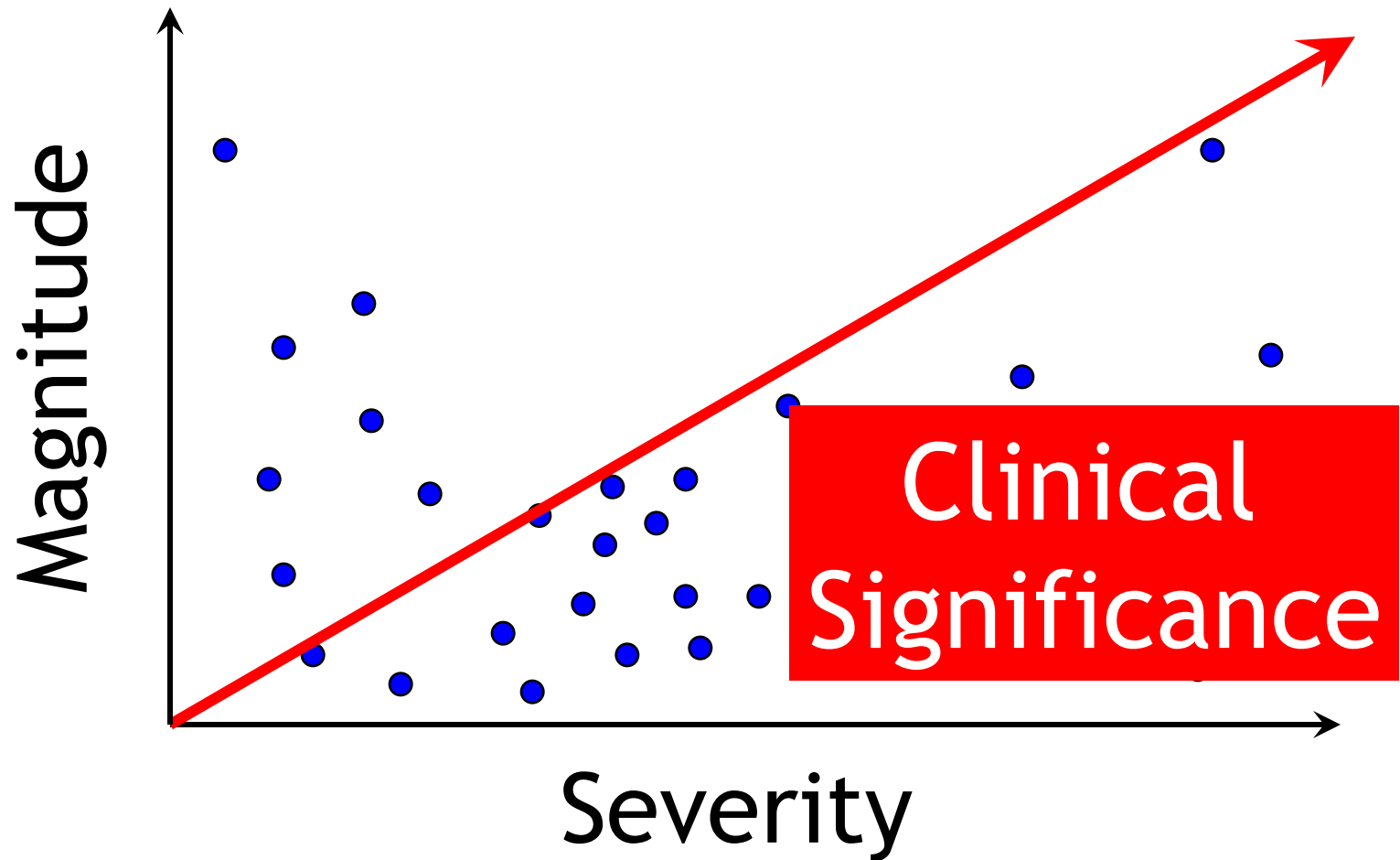
Two Dimensions of Risk



