Concepts in Clinical Epidemiology / Evidence Based Medicine[1]

1. **Mean, Mode, Median**[1]
    a. Mean = average
        i. found by adding up all of the given data and dividing by the number of data entries
    b. Median
        i. median = the middle number
        ii. first you arrange the numbers in order from lowest to highest, then you find the middle number by crossing off the numbers until you reach the middle
            1. e.g. 66 74 75 78 82 89
                a. when there are two middle numbers, take their average (or mean
                b. 75 + 78 = 153
                c. 153 / 2 = 76.5 (median)
    c. Mode
        i. mode = the number that occurs most often
        ii. e.g. mode of the following data is 78.
            1. 78 56 68 92 84 76 74 56 68 66 78 72 66 65 53 61 62 78 84 61 90 87 77 62 88 81

2. **Proportion vs Rate vs Ratio**[2]
    a. Rate
        i. a measure of the frequency with which an event occurs in a defined population in a defined time
            1. e.g. number of deaths per hundred thousand Canadians in one year
        ii. the important difference between a rate and a ratio is that for a rate, the numerator is included in the denominator
            1. e.g. number of new cases of a disease divided by the total population
    b. Proportion
        i. unlike a rate, does not have a time dimension
        ii. e.g. number of Canadians with cancer divided by the total population
    c. Ratio
        i. the value obtained by dividing one quantity by another

[1] Based on a study guide created by Timothy Rudd, Class of 2016

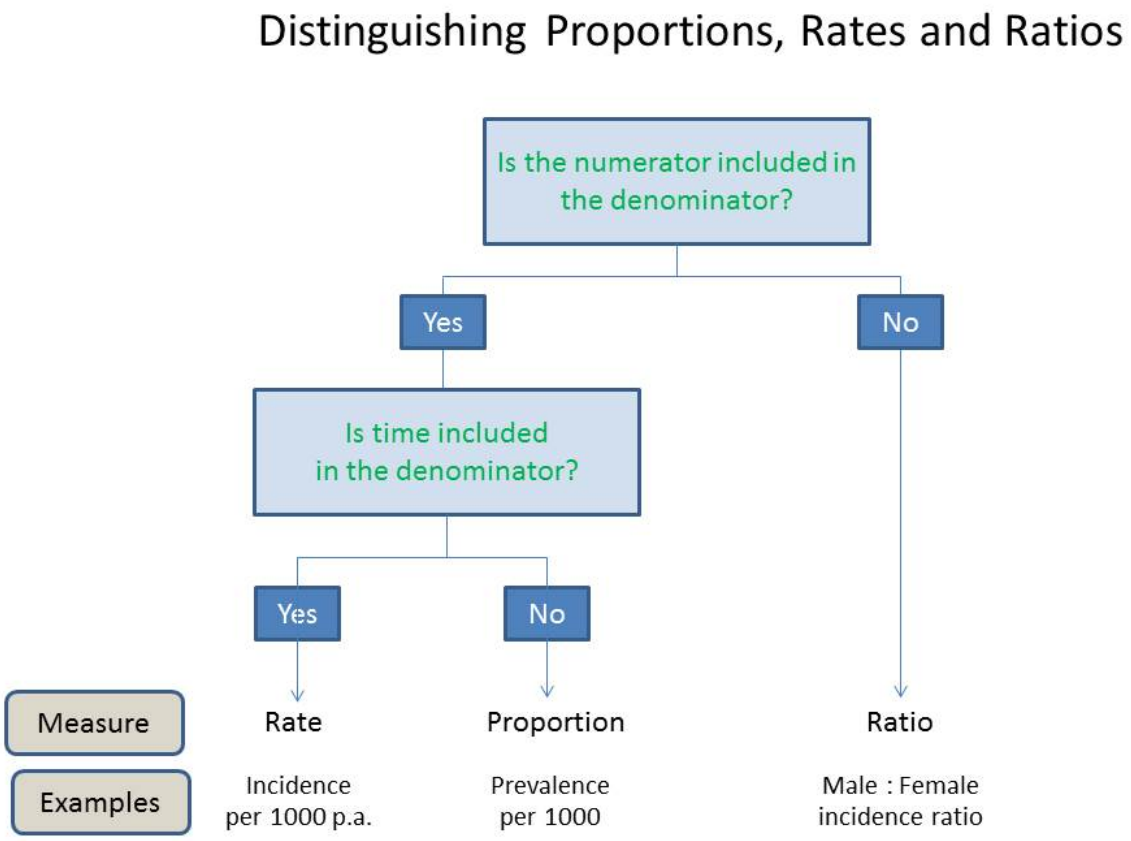
1. e.g. the male to female ratio in your class

ii. often compares two rates (the rate ratio)

