Medical College of Georgia
GEORGIA'S HEALTH SCIENCES UNIVERSITY

Department of Biostatistics
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Biostatistics for Librarians

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Purpose of Today's Presentation

- I'd like to show you some of the "poetry" of statistics (not the "plumbing").
- I'd like to help you become better "consumers" of statistics (not "practitioners").
- My goal is to help you better understand and evaluate the medical literature .

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Today's Topics

- Part I. Common Research Designs Used in Epidemiology
- Part II. Assessment of Risk & Benefit in Epidemiologic Studies
- Part III. Selecting Statistical Procedures

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Part I. Common Research Designs Used in Epidemiology

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FUNCTIONS OF RESEARCH DESIGN

- Research is the process of answering a question that can be answered by *appropriately collected data*. The question may simply be, "What is (or was) the frequency of a disease in a certain place at a certain time?" The answer to this question is *descriptive*, but, that does not mean that obtaining the answer (descriptive research) is a simple task.
- All research, whether *quantitative* or *qualitative*, is descriptive, and no research is better than the quality of the data obtained. The rules that govern the process of collecting and arranging the data for analysis are called *research designs*.

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FUNCTIONS OF RESEARCH DESIGN

- Another research question might be, "What caused this disease?" *Hypothesis generation* is the process of developing a list of possible candidates for the "causes" of the disease and obtaining initial evidence that supports one or more of these candidates.
- When one or more hypotheses are generated, they should be tested (*hypothesis testing*), by making predictions from the hypotheses and examining new data to determine if the predictions are correct.

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Epidemiological Designs

- **The basic function of most epidemiologic research designs is either to describe the pattern of health problems accurately or to enable a fair, unbiased comparison to be made between a group with and a group without a risk factor, a disease, or a preventive or therapeutic intervention.**

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A good *epidemiologic research design* should perform the following functions:

1. **Enable a *comparison* of a variable (e.g., disease frequency) between two or more groups at one point in time or, in some cases, between one group before and after receiving an intervention or being exposed to a risk factor**
2. **Allow the comparison to be *quantified* in absolute terms (as with a *risk difference* or *rate difference*) or in relative terms (as with a *relative risk* or *odds ratio*)**
3. **Permit the investigators to determine when the risk factor and the disease occurred, i.e., to determine the *temporal sequence***
4. **Minimize biases, confounding, and other *problems* that would complicate interpretation of the data.**

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- **The research designs discussed in this chapter are the primary ones used in epidemiology. Depending on the design chosen, they help with the development of hypotheses, the testing of hypotheses, or both.**
- ***Observational Designs:***
  - **Cross-sectional surveys and ecologic studies are useful for developing hypotheses;**
  - **Cohort studies and case-control studies can be used to develop hypotheses and to test them, although the hypothesis development and hypothesis testing must always be done on different data sets; and**
- ***Experimental Designs:***
  - **Randomized clinical trials or field trials are usually the best for testing new treatments or preventive measures.**

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TYPES OF RESEARCH DESIGN

- **Because some research questions can be answered by more than one type of research design, the choice of design depends on a variety of considerations, including speed, cost, and availability of data.**
- **Each type of research design has advantages and disadvantages (Tables 1 & 2).**

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Research Designs

- **Observational Designs for Generating Hypotheses:**
  - **Cross-Sectional Surveys**
  - **Ecologic Studies**
    - **Cross-Sectional or Longitudinal**
- **Observational Designs for Generating or Testing Hypotheses:**
  - **Cohort Studies**
    - **Retrospective or Prospective**
  - **Case-Control Studies**
- **Experimental Designs for Testing Hypotheses:**
  - **Randomized Controlled *clinical trials* (RCCTs)**
  - **Randomized Controlled *field trials* (RCFTs)**

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Cross-Sectional Surveys

- **A cross-sectional survey is a survey of a population at a single point in time. Examples are an interview survey and a mass screening program.**
- **They are useful for determining the prevalence of risk factors and the frequency of prevalent cases of some diseases for a defined population. They also are useful for measuring current health status and planning for some health services, including setting priorities for disease control.**

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Cross-Sectional Ecologic Studies

- Cross-sectional ***ecologic*** studies relate the frequency with which some characteristic (e.g., smoking) and some outcome of interest (e.g., lung cancer) occur in the same geographic area (e.g., a city, county, or state).
- These studies are often useful for suggesting hypotheses, but they cannot be used to draw causal conclusions because there is no information as to whether the people who smoked are the same people who developed lung cancer, it is unknown whether the exposure or the beginning of the lung cancer came first, and there may be other explanations for the observed association.

