UNIVERSITY OF ALBERTA
FACULTY OF MEDICINE & DENTISTRY

Clinical Research Seminar Series

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Biostatistics 101

Dr. Rhonda Rosychuk

UNIVERSITY OF ALBERTA FACULTY OF MEDICINE & DENTISTRY NACTRC Northern Alberta Clinical Trials + Research Centre

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Contact:
jill.byrne@ualberta.ca

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BIOSTATISTICS 101

An Introduction & Application to Research

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Overview

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- Empirical Problem Solving
- Study Designs
- Data Types
- Parametric vs Non-parametric Tests
- Common Statistical Methods
- Special Considerations
- Examples
- Questions

Empirical Problem Solving

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- Different ways to design and conduct a study.
- The choice of design depends the research question.
- Think QPDAC – 5-step problem solving approach.
  - **Q**uestion
  - **P**lan
  - **D**ata
  - **A**nalysis
  - **C**onclusions
- **Biostatistics** thinking figures prominently in problem solving.

QPDAC Details

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- **Q**uestion: Statement of what is to be learned.
- **P**lan: Procedures used to carry out the study.
- **D**ata: Data collected according to the Plan.
- **A**nalysis: Data summarized and analyzed to answer Question.
- **C**onclusion: Conclusions drawn about what has been learned.

Statistical analyses depend on the 5 steps, but the talk will touch on Plan, Data, and Analysis steps.

Study Protocol

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- The study design dictates many of the elements of the study protocol.
  - Study population
  - Sampling protocol
  - Measurement system
- Some plans are better than others in terms of reducing bias and variability.
- Have to decide if goal is to determine association or causation.

Association vs Causation

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- Three essential ingredients for strictly/statistically determining causation are:
  - Holding all other explanatory variables fixed,
  - Deliberately change the value of one explanatory variable (called focal variable) on all units in the population, and
  - Observe whether the attribute of interest has changed in value.
- If change occurs, say explanatory variable caused the change. Ex: A drug causes a drop in SBP.

Association vs Causation

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- Confounding can complicate the determination of causal relationships.
  - The effects of two explanatory variables on a response variable are said to be confounded when the effects cannot be distinguished from one another.
- For Plans for causative aspects, 2 basic options:
  - either the investigator can deliberately manipulate (experimental study), or
  - simply observe the focal variable (observational study).

Typical Designs

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- Experimental (+ many other names for RCTs)
  - Simple comparative: comparing 2 treatments/conditions
  - Single factor: comparing several levels of factor
  - Randomized block design: treatments appear in each block
  - Factorial design: compare 2 or more factors at the same time (can examine interactions)
  - Cluster RCT: groups are randomized rather than individual subjects
  - Stepped wedge: groups are randomized to when treatment is received, all groups eventually get treatment
  - …

Typical Designs

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- Observational
  - Descriptive: compare/describe outcomes
  - Cross sectional surveys: questionnaires at one point in time for a study group
  - Case control: pick cases and controls based on outcome, examine relationship with an exposure variable
  - Cohort: prospective or retrospective, choose groups based on exposure variable and examine outcome
  - …

Data Types

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- Data type will determine what you can/will do in summaries and analyses.
- Continuous vs Discrete
  - Continuous has potentially infinite number of possible values in any interval. Can be measured to different levels of accuracy. Ex: weight in kg
  - Discrete has only a finite number of values in any interval. Usually whole numbers or integers (e.g., counts). Ex: # ED visits in a year

Data Types

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- Interval (Quantitative, Scale)
  - Has numerical unit of measurement, difference between any 2 measurements is explicitly known. Ex: SBP
  - Survival data is a special case: censoring is a possibility.
- Nominal (Categorical)
  - Names or labels distinguish. No magnitude. Ex: health zone
- Ordinal (Categorical)
  - Has characteristics of nominal but implicit order relationship among labels/measurements. Ex: Strongly disagree,…, Strongly agree

Analysis Step - Descriptives

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- Categorical/Ordinal
  - Counts
  - Numerator/Denominator for ratios, percents
    - 50% (30/60) vs 50%, 3/20 vs 15%
  - Bar charts (please, no pies!)
- Continuous
  - Appropriate degree of precision
    - 18.873 kg vs 18.9 kg
  - Five number summary: min, mean, med, max, SD
    - 19 kg (sd=1 kg; r=16,22) vs 19 kg
    - avoid ± notation, can be confusing
  - Histograms, box plots, estimates with CIs

Analysis Step – Tests & Models

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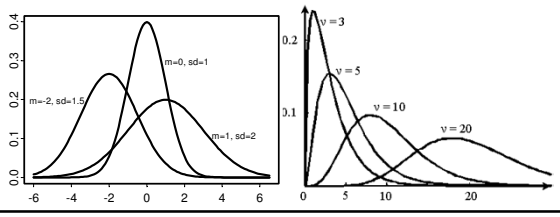
- Parametric tests are based on distributions that are indexed by a few parameters, e.g.,
  - Normal/Gaussian: mean, SD
  - Chi-square: degrees of freedom



Parametric vs. Non-parametric

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- Non-parametric tests are not based on such distributions (aka distribution free). Often based on ranks, e.g.,
  - Wilcoxon, Mann-Whitney, Kruskal-Wallis
- Not always easy to decide which test to use in which situation.
  - Parametric generally better if distribution assumption appropriate and sufficient sample size.
  - Several parametric tests can be very robust even if distribution assumption not met (i.e., t test).

