EE3211 Modelling Techniques

Lecture 9

Analytical Techniques for Epidemiological Studies

Overview

1. Common study designs (epidemiology)
    - Prospective, retrospective , and cross-sectional study

2. Commonly used measures of effect for categorial data
    - Risk Difference, Risk Ratio, and Odds Ratio
    - Parameters estimation with confidence intervals

3. Multiple Logistic regression

Study Design

Table 13.1 Hypothetical exposure–disease relationship

		Disease: Yes	Disease: No	
Exposure	Yes	a	b	$a + b = n_1$
	No	c	d	$c + d = n_2$
		$a + c = m_1$	$b + d = m_2$	

- n_1 = a + b exposed subjects (a have disease)
- n_2 = c + d unexposed subjects (c have disease)
- Three main study designs: prospective, retrospective, and cross-sectional study design
- **Prospective (Cohort) study design:** a group of disease-free individuals is identified at one point in time and are followed over a period of time until some of them develop the disease
  - development of disease over time is then related to other variables (*exposure variables)* measured at baseline
  - **Cohort:** study population in a prospective study

- **Retrospective (case-control) study:** two groups of individuals are initially identified:

  (1) Cases: a group that has the disease under study

  (2) Controls: a group that does not have the disease under study

  - relate their prior health habits to their current disease status

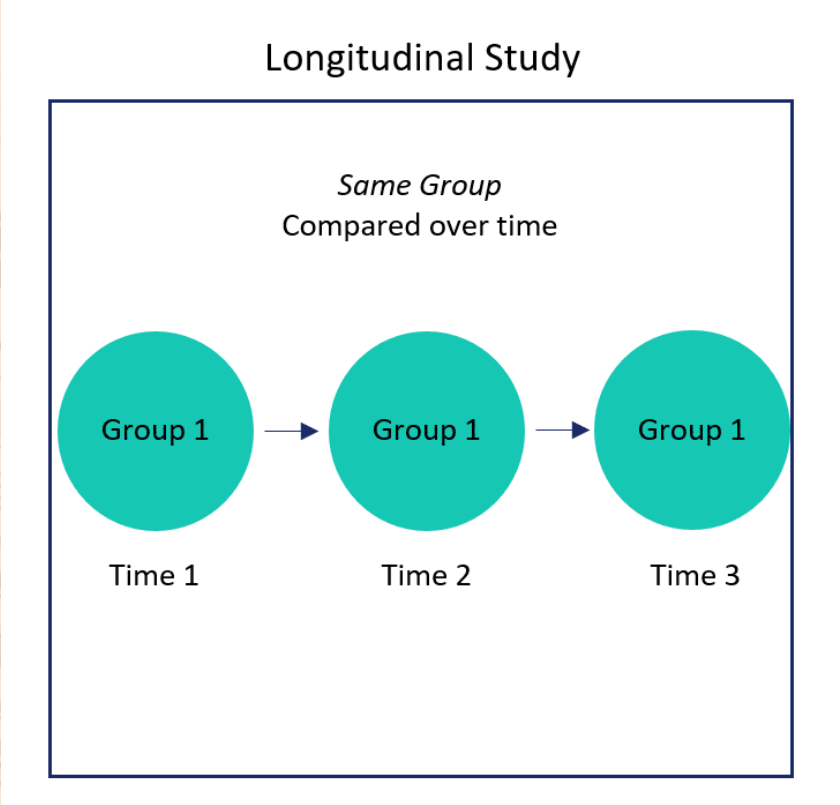
- **Cross-sectional (Prevalence) study:** study population is ascertained at a single point in time
  - Collect current disease status and current or past exposure status from study participants
  - Prevalence of disease at one point in time is compared between exposed and unexposed individuals (v.s. prospective study: incidence rather than the prevalence of the disease)

- A **prospective** study is usually more definitive
  - patient's knowledge of their current health habits is more precise than recall of their past health habits