1. e.g. comparing death rates for women and men at a given age

iii. unlike a rate, in a ratio the numerator and denominator are usually separate and distinct quantities, neither being included in the other

1. e.g. the ratio of males to females in the class



3. Attack Rate[3]

$$AR = \frac{\text{number of new cases of disease after a specific exposure}}{\text{number of people in population exposed}}$$

a. synonymous with case rate

b. attack rate = the cumulative incidence of infection over a period of time

c. useful during an epidemic

i. time frame typically refers to the period of the outbreak

d. e.g. an outbreak of gastroenteritis occurred after Oktoberfest

i. 50 people got sick
ii. 2500 attended the event
iii. AR = 50/2500 = 0.02 or 2% or 2 people per 100

4. Case Fatality Rate[3]

$$\text{CFR} = \frac{\text{number of deaths from disease in a given period}}{\text{number of diagnosed cases of that disease in the same period}}$$

a. the proportion of people with a specified condition who die within a specified time
b. time frame is typically the period during which the patient is sick from the disease
c. useful for an infectious disease but can be problematic for a chronic disease like a cancer that may remit for a period and then prove fatal after a recurrence
    i. mortality or survival rates are stats more commonly used for chronic disease

5. Incidence vs Prevalence[3]

a. Incidence
    i. Incidence = Number of new cases in a fixed time period / Number of people at risk
        1. expressed as a proportion, not a rate
    ii. period of study is usually one year = annual incidence
    iii. useful in communicating the idea of risk
        1. e.g. what is the probability that my patient will get this disease within the time-frame
b. Prevalence
    i. prevalence = number of people with the disease at a given time / number of people at risk
        1. expressed as a proportion, not a rate
    ii. useful for determining the burden of disease in a population and calculating pre-test probability
    iii. influenced by the incidence and by the duration of the condition
        1. usually, prevalence = incidence × disease duration
c. Summary
    i. incidence = new events
    ii. prevalence = all events (new and still present)

6. **Pre- and Post-test Probability**[4,5]
    d. pre-test probability = prevalence (number of cases in a given population at the current time)
        i. useful way to determine probability of a disease before application of the results of a clinical measurement
    e. post-test probability = determined using likelihood ratios (see below)
        i. useful for assessing the likelihood of a patient having a condition after carrying out clinical measurements

7. **Sensitivity and Specificity**[5]
    f. sensitivity = proportion of patients with a disease who have a positive clinical finding
        i. good for ruling out diseases (SNout) b/c if test or sign is highly sensitive and finding is negative, pt highly unlikely to have disease
    g. specificity = proportion of pt's w/out the disease who do not have the sign
        i. good for ruling conditions in (SPin) b/c if test or sign is highly specific for a disease and pt is positive, highly likely that pt has the condition

SIGN	DISEASE: Present	DISEASE: Absent
Present	**TRUE** + **a**	**FALSE** + **b**
Absent	**FALSE** - **c**	**TRUE** - **d**

    h. based on the above chart, the sensitivity or specificity of a test can be measured in the following way:

- $\text{Sensitivity} = \frac{a}{a+c}$ $\quad \text{Specificity} = \frac{d}{b+d}$

8. Likelihood Ratios[4,5]

$$\text{LR of a measurement} = \frac{\text{Probability of finding in patient with disease}}{\text{Probability of finding in patients without disease}}$$

a. likelihood Ratio (LR) is the likelihood that a given test result would be expected in a patient with the target disorder compared to the likelihood that that same result would be expected in a patient without the target disorder

$$+\text{LR} = \frac{\text{Proportion of patients with disease and finding}}{\text{Proportion of patients without disease BUT have finding}} = \frac{\text{sensitivity}}{(1 - \text{specificity})}$$

b. positive LR or negative LR reflects whether the physical finding or measurement is present (positive) or negative (absent)

