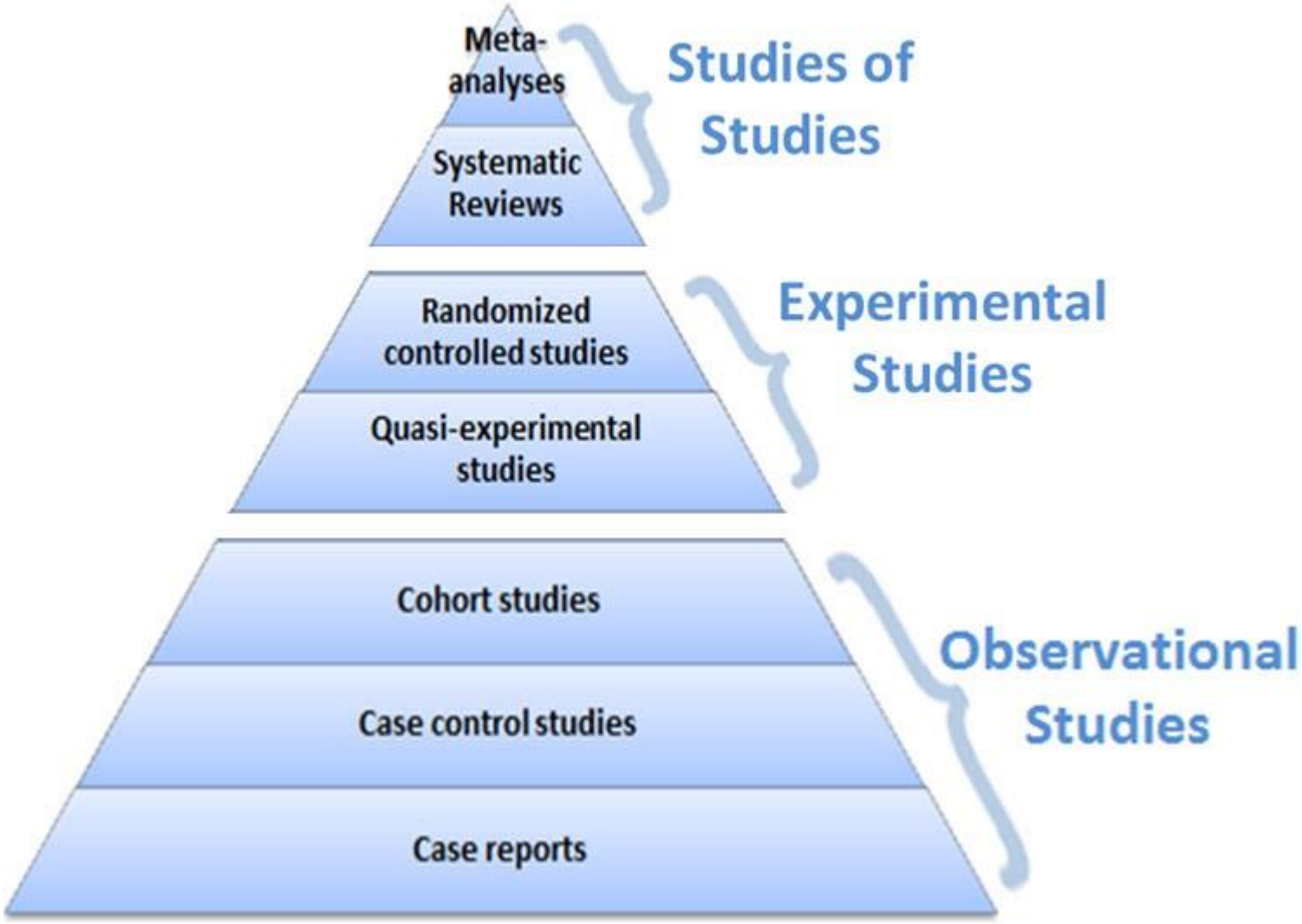
U3 STUDY DESIGNS

Measures of disease frequency and association


Meta-analyses
Systematic Reviews
Studies of Studies
Randomized controlled studies
Quasi-experimental studies
Experimental Studies
Cohort studies
Case control studies
Case reports
Observational Studies

Types of studies

- Observational
  - Descriptive
  - Cross-sectional
  - Cohort
- Experimental
  - Randomized controlled trial
- Studies of studies
  - Systematic reviews
  - Meta-analyses

Risk factors cluster! e.g. Alcohol and lung cancer are correlated.