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Cross-Sectional Ecologic Studies

- Sometimes people are unaware of these weaknesses (sometimes called the ***ecologic fallacy***) and use the findings in surveys to make statements such as the following, "There are high levels of both toxic pollution and cancer in northern New Jersey, so the toxins are causing the cancer." This conclusion may or may not be correct.

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Longitudinal Ecologic Studies

- Longitudinal ecologic studies use ongoing surveillance or frequent cross-sectional studies to measure trends in disease rates over many years in a defined population.
- By comparing the trends in disease rates with other changes in the society (e.g., wars, immigration, or the introduction of a vaccine or antibiotics), epidemiologists attempt to determine the impact of these changes on the disease rates.

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Cohort Studies

- A cohort is a clearly identified group of people to be studied. In cohort studies, investigators begin by assembling one or more cohorts, either by choosing persons specifically because they were and were not exposed to one or more risk factors to be studied or by taking a random sample of a population.
- After the cohort of study subjects is selected, the subjects are followed over time to determine whether or not they develop the diseases of interest, and whether the risk factors that were measured at the beginning of the study predict the diseases that occur.

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Cohort Studies

- The defining characteristic of cohort studies is that groups are defined on the basis of exposure and are followed for outcomes.
- This is in contrast to case-control studies (see later), in which groups are assembled on the basis of outcome status and are queried (back in time) for exposure status.
- There are two general types of cohort studies (prospective and retrospective). The time relationships of the two are shown in Fig. 1.

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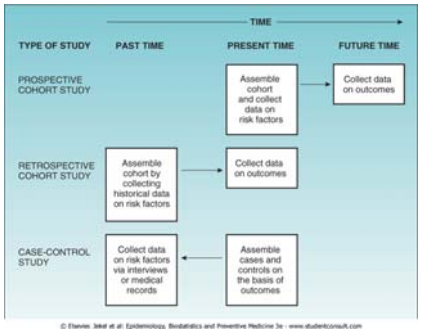

Figure 1. Illustration of the relationship between the time of assembling study subjects and the time of data collection in a prospective cohort study, a retrospective cohort study, and a case-control study.

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Prospective Cohort Studies

- **In a prospective cohort study, the investigator assembles the study groups in the present time, collects baseline data on them, and continues to collect data for a period that can last many years.**

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Retrospective Cohort Studies

- **Some of the time and cost limitations of the prospective cohort study can be mitigated by doing a retrospective cohort study.**
- **In this approach, the investigator goes back into history to define a risk group (e.g., people exposed to the Hiroshima atomic bomb in August 1945) and follows the group members up to the present to see what outcomes (e.g., cancer and death) have occurred.**

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Case-Control Studies

- **The investigator in a case-control study selects the case group and the control group on the basis of the outcome (i.e., having the disease of interest versus not having the disease of interest) and compares the groups in terms of their frequency of *past exposure* to possible risk factors (see Fig. 1).**

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Case-Control Studies

- **The *actual risk* of the outcome cannot be determined from case-control studies because the underlying population is unknown. An estimate of the *relative risk* of the outcome, called the *odds ratio*, can be determined in case-control studies.**
- **In this kind of study, the cases and controls are assembled, and they are questioned (or their relatives or medical records are consulted) regarding past exposure to risk factors.**
- **In past decades, case-control studies often were called retrospective studies for this reason.**

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Case-Control Studies

- **The time relationships in a case-control study are similar to those in a cross-sectional study in that the investigator learns simultaneously about the current disease state and any risk factors that may have existed in the past.**
- **In terms of assembling the subjects, however, a case-control study differs from a cross-sectional study in that the sample for the case-control study is chosen specifically from groups with and without the disease of interest.**
- **Often, all the people with the disease of interest in a geographic area and time period can be selected as cases. This reduces bias in case selection.**

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Case-Control Studies

- **Case-control studies are especially useful when a study must be done quickly and inexpensively or when the disease being studied is rare (e.g., has a prevalence of <1%).**
- **In determining the risk factors, a major problem is the potential for recall bias.**
- **It is not easy to know what is the correct control group for the cases.**
- **The controls usually are matched individually to cases on the basis of age, sex, and often race. If possible, the investigator obtains controls from the same diagnostic setting in which the cases were found, to avoid potential bias.**