$$-\text{LR} = \frac{1 - \text{sensitivity}}{\text{specificity}}$$

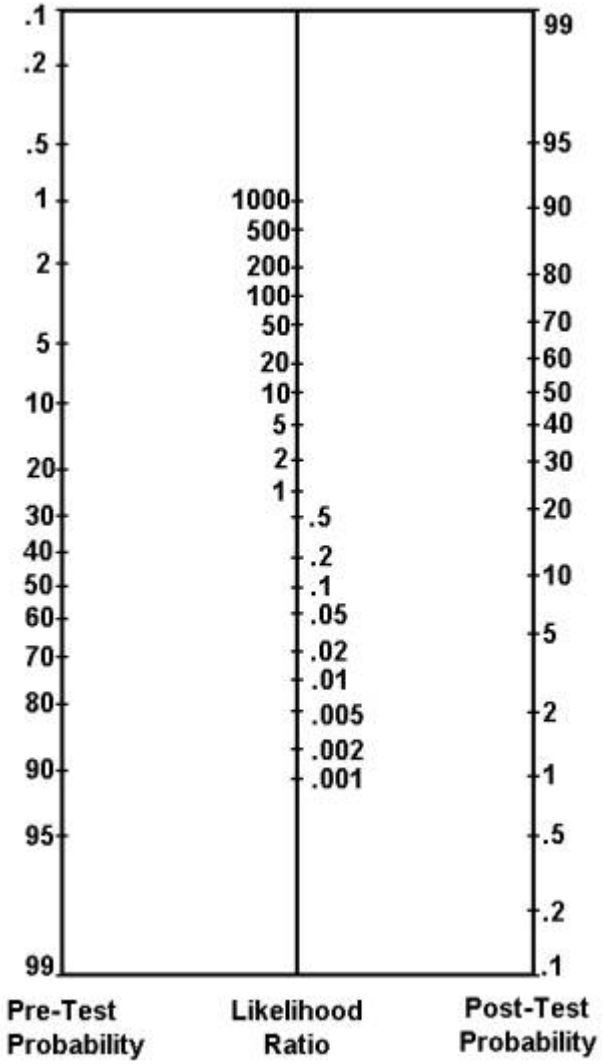
i. e.g. you have a patient with anemia and a serum ferritin of 60mmol/l and you find in an article that 90 per cent of patients with iron deficiency anemia have serum ferritins in the same range as your patient (= sensitivity) and that 15 per cent of patients with other causes for anemia have serum ferritins in the same range as your patient (1 – specificity)
    1. this means that your patient's result would be six times as likely (90/15) to be seen in someone with, as opposed to someone without, iron deficiency anemia, and this is called the LR (of 6 in this case) for a positive test result

c. useful for discriminating amongst diagnostic tests
    i. ideally, your goal is to order diagnostic tests that make post-test probability significantly higher or lower in order to get closer to definitively ruling in or ruling out a condition

d. can be used to estimate post-test probability – needs a bit of math to convert pre-test probability to odds, which can be multiplied by the LR to produce post-test odds, that can then be converted mathematically to post-test probability
    i. clinicians use graphs, nomograms and useful approximations
        1. LR nomogram
            a. a straight line can be drawn between a known pre-test probability and a known LR for a diagnostic test

i. this straight line can then be extended onwards until it intersects a post-test probability value

b. a LR greater than 1 produces a post-test probability which is higher than the pre-test probability
c. an LR less than 1 produces a post-test probability which is lower than the pre-test probability
d. when the pre-test probability lies between 30 and 70 per cent, test results with a very high LR (say, above 10) rule in disease
e. a very low LR (say, below 0.1) virtually rules out the chance that the patient has the disease



LR	Change in Probability
2	+15%
5	+30%
10	+45%

e. LR's from consecutive signs/tests can be multiplied together
    i. however, in order to combine diagnostic tests, they must each be independent of each other (e.g. can have nothing to do with each other, cannot measure the same thing)

9. Relative Risk and Odds Ratio[2,6]

a. Relative risk
    i. synonymous with risk ratio
    ii. the ratio of the risk of an event (e.g. disease or side effect) among people who are exposed to the risk factor, to the risk among people who are unexposed
        1. relative risk = (event rate in intervention group) ÷ (event rate in control group)
    iii. to estimate a relative risk you need a cohort study, from which incidence can be calculated
    iv. often used in the statistical analysis of binary outcomes where the outcome of interest has relatively low probability
    v. useful for clinical trial data
        1. used to compare the risk of developing a disease, in people not receiving the new medical treatment (or receiving a placebo) versus people who are receiving an established (standard of care) treatment
        2. can also be used to compare the risk of developing a side effect in people receiving a drug as compared to the people who are not receiving the treatment (or receiving a placebo)
    vi. e.g. in a simple comparison between an experimental group and a control group:
        1. a relative risk of 1 means that the two incidence rates are equal so the factor has no effect
        2. an RR of < 1 means the event is less likely to occur in the experimental group than in the control group
        3. an RR of > 1 means the event is more likely to occur in the experimental group than in the control group