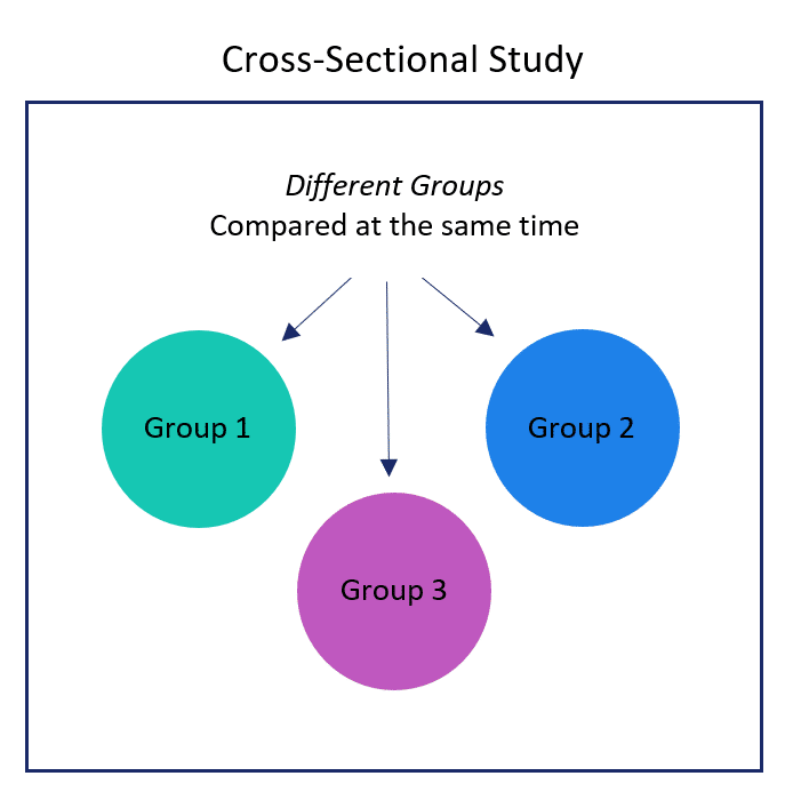
- A **retrospective** study has a greater chance of bias for two reasons
  - **Selection bias**: more difficult to obtain a representative sample of people who already have the disease in question
  - **Recall bias**: individuals with the disease or their surrogates may tend to give biased answers about prior health habits if they believe there is a relationship between these prior health habits and the disease
  - much less expensive to perform and can be completed in much less time than a prospective study

Two main study designs

Cohort Study

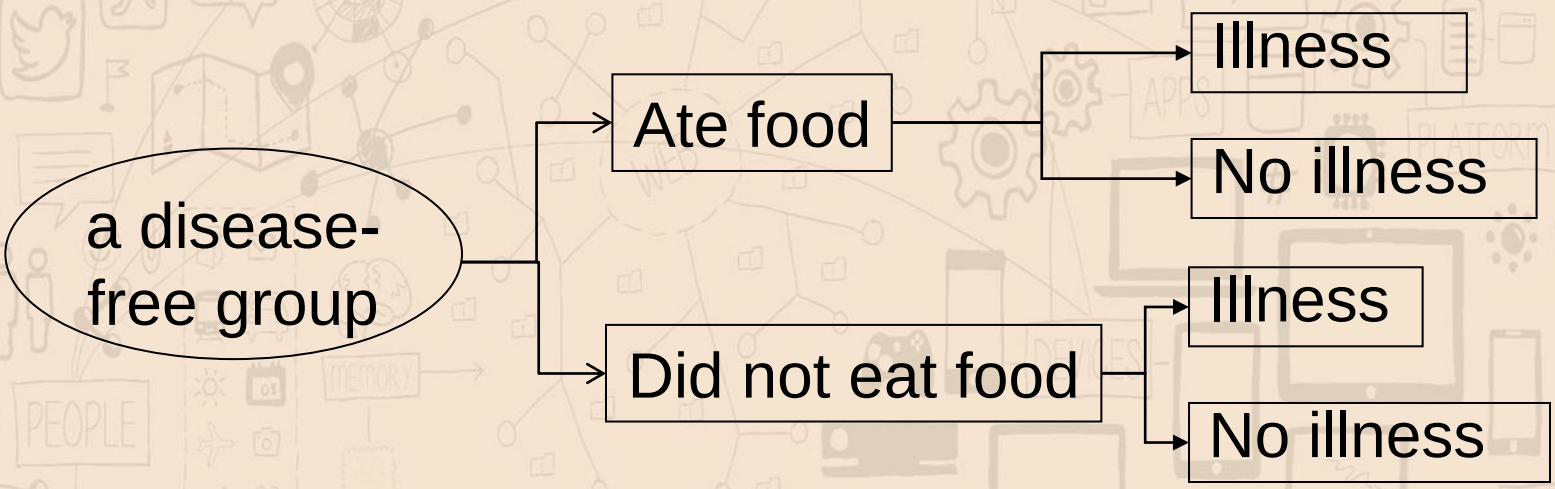


Cross-sectional Study



An Example of Cohort Study

- A disease-free group in which outbreak (expected) to occur later
- Compare attack rates among people who ate and did not eat certain food(s)
- Higher attack rates among people eating a food (compared to those not eating it) suggest the food might be associated with illness



Relative Risk / Risk Ratio (RR)

- Measure of association for a cohort study
- Compares proportion of people who ate the food who became ill with the proportion of people did not eat the food who became ill

$$\text{Relative risk} = \frac{\text{attack rate among exposed}}{\text{attack rate among unexposed}}$$

- Q: How much more likely is it for people who ate the food to become ill than people not eating the food?