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Case-Control Studies

- **A potential danger of studies using matching is what is known as ***overmatching*.**
- **If cases and controls were inadvertently matched on some characteristic that is potentially causal, that "cause" would be missed.**
- **In early studies of the causes of lung cancer, if cases and controls had been matched on smoking status, smoking would not have been found as a potentially causal factor.**

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Table 1. Advantages of Common Types of Studies Used in Epidemiology

Studies	Advantages
Cross-sectional surveys	Are fairly quick and easy to perform; are useful for hypothesis generation
Ecologic studies	Are fairly quick and easy to perform; are useful for hypothesis generation
Cohort studies	Can be performed retrospectively or prospectively; can be used to obtain a true (absolute) measure of risk; can study many disease outcomes; are good for studying rare risk factors
Case-control studies	Are fairly quick and easy to perform; can study many risk factors; are good for studying rare diseases
Randomized controlled trials	Are the "gold standard" for evaluating treatment interventions (clinical trials) or preventive interventions (field trials); allow investigator to have extensive control over research process

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Table 2. Disadvantages of Common Types of Studies Used in Epidemiology

Studies	Disadvantages
Cross-sectional surveys	Do not offer evidence of a temporal relationship between risk factors and disease; are subject to late-look bias; are not good for hypothesis testing
Ecologic studies	Do not allow for causal conclusions to be drawn because the data are not associated with individual persons; are subject to ecologic fallacy; are not good for hypothesis testing
Cohort studies	Are time-consuming and costly (especially prospective studies); can study only the risk factors measured at the beginning; can be used only for common diseases; may have losses to follow-up
Case-control studies	Can obtain only a relative measure of risk; are subject to recall bias; selection of controls may be difficult; temporal relationships may be unclear; can study only one disease outcome at a time
Randomized controlled trials	Are time-consuming and usually costly; can study only interventions or exposures that are controlled by investigator; may have problems related to therapy changes and dropouts; may be limited in generalizability; are often unethical to perform at all

Experimental Designs for Testing Hypotheses

- **Two types of randomized controlled trials are discussed here: randomized controlled ***clinical trials*** (RCCTs) and randomized controlled ***field trials*** (RCFTs). Both designs follow the same series of steps shown in Fig. 2 and have many of the same advantages and disadvantages.**
- **The major difference between the two is that clinical trials are usually used to test ***therapeutic interventions*** in ***ill persons*,**
- **field trials are usually done to test ***preventive interventions*** in ***well persons*** in the community.**

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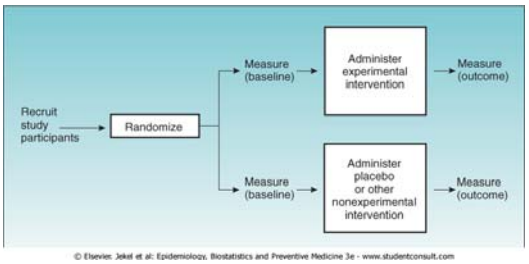

Figure 2. Illustration of the relationship between the time of assembling the study subjects and the time of data collection in an RCCT and an RCFT.

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Randomized Controlled Clinical Trials

- **In an RCCT, often referred to simply as randomized controlled trials, patients are enrolled in a study and randomly assigned to one of the following groups:**
  1. **the intervention group, which receives the experimental treatment, or**
  2. **the control group, which receives the nonexperimental treatment, consisting either of a placebo (inert substance) or of a standard method of treatment.**

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Randomized Controlled Clinical Trials

- **RCCTs are considered the "gold standard" for studying interventions because of their ability to minimize bias in the information obtained from the study subjects.**
- **Nevertheless, they do not entirely eliminate bias, and they pose some challenges and ethical dilemmas for investigators.**

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Randomized Controlled Field Trials

- **An RCFT is similar to an RCCT except that ordinarily the intervention in an RCFT is preventive rather than therapeutic, and usually it is done in the community.**
- **Appropriate subjects are randomly allocated to receive the preventive measure (e.g., a vaccine or an oral drug) or to receive the placebo (e.g., an injection of sterile saline or an inert pill).**
- **They are followed over time to determine the rate of disease in each group.**

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RCCT & RCFT Issues

- **Random selection & random assignment**
- **Blinding: single, double, triple**
- **Balance: Characteristics of subjects in each group must be very similar.**
- **Informed consent of subjects**
- **"Sham" treatments**
- **Drop-out & LTFU**
- **Cross-overs**
- **Publication bias**
- **Inclusion & exclusion criteria**
- **External validity, which is the ability to generalize the findings to other groups in the population**