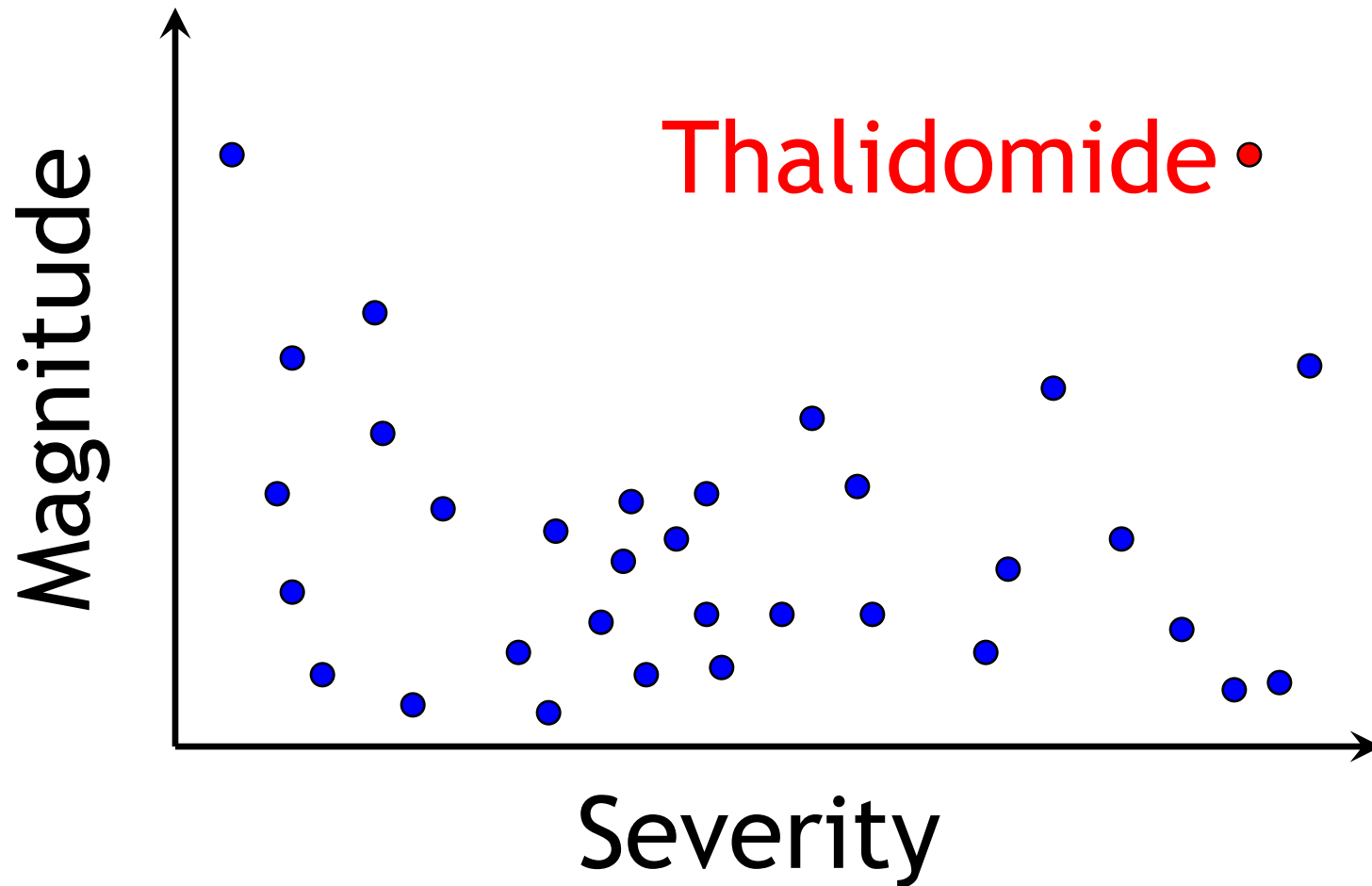
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