Example: Outbreak of Salmonella at a Hospital

Returning to the outbreak of salmonella:

- 212 (37%) of 571 attending lunch became ill *exposed*
- 12 (7%) of 165 not attending lunch became ill *unexposed*

$$\text{Relative risk} = \frac{\text{attack rate (attended)}}{\text{attack rate (did not attend)}} = \frac{37\%}{7\%} = 5.3$$

- A relative risk of 5.3 : people who attended the luncheon were about 5 times more likely to become ill than those who did not attend

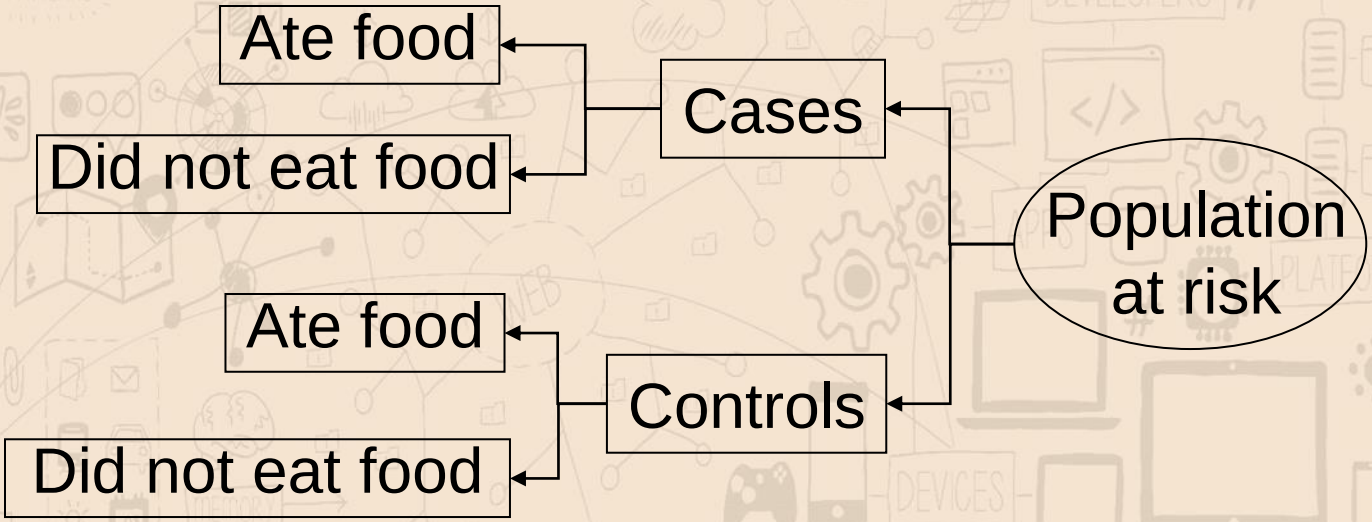
→ Attending the luncheon might be a risk factor for salmonellosis in this outbreak

Magnitudes of Relative Risk

- **Close to 1.0** = risk of disease is similar among people eating and not eating the food → food not associated with illness
- **Greater than 1.0** = risk of disease is higher among people eating the food than people not eating the food → food could be risk factor
- **Less than 1.0** = risk of disease is lower among people eating the food than people not eating the food → food could be "protective factor"
- **Magnitude** reflects strength of association between eating food and illness

Case-Control Study

- Also called **retrospective study**: 2 groups are identified
- Cases (people with illness) and controls (people with no illness)
- Compare foods eaten by cases and controls
- Foods more commonly eaten by cases than controls might be associated with illness



Example: Outbreak of Botulism in Vancouver, B.C.

- Two sisters and their mother from Vancouver developed signs and symptoms suggestive of botulism
- 36 cases of botulism among customers of Restaurant X
- Case-control study undertaken
  - 20 (91%) of 22 cases ate beef dip sandwich
  - 3 (14%) of 22 controls ate beef dip sandwich

Odds Ratio

- Measure of association for a case-control study
- Compares odds of cases having eaten a certain food to odds of controls having eaten the food

$$\text{odds ratio} = \frac{\text{odds of eating food among cases}}{\text{odds of eating food among controls}}$$

- Answers for “How much higher is the odds of eating the food among cases than controls?”