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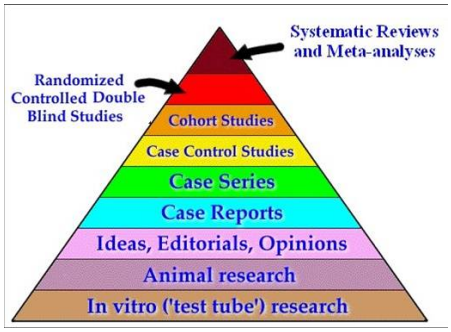

The Evidence Pyramid

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COMMON PITFALLS IN CAUSAL RESEARCH

- ***Bias:*** **A differential error that produces findings consistently distorted in one direction, owing to nonrandom factors.**
- ***Random error:*** **A nondifferential error that produces findings that are too high and too low in approximately equal frequencies, owing to random factors.**
- ***Confounding:*** **The confusion of two supposedly causal variables, so that part or all of the purported effect of one variable is actually due to the other.**
- ***Synergism:*** **The interaction of two or more presumably causal variables, so that the total effect is greater than the sum of the individual effects.**
- ***Effect modification (interaction):*** **A phenomenon in which a third variable alters the direction or strength of association between two other variables.**

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Reading the Literature: The Rules

Evaluate methodology - What kind of study?

Interventional

- **Blinded (single/double/triple)?**
- **Randomization?**
- **Who was excluded or included?**
- **Groups equal at baseline?**
- **Is there a control or comparison group?**
- **Attrition and LTFU?**
- **Generalizability of results?**
- **Bias risk: Lowest**
- **Confounding?**
- **Effect modification or interaction?**
- **Reliability: Highest**

Observational

Retrospective

- **Bias risk: Higher**
- **Confounding?**
- **Effect modification or interaction?**
- **Reliability: Lowest**

Prospective

- **Bias risk: Lower**
- **Confounding?**
- **Effect modification or interaction?**
- **Reliability: Higher**

Gold Standard: Randomized Controlled Trial (RCT)

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Part II.
Assessment of Risk & Benefit in Epidemiologic Studies

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Assessment of Risk & Benefit in Epidemiologic Studies

- **Causal research in epidemiology requires that two fundamental distinctions be made.**
  1. **The first distinction is between people who do *have* and people who *do not have* *exposure* to the risk (or protective) factor being studied (the *independent variable*),**
  2. **The second distinction is between people who do *have* and people who *do not have* the *disease* (or other outcome) being studied (the *dependent variable*).**
- **These distinctions are seldom simple, and their measurements are subject to random errors and biases.**

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Causal Research Complications:

- **Need to analyze several independent (possibly causal) variables at the same time, including how they interact.**
- **Need to measure different degrees of strength of exposure to the risk factor, the duration of exposure to the risk factor, or both.**
- **Need to measure different levels of disease severity.**
- **Exposure and outcome may vary across a range of values, rather than simply be "present" or "absent."**
- **Despite these complexities, much epidemiologic research still relies on the dichotomies of exposed/unexposed and diseased/non-diseased, which are commonly presented in the form of a standard 2 × 2 table (Table 3).**

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Table 3. Standard 2 × 2 Table for Showing the Association between a Risk Factor and a Disease

	Disease Status		
Risk Factor	**Present**	**Absent**	**Total**
Positive	***a***	***b***	***a + b***
Negative	***c***	***d***	***c + d***
Total	***a + c***	***b + d***	***a + b + c + d***
Interpretation of the Cells **(Note: Table entries are counts, i.e., frequencies.)**			
a **= subjects with both the risk factor and the disease**			
b **= subjects with the risk factor, but not the disease**			
c **= subjects with the disease, but not the risk factor**			
d **= subjects with neither the risk factor nor the disease**			
Marginal Totals & Grand Total			
a + b **= all subjects with the risk factor**			
c + d **= all subjects without the risk factor**			
a + c **= all subjects with the disease**			
b + d **= all subjects without the disease**			
a + b + c + d **= all study subjects**			