Confounding: risk factors don't happen in isolation, except in a controlled experiment.

Increasing level of evidence

Ways to avoid or control for confounding

- During the design phase: randomize or match
- In the analysis phase: use multivariate regression to statistically "adjust for" confounders
  - Statistical adjustment is not a panacea; you cannot control for all confounders and there is always "residual" confounding

Cross-sectional (prevalence) studies

- Measure prevalence of the event (disease) and exposure on a random sample of the population of interest at one time point

- Advantages: Cheap and easy!
- Limitations
  - Correlation does not imply causation
  - Cannot determine what came 1st
  - Confounding

- Researchers measured the prevalence of coronary artery calcification (atherosclerosis) and the prevalence of depressive symptoms in a large cohort of elderly men and women in Rotterdam (n=1920). (Tiemeier et al. Arch Gen Psychiatry, 2004).

Case-Control Studies

- Sample on disease status and ask retrospectively about exposures

- Advantages: Efficient for rare diseases and outbreak situations
- Limitations
  - Getting appropriate controls is tricky.
  - Recall bias
  - Confounding
  - The risk factor may have come after the disease

- Early case-control studies among AIDS cases and matched controls indicated that AIDS was transmitted by sexual contact or blood products.
- In 1982, an early case-control study matched AIDS cases to controls and found a large, positive association between amyl nitrites (“poppers”) and AIDS (Marmor et al. NEJM, 1982). This is an example of confounding.

Prospective cohort study

- Measure risk factors on people who are disease-free at baseline; then follow them over time and calculate risks or rates of developing disease

- Advantages:
  - Exposures are measured prior to outcomes!
  - Can study multiple outcomes
- Limitations
  - Time and money!
  - Confounding
  - Loss to follow-up

- The Framingham Heart Study enrolled 5209 residents of Framingham, MA, aged 28 -62 in 1948. Researchers measured their health and lifestyle factors (blood pressure, weight, exercise, etc.) and followed them for decades to determine the occurrence of heart disease.
- The study continues today, tracking the kids and grandkids of the original cohort.

Retrospective cohort study

- Conceptually similar to a prospective cohort study, but the cohort is assembled after outcomes have occurred using stored data.

- Advantages
  - Exposure data were collected before outcomes occurred.
  - Cheaper and faster than prospective designs
- Limitation: Data quality may be limited

- Mortality in former Olympic athletes: Using the Sports Reference database, researchers identified a cohort of 9889 athletes who participated in the Olympic Games between 1896 and 1936 and were born before 1910. They used the database to find dates of death for these athletes. Then they compared the mortality rates of athletes in different types of sports (BMJ 2012; 345: e7456.)

Randomized clinical trials

- Considered the **gold standard** of study design

- Advantages
  - Randomization minimizes confounding.
  - Blinding minimizes bias.
- Limitations
  - Expensive
  - Can only look at short-term outcomes.
  - Not always ethical to randomize
  - Results may not be generalizable

- Comparison of upper gastrointestinal toxicity of Vioxx and Naproxen in patients with rheumatoid arthritis. Researchers randomly assigned 8076 patients with rheumatoid arthritis to receive either Vioxx or Naproxen (non-steroidal anti-inflammatory) twice daily. The study was double blind. The primary end point was confirmed clinical upper gastrointestinal events (such as ulcers and bleeding).

(Bombardier et al. NEJM 2000; 343: 1520-8)

Measures of disease frequency

- Incidence
  - The **rate** (involves time) at which people are developing a disease (new cases).
    - There are 20 new cases of heart disease per 1000 men per year.
- Cumulative risk (cumulative incidence)
  - The **proportion** (percentage) of people who develop a disease in a specified time period (new cases).
    - During a two-year study, 1% of smokers developed heart disease.
- Prevalence
  - The **proportion** (percentage) of people who have a disease at a given point in time; **includes old and new cases.**
    - For example, 10% of men over 70 have heart disease.