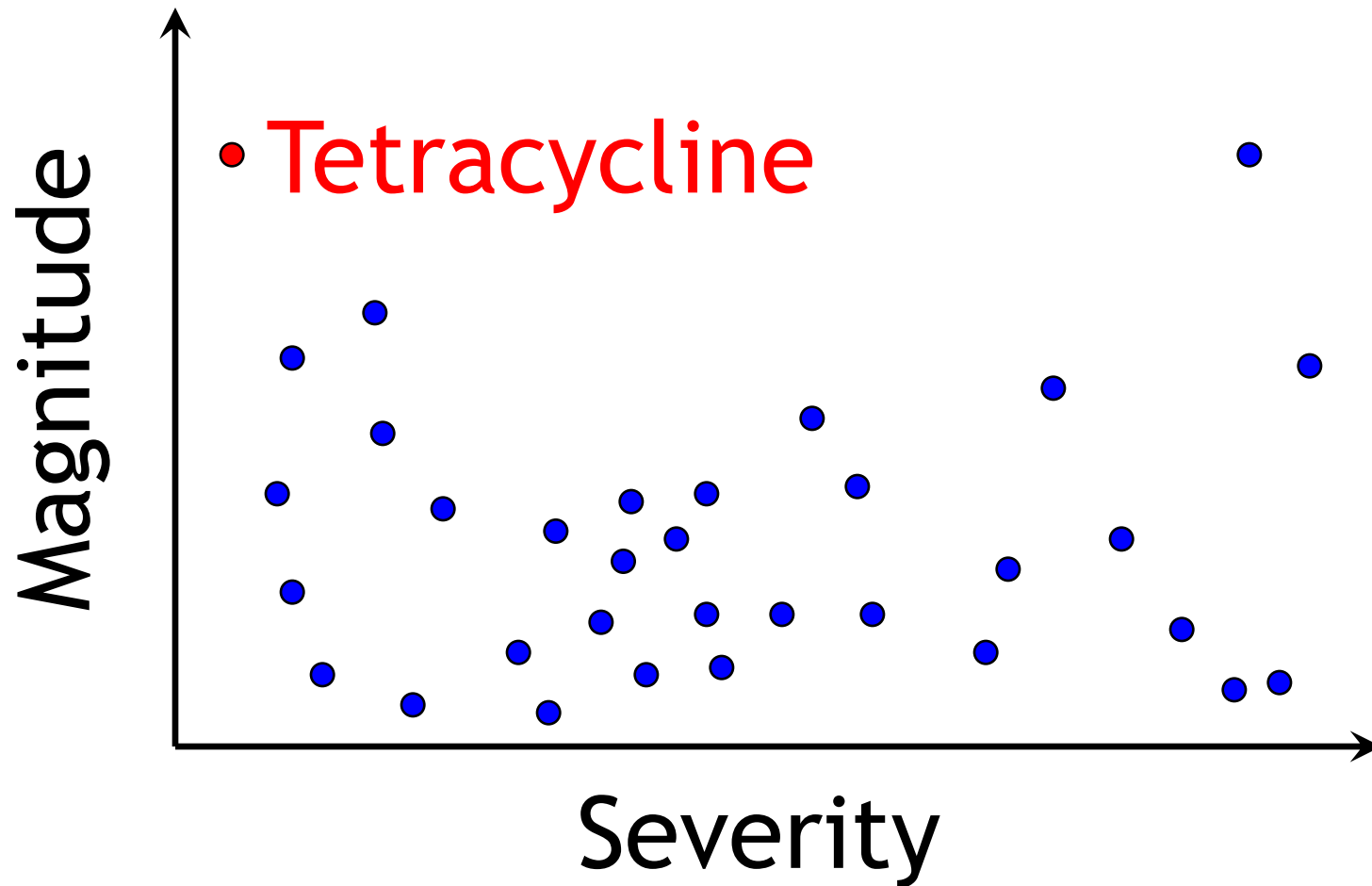
Two Dimensions of Risk