DEFINITION OF STUDY GROUPS

- **Causal research depends on the measurement of differences.**
- **In *cohort studies*, the difference is between the *frequency of disease* in persons *exposed* to a risk factor and the frequency of disease in persons *not exposed* to the same risk factor.**
- **In *case-control studies*, the difference is between the *frequency of the risk factor* in *case subjects* (persons with the disease) and the frequency of the risk factor in *control subjects* (persons without the disease).**

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- **Differences in risk can be measured in *absolute* terms or in *relative* terms, the method used depends on the type of study performed.**
- ***Case-control* studies allow investigators to obtain only a relative measure of risk, whereas**
- ***Cohort* studies and *RCCTs* allow investigators to obtain both absolute and relative measures of risk.**

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- After the differences in risk are calculated by the methods outlined in detail subsequently, the level of ***statistical significance*** must be determined to ensure that any observed difference is probably real (i.e., not due to chance).
- When the difference is statistically significant, but not clinically important, it is real but trivial.
- When the difference appears to be clinically important, but is not statistically significant, it may be a false-negative (beta) error if the sample size is small or it may be a chance finding.

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Absolute Differences in Risk

- When the level of risk in the exposed group is the same as the level of risk in the unexposed group, the risk difference is 0, and the conclusion is that the exposure makes no difference to the disease risk being studied.
- If an exposure is ***harmful*** (as in the case of cigarette smoking), the risk difference is expected to be greater than 0.
- If an exposure is ***protective*** (as in the case of a vaccine), the risk difference is expected to be less than 0 (i.e., a negative number, which in this case indicates a reduction in disease risk in the group exposed to the vaccine).
- The risk difference AKA the ***attributable risk*** because it is an estimate of the amount of risk that is *attributable* to the risk factor.

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Absolute Differences in Risk

In Table 3,

- The ***risk*** of disease in the ***exposed*** individuals is $a/(a + b)$, and
- The ***risk*** of disease in the ***unexposed*** individuals is $c/(c + d)$.
- The ***attributable risk*** (AR) can be expressed as the difference between the two:

$$AR = Risk_{(exposed)} - Risk_{(Unexposed)} = \frac{a}{(a+b)} - \frac{c}{(c+d)}$$

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Relative Differences in Risk

- Relative risk (RR) can be expressed in terms of
  - a ***risk ratio*** (also abbreviated as RR) or
  - estimated by an ***odds ratio***.
- The ***relative risk***, is the ratio of the risk in the exposed group to the risk in the unexposed group.

$$RR = Risk_{(exposed)} / Risk_{(Unexposed)} = \frac{a}{(a+b)} / \frac{c}{(c+d)}$$

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Risk, Odds & Probability

- The ***risk*** of disease ***given*** one is ***exposed*** to the risk factor

  = a/(a+b) = Pr(Disease|Exposed) = R1
- The ***risk*** of disease ***given*** one is ***not exposed*** to the risk factor

  = c/(c+d) = Pr(Disease|Not Exposed) = R2
- The ***Relative Risk*** = RR = R1/R2

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Risk, Odds & Probability

- In general, the odds of some event occurring

  Odds(E) = Pr(E)/Pr(Not E) = Pr(E)/[1 – Pr(E)]
- Also, given the odds of some event occurring one can calculate the probability of it occurring

  Pr(E) = Odds(E)/[1+Odds(E)]

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Risk, Odds & Probability

- **For example, if the probability of winning a game is Pr(Win) = 1/3**
  then the odds of winning is
  Odds(Win) = (1/3)/(2/3) = 1/2 or 1 to 2
  Note: Pr(Win) = 0.5/1.5 = 1/3

- **If the odds of winning a game is 4 to 1 (for) then the probability of winning is**
  Pr(Win) = 4/(1+4) = 4/5 = 0.8
  Note: Odds(Win) = 0.8/0.2 = 4 or 4 to 1

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Odds Ratio

- **The *odds* of exposure to the risk factor *given* one has the *disease***

$$= a/c = \frac{\Pr(\text{Exposed}|\text{Disease})}{\Pr(\text{Not Exposed}|\text{Disease})} = O1$$

- **The *odds* of exposure to the risk factor *given* one *does not have the disease***

$$= b/d = \frac{\Pr(\text{Exposed}|\text{Not Diseased})}{\Pr(\text{Not Exposed}|\text{Not Diseased})} = O2$$

- **The (exposure) *Odds Ratio***

  = OR = O1/O2 = (a/c)/(b/d) = (ad)/(bc)
  Note: Also called the cross-product ratio.