b. Odds ratio
    i. odds ratio = the ratio of the probability of occurrence of an event to that of non-occurrence
    ii. expresses the association between a risk factor and a disease by comparing the likelihood of disease under two circumstances, such as the risk of a cough among smokers compared to non-smokers
        1. e.g. if 60 smokers develop a cough and 40 do not, the odds of developing the cough are 60:40 (or 1.5)
            a. Note that the probability of developing a cough is 60/100 (or 0.6)
    iii. the ratio of the two odds is closely related to the concept of relative risk,
    iv. useful because it can be calculated from a case-control study without requiring incidence rates, unlike relative risk

10. Event Rate[7]

c. the number of people experiencing an event as a proportion of the number of people in the population
d. useful for calculating risk reduction

11. Absolute Risk Reduction vs Relative Risk Reduction[7]

e. absolute risk reduction
    i. the arithmetic difference between 2 event rates; varies with the underlying risk of an event in the individual patient
        1. ARR = (event rate in intervention group) – (event rate in control group)
f. relative risk reduction
    i. the difference in event rates between 2 groups, expressed as a proportion of the event rate in the untreated group; usually constant across populations with different risks
        1. can be calculated in 2 different ways:
            a. relative risk reduction = 1 – relative risk
            b. relative risk reduction = (absolute risk reduction) ÷ (event rate in control group)