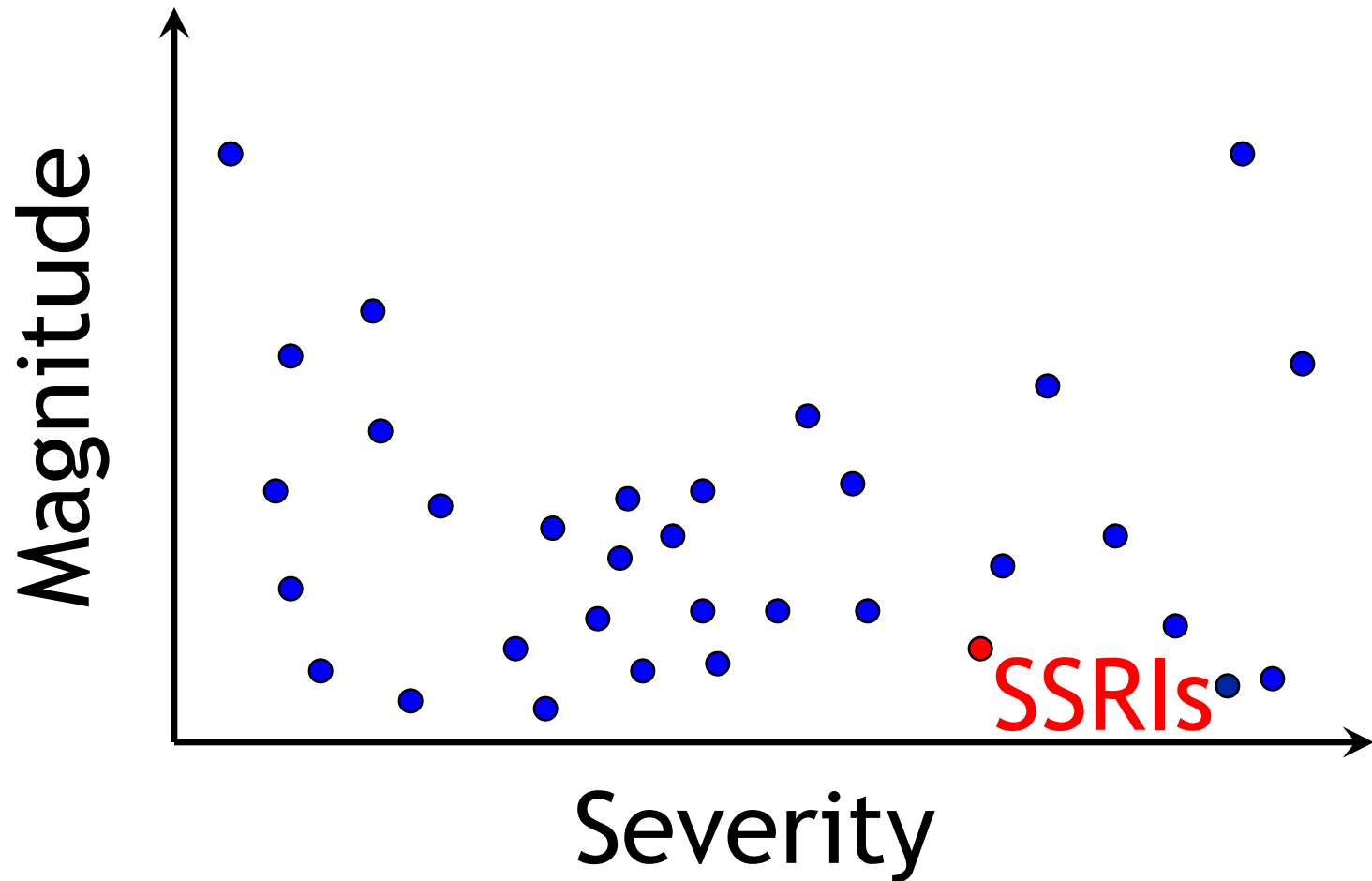
Two Dimensions of Risk



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Two Dimensions of Risk



Factors Supporting A Causal Inference

- Consistency
 - Reproducibility of findings
 - Different populations
 - Different study designs
- Dose response
- Time of exposure
- Animal model
- Biological plausibility

Interpreting Information from Multiple Studies

- Formal meta-analysis
- Expert consensus
- Flying by the seat of your pants

Formal Meta-analysis

- Systematic approach to identifying, evaluating, synthesizing and combining the results of relevant studies in a particular area

Formal Meta-analysis

- May permit quantitative conclusions that cannot be drawn from individual studies to emerge from multiple studies
- Effects of biases and limitations of individual studies can be assessed

Formal Meta-analysis

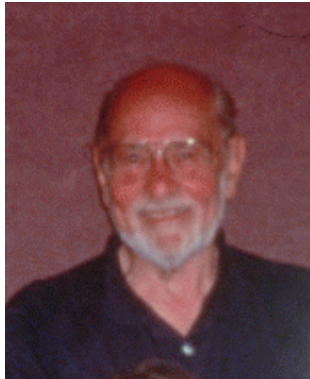
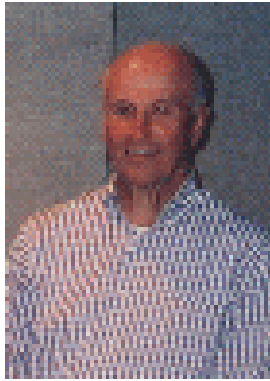
- “Statistical alchemy for the 21st century”
...Alvin Feinstein
 - Garbage in, garbage out
 - Mixing apples and oranges
 - The file drawer problem

Expert Consensus

- Can simultaneously evaluate studies of different types, sizes, and quality, including non-epidemiological studies

Expert Consensus

- Consensus is qualitative, not rigorously quantitative
- Consensus depends on who is making it



TERIS

***The
Teratogen
Information
System***

Flying by the Seat of Your Pants

- Quality depends on who is doing the flying
- Can be done quickly and cheaply (often not well)
- Difficult and time consuming to do well

Lack of Knowledge Is a Problem

- Pregnant women may not receive treatments that benefit their own health or that of the fetus
- Women may be advised or choose to terminate pregnancy to avoid risk

Lack of Knowledge Is a Problem

Babies are being harmed
unnecessarily!