Randomized trial

Gastrointestinal events in Vioxx vs. Naproxen

Depends on the duration of follow-up

Group	Number per group	Person-years of follow-up (PY)	Number of GI events	Incidence Rate	Incidence Rate	Cumulative risk
Vioxx	4047	2315	56	56/2315 =.021 PY	**2.1 events per 100 PY**	56/4047=**1.4%**
Naproxen	4029	2316	121	121/2316 =.045 PY	**4.5 events per 100 PY**	121/4029=**3.%**

If follow-up had been 1 year, we'd expect the cumulative risks to be about 2.1% in the Vioxx group and 4.5% in the Naproxen group

Researchers randomly assigned 8076 patients with rheumatoid arthritis to receive either Vioxx or Naproxen (non-steroidal anti-inflammatory) twice daily. The study was double blind. The primary end point was confirmed clinical upper gastrointestinal events (such as ulcers and bleeding).

Comparison of upper gastrointestinal toxicity of Vioxx and Naproxen in patients with rheumatoid arthritis. (Bombardier et al. *N Engl J Med* 2000; 343: 1520-8).

Cross-sectional study

Prevalence of depressive disorders

Researchers measured the prevalence of coronary artery calcification (atherosclerosis) and the prevalence of depressive symptoms in a large cohort of elderly men and women in Rotterdam (n=1920).
Tiemeier et al. *Arch Gen Psychiatry*, 2004

Coronary calcification	Total number	Number with dep. disorders	Prevalence of depressive disorders
0-100	894	9	9/894=0.9%
101-500	487	11	11/487=2.3%
>500	539	16	16/539=3.0%

Measures of absolute risk differences:

- Difference in rates
- Difference in risks (proportions/percentages)
  - Difference in cumulative risk
  - Difference in prevalence

Difference risks in GI events

Group	Number per group	Person-years of follow-up (PY)	Number of GI events	Incidence Rate	Incidence Rate	Cumulative risk
Vioxx	4047	2315	56	56/2315 =.021 PY	**2.1 events per 100 PY**	56/4047=**1.38%**
Naproxen	4029	2316	121	121/2316 =.045 PY	**4.5 events per 100 PY**	121/4029=**3.%**

4.5 – 2.1 = 2.4 fewer GI events in the Vioxx per 100 PY

1.38% – 3% = 1.62% decrease in the risk of GI events in the Vioxx

Note that the rate difference is a better measure *when it's available!*

Heart attack data, Vioxx vs. Naproxen

Group	Number per group	Person-years of follow-up (PY)	Number of heart attacks	Incidence Rate	Cumulative risk
Vioxx	4047	2315	17	1000*17/2315 =7.3 **events per 1000 PY**	17/4047=**.42%**
Naproxen	4029	2316	4	1.7 **events per 1000 PY**	4/4029=**.10%**

Rate difference=7.3 – 1.7 = 5.6 excess heart attacks in the Vioxx group per 1000 PY

Number Needed to Harm (NNH) = 1000/5.6 = 179

Cumulative risk difference=0.42%-0.10% = 0.32% increase in the risk of heart attacks in the Vioxx group

Bombardier C, Laine L, Reicin A, et al. *N Engl J Med* 2000; 343: 1520-8.
Curfman GD, Morrissey S, Drazen JM. *N Engl J Med* 2005; 353:2813-4.

Paper's abstract:

They've reported the cumulative risks not the incidences!

- "The incidence of myocardial infarction was lower among patients in the Naproxen group than among those in the Vioxx group (0.1% vs. 0.4%)."

- How would an alternate presentation change the message?
- The incidence of myocardial infarction was higher among patients in the Vioxx group than among those in the Naproxen group (7.3 events per 1000 person-years vs. 1.7 events per 1000 person-years).

Bombardier C, Laine L, Reicin A, et al. *N Engl J Med* 2000; 343: 1520-8.

Measures of relative risk

- Rate ratio/hazard ratio
  - Ratio of incidence rates
  - Hazard ratio: ratio of hazard rates, which are instantaneous incidence rates; calculated using Cox regression.
- Risk ratio
  - Ratio of cumulative risks (proportions)
  - Ratio of prevalences (proportions)
- Odds ratio
  - Odds ratios are the only valid measure of relative risk for **case-control** studies.
  - Odds ratios are calculated from logistic regression.

Interpretation: Percent increase (or decrease) in the rate/risk/odds of the outcome.