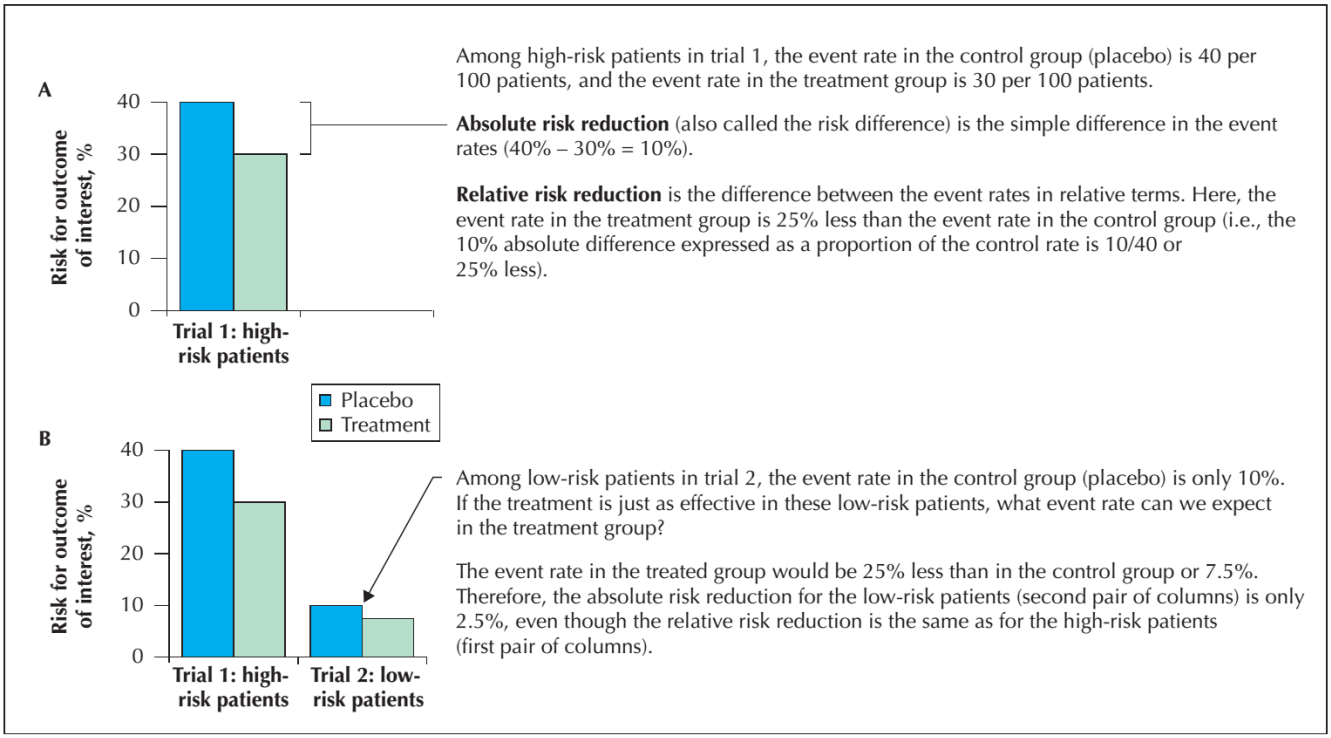


Fig. 1: Results of hypothetical placebo-controlled trials of a new drug for acute myocardial infarction. The bars represent the 30-day mortality rate in different groups of patients with acute myocardial infarction and heart failure. A: Trial involving patients at high risk for the adverse outcome. B: Trials involving a group of patients at high risk for the adverse outcome and another group of patients at low risk for the adverse outcome.

g. the absolute risk reduction becomes smaller when event rates are low, whereas the relative risk reduction, or "efficacy" of the treatment, often remains constant
    i. useful for calculating efficacy and magnitude of effect of a therapy
    ii. can also be used to weigh risk vs benefit (see Table 1B)

Table 1B: Benefit and harm table

	3-yr event rate for stroke, %			3-yr event rate for severe gastric bleeding, %		
Patient group	No treatment	With treatment (drug X)	Absolute risk reduction (no treatment – treatment)	No treatment	With treatment (drug X)	Absolute risk increase (treatment – no treatment)
At lower risk (e.g., Pat)	3	2	1	0.3	0.9	0.6
At higher risk (e.g., Dorothy)	30	20	10	0.3	0.9	0.6

*Based on data from randomized controlled trials of drug X reporting a 33% relative risk reduction for the outcome (stroke) over 3 years and a 3-fold increase for the adverse effect (severe gastric bleeding) over the same period.

12. Number Needed to Treat (NNT) and Number Needed to Harm (NNH) [7]

h. NNT = the number of patients who would have to receive the treatment for 1 of them to benefit
    i. calculated as 100 divided by the absolute risk reduction expressed as a percentage
        1. NNT = 1 ÷ (absolute risk reduction)
    ii. e.g. see Tables 2 and 3

Table 2: Benefit table for patients with cardiovascular problems

Clinical question	Event rate, %		ARR, %	NNT
	Control group	Treatment group		
What is the reduction in risk of stroke within 5 years among 60-year-old patients with hypertension who are treated with diuretics?[11]	2.9	1.9	1.00	100
What is the reduction in risk of death within 2 years after MI among 60-year-old patients treated with β-blockers?[12]	9.8	7.3	2.50	40
What is the reduction in risk of death within 5 weeks after acute MI among 60-year-old patients treated with streptokinase?[13]	12.0	9.2	2.80	36

Note: MI = myocardial infarction, ARR = absolute risk reduction, NNT = number needed to treat.

Table 3: Calculation of NNT from absolute risk reduction*

Form of absolute risk reduction	Calculation of NNT	Example
Percentage (e.g., 2.8%)	100/ARR	100/2.8 = 36
Proportion (e.g., 0.028)	1/ARR	1/0.028 = 36