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Prospective studies (cohort studies, clinical trials, and basic experimental research)

Conceptual Framework - The 2 X 2 Table:

	Outcome ("in future") +	Outcome ("in future") -	
Risk factor or treatment +	a	b	a+b
Risk factor or treatment -	c	d	c+d
	a+c	b+d	a+b+c+d

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- **Stating Conclusions for Prospective Study:**

  Quantifying Risk - If the Relative Risk turns out to be Y, then you can say-"Subjects who had the risk factor were Y-times more likely to have a positive outcome than were subjects who did not have the risk factor."

  Evaluating Treatment - In a therapeutic trial, treatment plays the role of "risk". If the Relative Risk turns out to be Y, then you can say-"Subjects who received treatment were Y-times more likely to have a positive outcome than were subjects who did not receive treatment."

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- ***Example*: -- A budding clinical researcher in the first-year class decided to *test the hypothesis* that eating cold sandwiches in the Student Grill causes diarrhea. This student-researcher persuaded 30 of her classmates, none that had diarrhea, to participate in a clinical trial in exchange for a free lunch at the Grill. She randomly selected 15 of the students and bought them cold sandwiches; the other 15 got hamburgers. A follow-up questionnaire revealed that 10 of the students in the "cold-sandwich group" had diarrhea the next day, but only 2 of the students in the "hamburger group" had diarrhea. (*Prospective RCT*)**

			Disease (Diarrhea)		Total
			D+	D-	
Risk Factor	Cold	+	10 = a	5 = b	15 = a+b
	Hot	-	2 = c	13 = d	15 = c+d
Total			12 = a+c	18 = b+d	30 = a+b+c+d

- **R1 = a/(a+b) = 10/15; R2 = c/(c+d) = 2/15; RR = R1/R2 = 10/2 = 5**
- **Relative Risk = 5, p-value = 0.003, 95% CI: [1.31, 19.07]**
  Conclusion: "Subjects who ate cold sandwiches were 5 times more likely to have diarrhea the next day than subjects who ate hamburgers." This supported her hypothesis that eating cold sandwiches in the Student Grill causes diarrhea.

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Retrospective (Case-Control) Studies
Independent Samples

Conceptual Framework - The 2 X 2 Table:

	Cases Outcome ("present") +	Controls Outcome ("present") -	
Exposure ("in the past") +	a	b	a+b
Exposure ("in the past") -	c	d	c+d
	a+c	b+d	a+b+c+d

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- **Stating Conclusion for Retrospective Study**:

  Quantifying Risk - If the Odds Ratio turns out to be X, then you can say-"Subjects with a positive outcome are X-times more likely to have had prior exposure than are subjects without a positive outcome ."

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- ***Example*** **(Independent Samples): -- 25 first-year students have diarrhea today (positive outcome). 20 of these students ate cold sandwiches at the Student Grill yesterday (positive prior exposure). 90 other first-year students don't have diarrhea today (negative outcome). 9 of these ate cold sandwiches at the Student Grill yesterday. *Is there an association* between eating cold sandwiches at the Grill and contracting diarrhea? (*Retrospective Case-Control Study*)**

			Disease (Diarrhea)		Total
			D+	D-	
Risk Factor	Cold	+	20 = a	9 = b	29 = a+b
	Hot	-	5 = c	81 = d	86 = c+d
Total			25 = a+c	90 = b+d	115 = a+b+c+d

- **OR = (ad)/(bc) = (20 x 81)/(9 x 5) = (4 x 9) = 36**
- **Odds Ratio = 36, p < 0.0001, 95% CI: [11.11, 116.08]**
- **Conclusion: "First-year students who have diarrhea today are 36 times more likely to have eaten cold sandwiches at the Grill yesterday than those without diarrhea ."**

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Ho Tests, Significance, & CIs

Hypothesis tests and CIs can be expressed in terms of

- **Differences in Rates/proportions: R1 - R2 = 0**
- **RR = R1/R2 = 1**
- **OR = O1/O2 = 1**

If the RR (or the OR) is > 1, then "Exposure" is "Harmful".

If the RR (or the OR) is < 1, then "Exposure" is "Protective".

If a matched case-control study then use methods for correlated proportions.