Choosing a Statistical Method

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- Lots of resources out there to help you determine appropriate methods and test to use, just a few listed:
  - http://udel.edu/~mcdonald/statbigchart.html
  - http://www.whichtest.info/
  - http://www.wadsworth.com/psychology_d/templates/student_resources/workshops/stat_workshp/chose_stat/chose_stat_01.html
  - http://www.ats.ucla.edu/stat/mult_pkg/whatstat/default.htm
  - http://www.bmj.com/collections/statsbk/13.dtl
  - http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1924630/
  - http://www.helpwithstatistics.com/articles/choosing-statistical-tests.shtml
- I like GraphPad.com's approach (next slide)
  - www.graphpad.com/www/Book/Choose.htm

	Type of Data			
Goal	**Measurement (from Gaussian Population)**	**Rank, Score, or Measurement (from Non-Gaussian Population)**	**Binomial (Two Possible Outcomes)**	**Survival Time**
Describe one group	Mean, SD	Median, interquartile range	Proportion	Kaplan Meier survival curve
Compare one group to a hypothetical value	One-sample *t* test	Wilcoxon test	Chi-square or Binomial test	
Compare two unpaired groups	Unpaired *t* test	Mann-Whitney test	Fisher's test (chi-square for large samples)	Log-rank test or Mantel-Haenszel
Compare two paired groups	Paired *t* test	Wilcoxon test	McNemar's test	Conditional proportional hazards (PH) regression
Compare three or more unmatched groups	One-way ANOVA	Kruskal-Wallis test	Chi-square test	Cox PH regression
Compare three or more matched groups	Repeated-measures ANOVA	Friedman test	Cochrane Q	Conditional PH regression
Quantify association between two variables	Pearson correlation	Spearman correlation	Contingency coefficients	
Predict value from another measured variable	Simple linear regression, Nonlinear regression	Nonparametric regression	Simple logistic regression	Cox PH regression
Predict value from several measured or binomial variables	Multiple linear regression, or Multiple nonlinear regression		Multiple logistic regression	Cox PH regression

Tests vs. Modelling

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- Depends on the Question.
- Tests generally look at comparing an outcome and another variable.
- Modelling allows the relationship between multiple variables and outcome to be handled at the same time.
  - Lots of different approaches and the appropriate methods will depend on the question and type of data.
  - Fixed and/or random effects can be included to adjust for a variety of data situations. Models with both fixed and random effects are called mixed models.

ANOVA vs. Ordinary Regression

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- Commonalities:
  - Concerned about statistical relationship between ≥1 independent variables and dependent variable.
  - Appropriate for observational and experimental.
  - ANOVA dependent variable is quantitative, like most ordinary regression models.
- Differences:
  - ANOVA: independent variables may be **qualitative**.
  - If quantitative independent variables, **no assumption** is made on the **nature of the statistical relationship** for ANOVA: no specification of regression function.

Special Considerations

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- Careful consideration needed for some data types and situations.
- Time-to-event (survival) data requires special methods because of censoring.
- Correlated data, e.g., repeated measures on a subject, can be handled with mixed models.
- Clustered/hierarchical data can also be handed with mixed or other models.
- Missing data can be handled with mixed models or with imputation methods.

Examples

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- Sex Differences in Outcomes After Discharge from the Emergency Department for Atrial Fibrillation/Flutter

BACKGROUND: Atrial fibrillation and flutter (AFF) are the most common arrhythmias presenting to emergency departments (EDs). We examined sex differences in outcomes for patients with AFF discharged from the ED in Alberta, Canada. **METHODS:** ED presentations for AFF during 1999-2011 that ended in discharge were extracted from administrative databases for all Alberta residents (age ≥ 35 years). Multivariable models determined the effect of sex on the time to ED return for AFF, the first follow-up visit with a physician, the first follow-up visit with a specialist (cardiologist or internal medicine physician), and death. **RESULTS:** There were 21,062 patients/ED presentations (47.5% women). About 10% returned to the ED for AFF after discharge; the time to return was similar for both sexes ($P = 0.39$). Time to a first physician visit was shorter (unadjusted hazard ratio [uHR] = 1.10) and time to a specialist follow-up visit was longer (uHR = 0.93) for women than for men. Interactions between sex and age, socioeconomic groups, and comorbidities were identified that changed the effect of sex on time to follow-up. More women died by 30 (1.3% vs 0.9%; $P = 0.009$) and 90 (2.9% vs 2.4%, $P = 0.02$) days. The time between ED discharge and death was shorter for women in 1 socioeconomic group ($P = 0.008$) and for those with peripheral vascular disease ($P = 0.02$) or diabetes ($P = 0.03$). **CONCLUSIONS:** We identified sex differences for time to return to the ED, follow-up visit, and death (most importantly, increased mortality rates among women at 30 and 90 days), and time to death remained significant after adjustment for other demographic and health-related variables. Our findings have important potential implications for physicians in the emergency setting. *Canadian Journal of Cardiology* 2017;33:806–13