1.0 = NULL value (no difference)
<1.0 = protective effect (decreased risk)
>1.0 = harmful effect (increased risk)

Relative risks of GI events

Group	Number per group	Person-years of follow-up (PY)	Number of GI events	Incidence Rate	Incidence Rate	Cumulative risk
Vioxx	4047	2315	56	56/2315 =.021 PY	**2.1 events per 100 PY**	56/4047=**1.38%**
Naproxen	4029	2316	121	121/2316 =.045 PY	**4.5 events per 100 PY**	121/4029=**3.%**

Rate ratio = 2.1/4.5= 0.46

Risk ratio = 1.4/3.0 =0.46

The risk ratio and rate ratio are identical here since the groups were followed for equal amounts of time.

Interpretation: Vioxx reduces the rate of GI events by 54%

Relative risks of heart attacks

Group	Number per group	Person-years of follow-up (PY)	Number of heart attacks	Incidence Rate	Cumulative risk
Vioxx	4047	2315	17	1000*17/2315 =7.3 **events per 1000 PY**	17/4047=**.42%**
Naproxen	4029	2316	4	1.7 **events per 1000 PY**	4/4029=**.10%**

Rate ratio = 7.3/1.7= 4.2

Risk ratio = 0.42/0.10 =4.2

Vioxx increases the rate/risk of heart attacks by 4-fold (320%)

n+10%n=1.1n=1.1-fold

n+100%n=2n=2-fold

From the paper's…

Abstract: "The incidence of myocardial infarction was lower among patients in the naproxen group than among those in the rofecoxib group (0.1 percent vs. 0.4 percent; relative risk, 0.2; 95 percent confidence interval, 0.1 to 0.7)."

Conclusion: "Thus, our results are consistent with the theory that naproxen has a coronary protective effect and highlight the fact that rofecoxib does not provide this type of protection...

They reported risks rather than rates (whereas for the primary outcome, GI events, they reported rates).

They "flipped" the relative risk, implying that Naproxen is protective rather than that Vioxx is harmful. (0.1/.42=0.24)

Introduction to odds ratios

- Odds ratios are another measure of relative risk.
- For case-control studies, the odds ratio is the only valid measure of relative risk.
- Logistic regression (commonly used with binary outcome variables) gives multivariate-adjusted odds ratios.

$$ODDs = \frac{p}{q} = \frac{p}{1-p}$$

Risk (prevalence) ratios for depression and artery blockage data:

Those with moderate blockage have a 156% increased prevalence of depressive disorder compared with those with the least blockage.

Those with severe blockage have a 233% increased prevalence of depressive disorder compared with those the least blockage.

Coronary calcification level	Prevalence of depressive disorders	Risk ratio (compared with none/low group)
0-100	0.9%	reference
101-500	2.3%	2.3/0.9=2.56
>500	3.0%	3.0/0.9=3.33

Tiemeier et al. *Arch Gen Psychiatry*, 2004

The **ODDS** of depressive symptoms by coronary calcification level

Coronary calcification level	Prevalence of depressive symptoms	Risk ratio	ODDS of depressive symptoms	ODDS Ratio
0-100	0.9%	Ref.	0.9%/99.1%	Ref.
101-500	2.3%	2.56	2.3%/97.7%	(2.3/97.7)/(.9/99.1) =2.59
>500	3.0%	3.33	3.0%/97.0%	(3/97)/(.9/99.1) =3.41

When the outcome is rare, the odds ratio and risk ratio are very similar!
When the outcome is common, this is not true and odds ratios can be misleading!

Odds ratios and risk ratios are similar for rare outcomes…

- Risk ratio:

$$\frac{3\%}{1\%} = 3.0$$

- Corresponding Odds ratio:

$$\frac{\frac{3\%}{97\%}}{\frac{1\%}{99\%}} = 3.06$$

But odds ratios distort effects for common outcomes…

- Risk ratio: $\frac{60\%}{20\%} = 3.0$

- Corresponding Odds ratio: $\frac{\frac{60\%}{40\%}}{\frac{20\%}{80\%}} = 6.0$

Why do we ever use an odds ratio??

- We cannot calculate risk or rate ratios from a case-control study (since we cannot calculate the risk or rate of developing the disease).
- The multivariate regression model for binary outcomes (logistic regression) gives odds ratios, not risk ratios.