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More on Odds Ratios & Relative Risk

- **Although a risk or a risk ratio cannot be calculated from a case-control study, an odds ratio can be calculated. Under most real world circumstances, the odds ratio from a carefully performed case-control study is a good estimate of the risk ratio that would have been obtained from a more costly and time-consuming prospective cohort study.**
- **The odds ratio may be used as an estimate of the risk ratio if the risk of disease in the population is low. (It can be used if the risk ratio is <1%, and it probably can be used if it is <5%.)**
- **The odds ratio (OR) is also used in logistic methods of statistical analysis (logistic regression and log-linear models); the relative risk (RR) AKA Hazard Ratio (HR) is used in Cox PH regression analyses (Survival Analysis).**

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OTHER MEASURES OF THE IMPACT OF RISK FACTORS

- **One of the most useful applications of epidemiology is to estimate how much disease burden is caused by certain modifiable risk factors.**
- **In addition to the risk difference, relative risk, and odds ratio, the most common measures of the impact of exposures are**
  1. **the attributable risk percent in the exposed,**
  2. **the population attributable risk, and**
  3. **the population attributable risk percent.**

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Other Ways of Describing the Value of Interventions

The anticipated value of an intervention is frequently expressed

- **in absolute terms (the *absolute risk reduction*),**
- **in relative terms (the *relative risk reduction*), or as**
- **As the *reduction in incidence density* (e.g., the reduction in risk per 100 person-years).**
- **Also *Number Needed to Treat* (NNT) or *Number Needed to Harm* (NNH)**

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Absolute & Relative Risk Reduction

- **The *absolute risk reduction* (ARR) and the *relative risk reduction* (RRR) are descriptive measures. Assume that the yearly risk of a certain disease is 0.010 in the presence of the risk factor and 0.004 in the absence of the risk factor. The ARR and RRR would be calculated as follows:**

$$ARR = Risk_{(exposed)} - Risk_{(unexposed)} = 0.010 - 0.004 = 0.006$$

$$RRR = \frac{Risk_{(exposed)} - Risk_{(unexposed)}}{Risk_{(exposed)}} = \frac{0.010 - 0.004}{0.010} = \frac{0.006}{0.010} = 0.6 \text{ or } 60\%$$

- **In this example, an intervention that removed the risk factor would reduce the risk of disease by 0.006 in absolute terms (ARR) or produce a 60% reduction of risk in relative terms (RRR). When the RRR is applied to the effectiveness of vaccines, it is called the *vaccine effectiveness* or the *protective efficacy*.**

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Number Needed to Treat or Harm

- **An increasingly popular EBM measure used to describe the practical value of treatment is called the number needed to treat (*NNT*), meaning the number of patients who would need to receive a specific type of treatment for one patient to benefit from the treatment. The NNT is calculated as the number 1 divided by the absolute risk reduction (ARR). In its simplest form, this is expressed as a proportion:**

NNT = 1/ARR

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Number Needed to Treat or Harm

- **The idea behind the number needed to harm (*NNH*) is similar to that of the NNT, but it is applied to the negative effects of treatment, i.e., adverse events or side effects.**
- **The fundamental item of data is the *absolute risk increase* (*ARI*), which is analogous to the absolute risk reduction (ARR) in the NNT. The NNH formula is similar to that of the NNT:**

NNH = 1/ARI

63

Number Needed to Treat or Harm

- **The NNT and NNH are helpful for making comparisons of the effectiveness of different types of interventions.**
- **Smaller NNTs are better. Best NNT = 1, since every patient would benefit from treatment.**
- **Larger NNHs are better, since that means that adverse events occur less frequently.**
- **One should attempt to calculate these measures for any RCCT or RCFT that is testing an intervention.**

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Calculating NNT & NNH for RCCTs

- **In RCCTs "Treatment" plays the role of "Risk Factor".**
- **The Event Rate is the group specific rate of occurrence of the event of interest**
- **The event of interest is the "disease" or "condition" treated or that for which the intervention is designed to ameliorate.**
- **Control group event rate = CER**
- **Experimental group event rate = EER**
- **ARR = CER – EER = Abs. Risk Reduction**
- **NNT = 1/ARR**
- **The event of interest for NNH is any "adverse" event(s).**
- **ARI = EER – CER = Abs. Risk Increase**
- **NNH = 1/ARI**

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Calculating NNT & NNH for RCCTs

- **A RCCT of a new drug "Ligatite" reveals that 25% (EER) of World Cup skiers who take the drug for one year have an ACL tear where as 50% (CER) of World Cup skiers who take the placebo for the year have an ACL tear.**