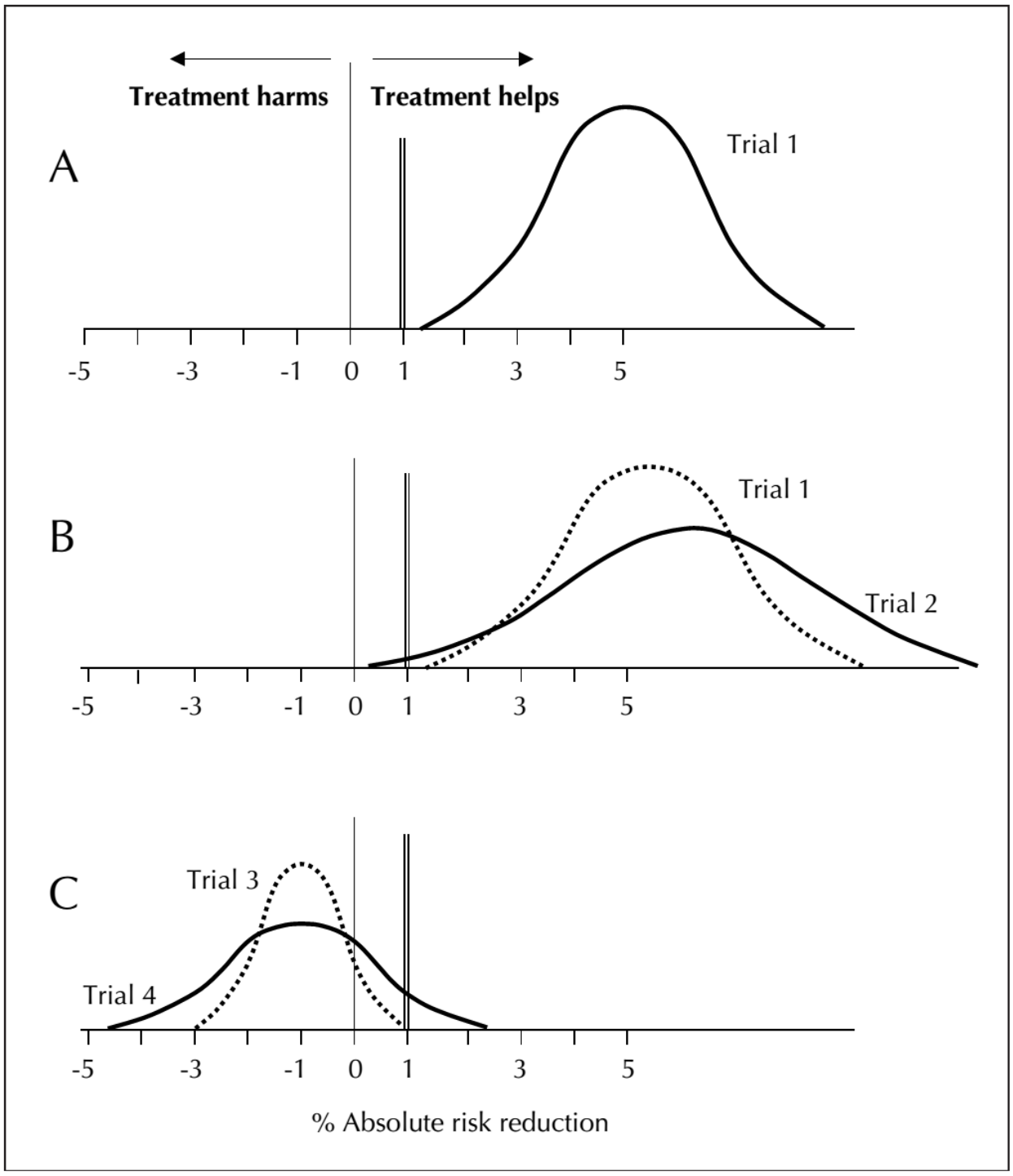
    iii. NNT is useful for as a tool for guiding clinical decisions about whether or not to treat with a specific therapy
        1. can be weighed against NNH

i. NNH = the number of patients who would have to receive the treatment for 1 of them to experience an adverse effect
    i. calculated as 100 divided by the absolute risk increase expressed as a percentage
        1. NNH = 1 ÷ (absolute risk increase)

13. Confidence Interval[8,9]

a. confidence intervals inform clinicians about the range within which the true treatment effect might plausibly lie, given the trial data
    i. greater precision (narrower confidence intervals) results from larger sample sizes and consequent larger number of events
    ii. statisticians and statistical software can calculate 95% confidence intervals around any estimate of treatment effect

b. confidence intervals are useful for determining whether a treatment is likely to provide enough benefit to the patient
    i. to determine whether a trial with a positive result is sufficiently large, clinicians should focus on the lower boundary of the confidence interval and determine if it is greater than the smallest treatment benefit that patients would consider important enough to warrant taking the treatment
    ii. for studies with a negative result, clinicians should examine the upper boundary of the confidence interval to determine if this value is lower than the smallest treatment benefit that patients would consider important enough to warrant taking the treatment
    iii. in either case, if the confidence interval overlaps the smallest treatment benefit that is important to patients (e.g. 1% in the example in Figure 1), then the study is not definitive and a larger study is needed
        1. Fig. 1: Results of 4 hypothetical trials. For the medical condition under investigation, an absolute risk reduction of 1% (double vertical rule) is the smallest benefit that patients would consider important enough to warrant undergoing treatment. In each case, the uppermost point of the bell curve is the observed treatment effect (the point estimate), and the tails of the bell curve represent the boundaries of the 95% confidence interval.