	Cases	Control	
Exposed	a	b	Total of exposed (m_i)
No Exposed	c	d	Total of no exposed (m_o)
	Total cases (n_i)	Total control (n_o)	Population size (n)

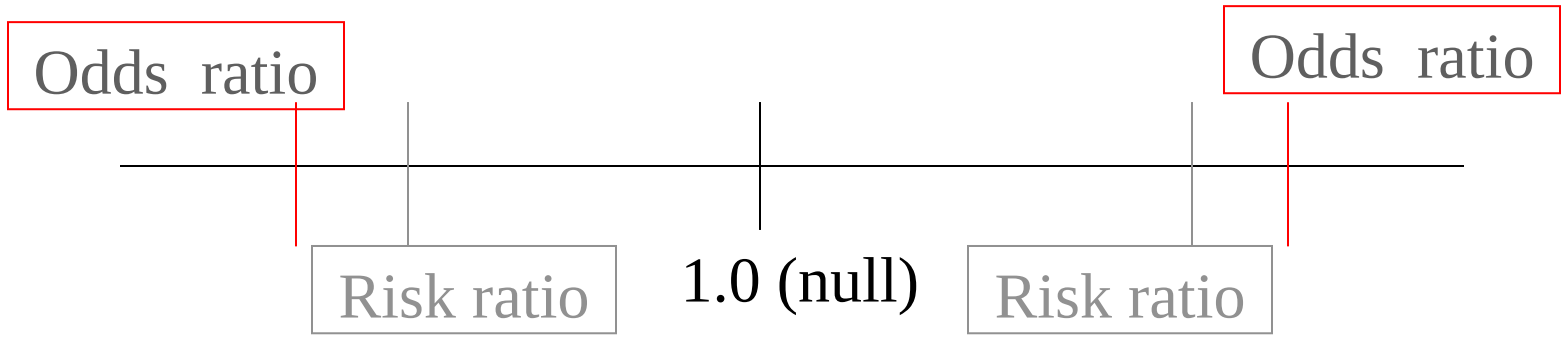
OR=(a/c)/(b/d)
=a*d/b*c

If a and c are low, then OR ≈RR

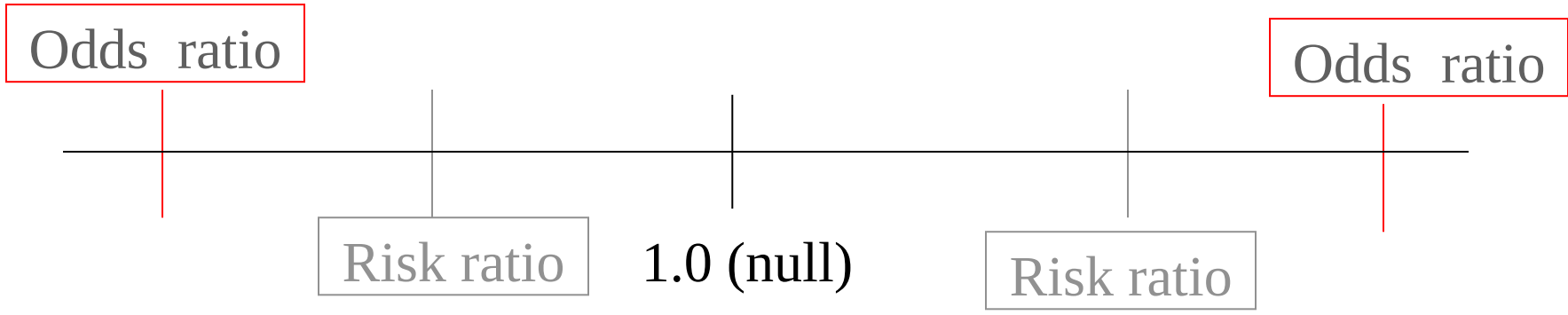
RR=(a/a+b)/(c/c+d)

The odds ratio vs. the risk ratio

Rare Outcome



Common Outcome



Interpretation of the odds ratio

- Odds ratios can be interpreted as risk ratios for rare outcomes
  - Rule of thumb for defining “rare”: outcome occurs in <10% of the reference/control group
- But, when the outcome is common, odds ratio distort the effect size and need to be interpreted cautiously.