Examples

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- Improvement of Short- and Long-Term Outcomes for Very Low Birth Weight Infants: Edmonton NIDCAP Trial

OBJECTIVE: Our objective was to determine the impact of Newborn Individualized Developmental Care and Assessment Program (NIDCAP)-based care on length of stay of very low birth weight (VLBW) infants. Secondary outcome measures were days of ventilation, incidence of chronic lung disease, and 18-month neurodevelopmental outcomes. **METHODS:** This cluster-randomized, controlled trial took place in a large NICU in Canada, with follow-up evaluation at 18 months of age, from September 1999 to September 2004. One hundred VLBW singleton infants and 10 VLBW twin sets were assigned randomly to NIDCAP based or control care, and 90% participated in follow-up assessments. The intervention was NIDCAP-based care ($N = 56$), that is, care by NIDCAP-educated staff members and behavioral observations. The control group ($N = 55$) received standard NICU care. Statistical analyses were adjusted for cluster randomization. Although the intervention was not blinded, the pediatricians making the decisions to discharge the infants were not involved in the study, and the follow-up staff members were blinded with respect to group. **RESULTS:** NIDCAP group infants had reduced length of stay (median: NIDCAP: 74 days; control: 84 days; $P = .003$) and incidence of chronic lung disease (NIDCAP: 29%; control: 49%; odds ratio: 0.42 [95% confidence interval: 0.18–0.95]; P .035). At 18 months of adjusted age, NIDCAP group infants had less disability, specifically mental delay(NIDCAP: 10%; control: 30%; odds ratio: 0.25 [95% confidence interval:0.08–0.82]; P .017). **CONCLUSION:** NIDCAP-based care for VLBW infants improved short and long-term outcomes significantly. *Pediatrics* 2009;124:1009–1020

Examples

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- Enhanced Multidisciplinary Care for Inner City Patients with High Acute Care Use: Study Protocol

OBJECTIVES: Socioeconomically disadvantaged people living with addiction are underserved by traditional models of acute care despite high service utilization rates. In response to this shortfall, Edmonton's Royal Alexandra Hospital has launched a multidisciplinary consult team offering best practices in addiction stabilization, health promotion, harm reduction, social stabilization, and connection to community supports. We hypothesize that exposure to this multicomponent intervention will lead to improved use of health care resources compared to usual care. **METHODS:** A parallel-group, pre/post longitudinal quasi-experimental design will compare patients exposed to the intervention at the Edmonton site to patients exposed to usual care at two Calgary acute care facilities. Eligible patients are recruited for study participation if they have unstable housing, no stable income, and/or are actively using alcohol or other drugs, and are 18 years or older. Administrative health and social service data for the period six months prior to and 12 months after study enrolment will be linked to a longitudinal survey dataset from baseline and follow-up survey data collected over the same time period. **EXPECTED OUTCOMES:** The primary outcome is decreased emergency department use at 12 months post-enrolment. Secondary outcomes include stabilization/reduction of substance use, initiation of addiction treatment, and connections to primary care, housing, and income support. **IMPLICATIONS:** The future results of this study have the potential to inform the systematic development and implementation of acute care interventions in meeting the needs of inner city patients with addiction and/or social instability. *The Canadian Journal of Addiction* 2016;7:34–41

Final Thoughts

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- QPDAC helpful in thinking through the data and statistical aspects of a study.
- Statistical analysis techniques will be dictated by data type, data features, and question.
- May be multiple ways to do similar things.
- Statistical packages can give results but proper methods determination is required.
- Consult a statistician for analyses outside your expertise/experience (e.g., regression).
  Ex: www.biostatsconsultgroup.ualberta.ca

Reference Materials

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- Many very good references available.
  - Lang TA, Secic M (1997). How to Report Statistics in Medicine. Philadelphia: American College of Physicians.
- Software is key for any biostatistics endeavour.
  - Learning/using SPSS: www.ats.ucla.edu/stat/spss
  - Downloading and using R (free): www.r-project.org
- My contact: rhonda.rosychuk@ualberta.ca
- Thank you for your attention. Thank you Dr. Byrne!
- Let's discuss!