14. 6S Heirarchy of Evidence[10,11]

i. focuses on appraised literature

i. resources at the bottom of the hierachy have not been appraised

    ii. resources from higher on the hierarchy are critically appraised and the evidence is synthesized and often presented in the policy content of a particular country

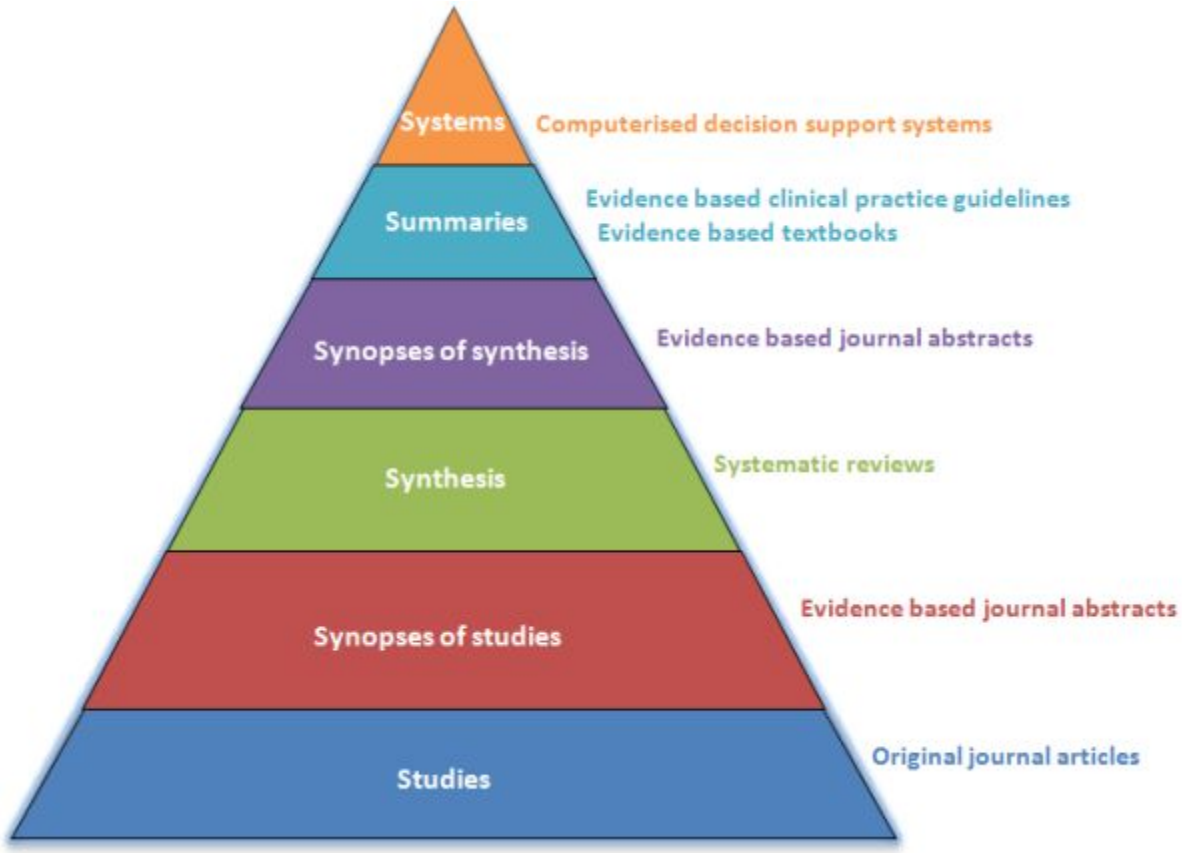
j. works very well when researching for answers to therapy questions

k. Table 2-3 represents the original 4S model as proposed by Guyatt et al
    i. has gone from 4S to 5S and now to 6S as represented by the pyramid
    ii. Guyatt et al make the important point that while the above hierarchies are excellent for decreasing bias and overcoming issues of small sample size for making clinical judgement, situational factors such as patient age, overall health and value judgements must also be taken into account

TABLE 2-3

A Hierarchy of Preprocessed Evidence[16]

Studies	Preprocessing involves selecting only those studies that are both highly relevant and characterized by study designs that minimize bias and thus permit a high strength of inference
Systematic reviews	Reviews involving the identification, selection, appraisal, and summary of primary studies addressing a focused clinical question using methods to reduce the likelihood of bias
Synopses	Brief summaries that encapsulate the key methodologic details and results of a single study or systematic review
Systems	Practice guidelines, clinical pathways, or evidence-based textbook summaries that integrate evidence-based information about specific clinical problems and provide regular updates to guide the care of individual patients



