

Evidence-Based Medicine Journal Club: How to Use an Article about Association

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Peds EBM teaching slides credits-- materials developed with help from:

- User's Guide to EBM (reproduced with permission of JAMA): <http://www.cche.net/usersguides/main.asp>
- Dr. Susan Guralnick of Stony Brook (SUNY)
- EBM Pediatric Program Directors and Educators Workshop at University of Illinois at Chicago
- Epidemiology and Preventive Medicine Dept. at Univ. of MD (Masters Program)

Association

Harm or Etiology

Association: Harm or Etiology

- Are the results likely to be valid?
- Are the results clinically significant?
- Are the results applicable to my patient?
- Will the results change my practice/management?

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- Are the results likely to be valid ?

Were there clearly defined groups of patients, similar in all important ways other than exposure to the treatment / cause?

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The choice of *comparison groups* has an enormous influence on the credibility of the results

The *design of the study* determines the comparison groups

- What study designs can be used?

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Randomized Controlled Trial

Rarely used in harm studies due to ethical issues

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Cohort Studies

The investigator identifies exposed and non-exposed groups of patients and follows them forward in time monitoring the occurrence of the outcome

- Useful when harmful outcomes are infrequent
- Useful when subjects cannot be assigned to an exposure group, e.g. occupational exposure
- Investigator must document the characteristics of each group and either demonstrate comparability or use statistical techniques to adjust for differences

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Case-Control

Investigators identify patients who already have developed the outcome of interest, then choose controls – persons who do not have the outcome of interest, but are otherwise similar to the cases

- Retrospective
- Susceptible to unmeasured confounders

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Case Series and Case Reports

- Do not provide any comparison group!
- Do not fulfill first requirement for validity

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Cross-Sectional Studies (Prevalence studies)

- Can be used to study potentially causal relationships between risk factors & outcomes
- Measure prevalence (not incidence)
- Exposures (risk factors) and outcomes (disease) are measured simultaneously
 - Temporal relationship is lost

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- Are the results likely to be valid?

- Was the assessment of outcomes either objective or blinded to the exposure?

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- Were the exposures and outcomes measured the same way in both groups?
 - *How was the exposure ascertained?*
 - Recall Bias or Interviewer Bias
 - Look for strategies that minimize bias, such as blinding the subjects and interviewers to the hypothesis of the study
 - Exposure Opportunity
 - *How was the outcome ascertained?*
 - Surveillance Bias

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- Are the results likely to be valid?
 - Was the follow-up of the study patients sufficiently long (for the outcome to occur) and complete?

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- Follow-Up
 - Patients lost to follow-up threaten validity as they may have very different outcomes from those available for assessment
 - The longer the follow-up required, the more likely it will be incomplete

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- Are the results likely to be valid?
 - Do the results of the harm study fulfill some of the diagnostic tests for causation?

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- Diagnostic Tests for Causation:
 - Is it clear that the exposure preceded the onset of the outcome?
 - Is there a dose-response gradient?
 - Is there any positive evidence from a de-challenge / re-challenge study?
 - Is the association consistent from study to study?
 - Does the association make biological sense?

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Are the results clinically significant?

	Adverse Outcome		Totals
	Present	Absent	
Exposure Yes	a	b	a+b
Exposure No	c	d	c+d
Totals	a+c	b+d	a+b+c+d

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	Adverse Outcome		Totals
	Present	Absent	
Exposure- Yes	a	b	a+b
Exposure- No	c	d	c+d
Totals	a+c	b+d	a+b+c+d

$$\text{Relative Risk (RR)} = [a / (a+b)] / [c / (c+d)]$$

$$\text{Odds Ratio} = (a/b) / (c/d) = (a/c) / (b/d) = ad/bc$$

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Relative Risk (RR)

- Disease Prevalence in an exposed vs. non-exposed population
- The risk (or incidence) of the adverse effect in the exposed group divided by the risk of the adverse effect in the unexposed group
- Actual prevalence data needed for 2x2 chart
- Describes the disease prevalence in specific exposed vs. non-exposed populations

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Relative Risk (RR)

RR > 1 represent an increase in risk associated with the exposure

e.g. cohort study, in-hospital mortality following noncardiac surgery in male veterans, 23 of 289 patients with hx HTN died, compared with 3 of 185 patients without hx HTN.
RR of death for Hypertensive men = 4.9
Death occurs almost 5x more often

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Relative Risk (RR)

$$RR = (a / a+b) / (c / c+d) = (23 / 289) / (3 / 185) = 4.9$$

	Death	No Death	
HTN	23	266	289
No HTN	3	182	185
	26	448	

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Relative Risk (RR)

- RR depends on having actual data on exposed and unexposed patients in a designated population
- It is not applicable in Case-Control studies, where the number of cases and controls is chosen by the investigator
- For C-C studies, the Odds Ratio is used

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Odds Ratio (OR)

- Ratio of Odds
- The odds of a case patient being exposed divided by the odds of a control patient being exposed
- Proportion exposed in a diseased vs. non-diseased patient sample
- When the outcome of interest is rare in the population from which the sample was drawn (often the reason for using a case-control study), the OR closely approximates the RR

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- Odds Ratio (OR)

- Describes the relative harm of an exposure independent of disease prevalence

OR = 1 No effect
OR > 1 + Harm

- If the disease prevalence is small, then RR=OR

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- Examine the confidence interval around the estimate of risk (or measure of association)
 - OR or RR

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What is the Magnitude of the Risk?

The RR and the OR *do not tell us how frequently a problem occurs*, only that the effect occurs more or less often in the exposed group compared with the unexposed group

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What is the Magnitude of the Risk?

Calculate the NNH = Number Needed to Harm

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What is the Magnitude of the Risk?

Calculate the NNH = Number Needed to Harm

NNH = 1 / ARI

ARI = Absolute Risk Increase

ARI = $c / c+d - a / a+b$

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What is the Magnitude of the Risk?

Cardiac Arrhythmia Suppression Trial

Mortality : 3.0% placebo

 7.7% encainide/flecainide

ARI = $(c/c+d) - (a/a+b) = 7.7\% - 3\% = 4.7\%$

NNH = $1 / .047 = 21.3$

NNH = 21

For every 21 patients treated with encainide/flecainide, there will be on average, one excess death

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- Are the results applicable to my patient?
 - Is my patient so different from those in the study that the results don't apply?
 - What is my patient's risk of an adverse event?
 - What is my patient's potential benefit from the therapy?
 - *What are my patient's preferences, concerns, and expectations from this treatment?*
 - What alternative treatments are available?