  NNT = 1/ARR = 1/(CER – EER) = 1/(0.50-0.25) = 4

- **The study reports that 5% (EER) of the athletes taking the drug develop clinical depression whereas 3% (CER) of the athletes taking the placebo develop depression.**

  NNH = 1/ARI = 1/(EER – CER) = 1/(0.05-0.03) = 50

- **Conclusions:**
  1. **Need to treat 4 skiers for one year with the new drug to prevent one skier from having an ACL tear.**
  2. **For every 50 skiers treated with the new drug (for one year), one will develop clinical depression.**
  3. **If we treat 100 skiers for one year, 25 will be "helped" and 2 will be "harmed".**

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Part III. Selecting Statistical Procedures

The following points need to be considered

- The research question
- The level of measurement of the dependent variable
- The type of experimental or quasi-experimental design
- The sample type

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The research question - Are we interested in testing hypotheses about

- Population differences, or
- Assessing the association between variables?

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The level of measurement of the dependent variable

- Nominal level – weakest level – can only classify objects, e.g., dog, cat, bird
- Ordinal level – can place objects in a natural order, e.g., low, medium, high
- Interval level – same as ordinal level with the added characteristic that the "distance" between any two numbers on the scale are of known size. The ratio of any two intervals on the scale is independent of the unit of measurement and of the zero point, e.g., Fahrenheit or Celsius temperature scales.
- Ratio level – same as interval but true zero point as its origin, e.g., mass or weight measures.

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The type of experimental or quasi-experimental design

- One group design
- Two group design, or
- More-than-two group design

70

The sample type – Whether samples arise from

- Independent simple random sampling,
- Paired sampling, or
- Mixed sampling schemes?

71

We are most familiar with parametric procedures.

- For example
  - t-test,
  - analysis of variance (ANOVA),
  - analysis of covariance (ANCOVA),
  - simple and
  - multiple linear regression, etc

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Choice of methodology complicated by variety of procedures available

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Top portion of decision tree concerned with detecting differences

74

Bottom portion of decision tree is concerned with assessing associations or testing hypotheses about independence or dependence

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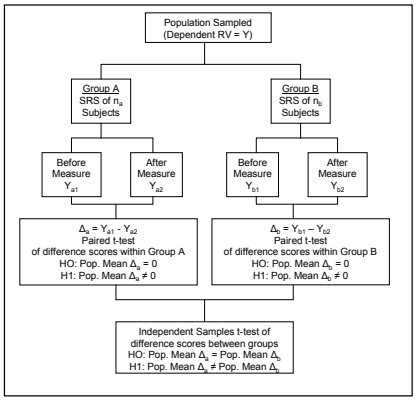
One way to analyze a mixed sample is to form gain (or difference) scores within groups and then apply independent sample procedures to the gain (or difference) scores.

76

Two-Group Mixed-Sample Longitudinal RCT



Note: Each subject has a before and after measure. Therefore, we have paired/correlated observations within groups. The between-group difference scores are independent. The difference score can be calculated as either a "gain" or "loss" depending on ones definition of "improvement".

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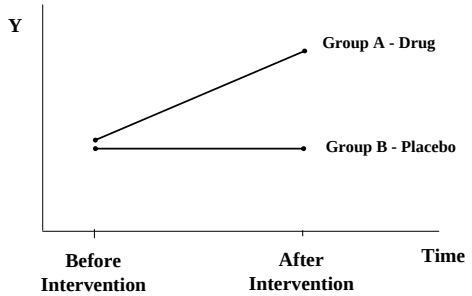
Profile Plot of Group Means by Time



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Alternately, if measurement is at least at the interval level, one can use ANCOVA procedures with one of the repeat measures as a covariate (usually the "before" measurement is the covariate).

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Another alternative is to use repeated-measures ANOVA.

80

The statistical analysis column suggests one or two procedures appropriate to the situation. There are usually several methods to choose from. I have tried to balance my choice by suggesting simple and easy-to-use methods that are the most powerful procedures applicable. I have also considered the nature of assumptions for the methodology.

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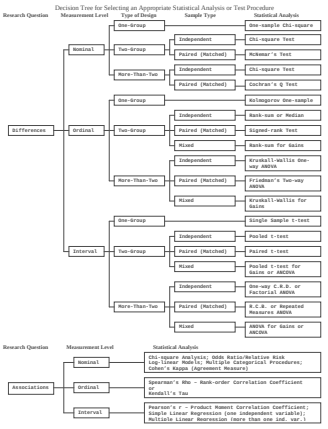

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