15. Study Design[12,13]

l. Experimental vs Observational

i. experimental studies are defined by investigator involvement assigning interventions or exposures
    1. generally RCTs, but may also non-randomised
    2. e.g. a study where one group is given a placebo and another is given an active drug by the investigator

ii. observational studies are defined by the lack of investigator involvement in interventions/exposures
    1. includes case control, cohort and cross-sectional studies
    2. most likely to be used when assigning an exposure or intervention is unethical
    3. e.g. a study done retrospectively looking for differences in health outcomes in people exposed to asbestos and those not exposed

m. Case Control vs Cohort vs Cross-sectional

i. these study types are useful for identifying disease or disease remission, disability or complications, death or survival, and the occurrence of risk factors

1. Case Control

a. exposures are compared between people with a particular disease outcome (cases) and people without that outcome (controls)

b. investigators aim to collect cases and controls that are representative of an underlying cohort or a cross-section of a population
    i. that population can be defined geographically, but also more loosely as the catchment area of health care facilities
    ii. the case sample may be 100% or a large fraction of available cases, while the control sample usually is only a small fraction of the people who do not have the pertinent outcome
    iii. controls represent the cohort or population of people from which the cases arose. Investigators calculate the ratio of the odds of exposures to putative causes of the disease among cases and controls

c. useful because, depending on the sampling strategy for cases and controls and the nature of the population studied, the odds ratio obtained in a case-control study can be interpreted as the risk ratio, rate ratio or (prevalence) odds ratio

d. e.g. a study done retrospectively looking for differences in health outcomes in people exposed to asbestos (cases) and those not exposed (controls)

2. Cohort

a. synonymous with follow-up study and longitudinal study
b. follow people over time
c. information is gathered about subjects and their exposures at baseline and then the occurrence of outcomes is assessed later after some time has passed
d. investigators commonly make contrasts between individuals who are exposed and not exposed or among groups of individuals with different categories of exposure
    i. investigators may assess several different outcomes, and examine exposure and outcome variables at multiple points during follow-up
e. closed cohorts
    i. enrol a defined number of participants at study onset and follow them from that time forward, often at set intervals up to a fixed end date
    ii. useful because cumulative incidences (risks) and incidence rates can be estimated; when exposed and unexposed groups are compared, this leads to risk ratio or rate ratio estimates
    iii. e.g. a prospective study done looking for differences in health outcomes in people exposed to asbestos and those not exposed, where all subjects are enrolled at the same time and followed for a period of 10 years, with no new subjects added to the group
f. open cohorts
    i. study population is dynamic
        1. people enter and leave the population at different points in time (for example inhabitants of a town)
        2. change due to deaths, births, and migration, but the composition of the population with regard to variables such as age and gender may remain approximately constant, especially over a short period of time
    ii. useful because they can be used to estimate incidence rates and rate ratios
    iii. e.g. Framingham study

3. Cross-sectional

a. synonymous with prevalence study, census
b. all individuals in a sample are assessed at the same point in time
c. often done to examine the prevalence of exposures, risk factors or disease
d. some are analytical and aim to quantify potential causal associations between exposures and disease
    i. such studies may be analysed like a cohort study by comparing disease prevalence between exposure groups
    ii. they may also be analysed like a case-control study by comparing the odds of exposure between groups with and without disease
e. a difficulty that can occur in any design but is particularly clear in cross-sectional studies is to establish that an exposure preceded the disease, although the time order of exposure and outcome may sometimes be clear
    i. in a study in which the exposure variable is congenital or genetic, for example, we can be confident that the exposure preceded the disease, even if we are measuring both at the same time
f. useful because they are versatile as noted above, and also cheaper because they often use routinely collected data
    i. conclusions are generally weaker than those garnered from cohort studies
g. e.g. a study done looking for differences in health outcomes in people exposed to asbestos and those not exposed, where outcomes are measured only once, at the same time as the data on whether each of the subjects was exposed to asbestos is gathered

n. Types of RCT

i. RCTs are defined by the fact that interventions and exposures are randomly allocated
ii. there are 2 types
    1. If individual participants are randomised, you have an individual randomised trial
    2. If groups of participants are randomised, you have a cluster randomised trial

o. Case Series/Study

i. non-comparative – there is no comparison made between interventions and exposures
ii. useful for very rare conditions where a paucity of data exists and in cases where any other type of study is impossible or unethical

iii. e.g. a study done examining the health outcomes of a worker in an asbestos mine

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