Odds Ratio

- **Close to 1.0** = odds of eating food is similar among cases and controls → no association between food and illness
- **Greater than 1.0** = odds of eating food among cases is higher than among controls → food could be risk factor
- **Less than 1.0** = odds of eating food among cases is lower than among controls → food could be "protective factor"
- **Magnitude** reflects strength of association between illness and eating the food

Odds Ratio Calculation

- Let p = probability of a success →

  the odds in favor of success = $p/(1-p)$

- p_1, p_2 : the odds in favor of success are computed for each of two proportions → ratio of odds (*OR):* useful measure for relating the two proportions

Table 13.2 Hypothetical exposure–disease relationships in a sample and a reference population

		Sample				Population	
		Disease				Disease	
		Yes	No			Yes	No
Exposed	Yes	*a*	*b*	Exposed	Yes	*A*	*B*
	No	*c*	*d*		No	*C*	*D*

Let p_1, p_2 : underlying probability of success for two groups

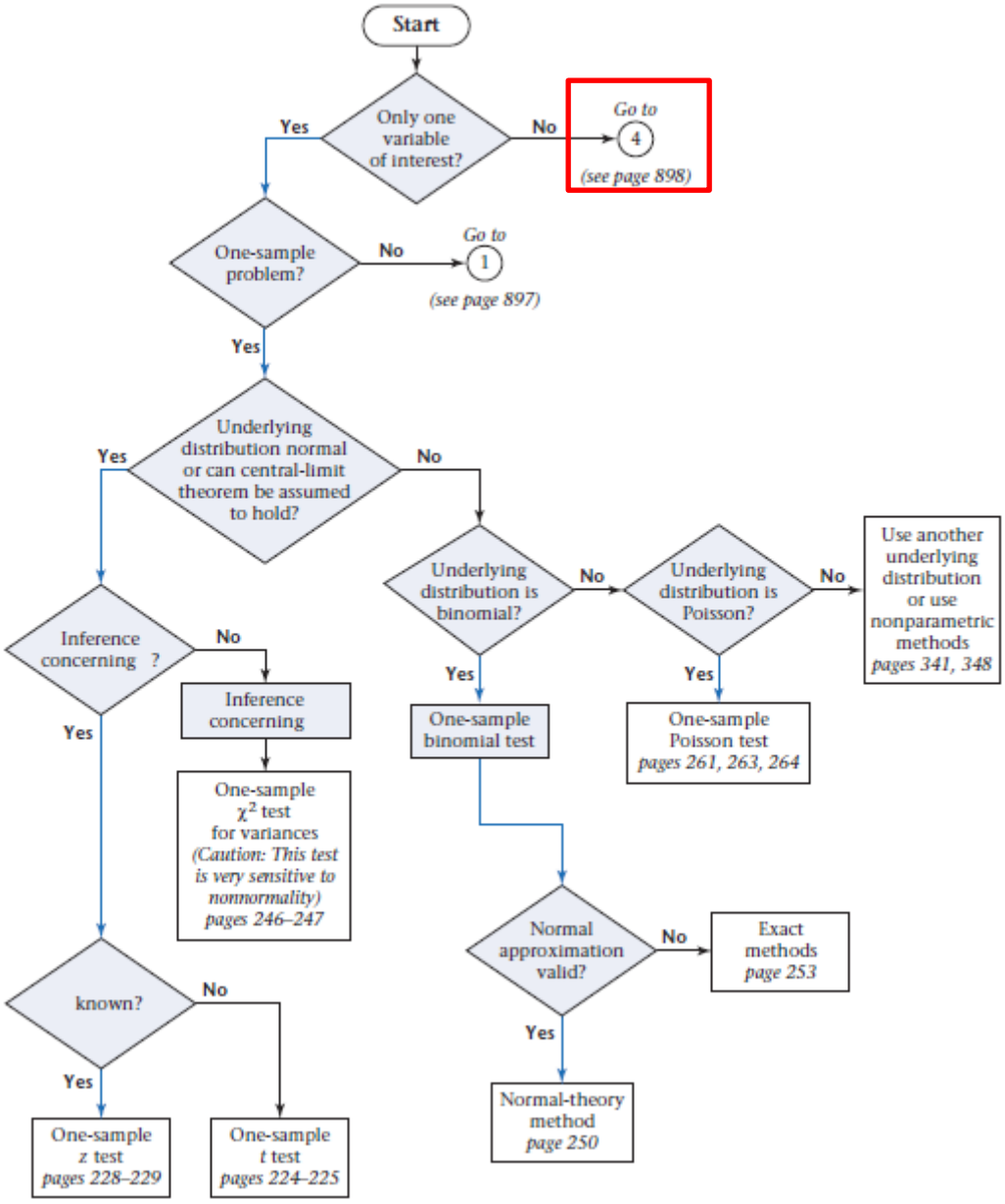
OR : $OR = \frac{p_1 / q_1}{p_2 / q_2} = \frac{p_1 q_2}{p_2 q_1}$ and estimated by $\hat{OR} = \frac{\hat{p}_1 \hat{q}_2}{\hat{p}_2 \hat{q}_1}$

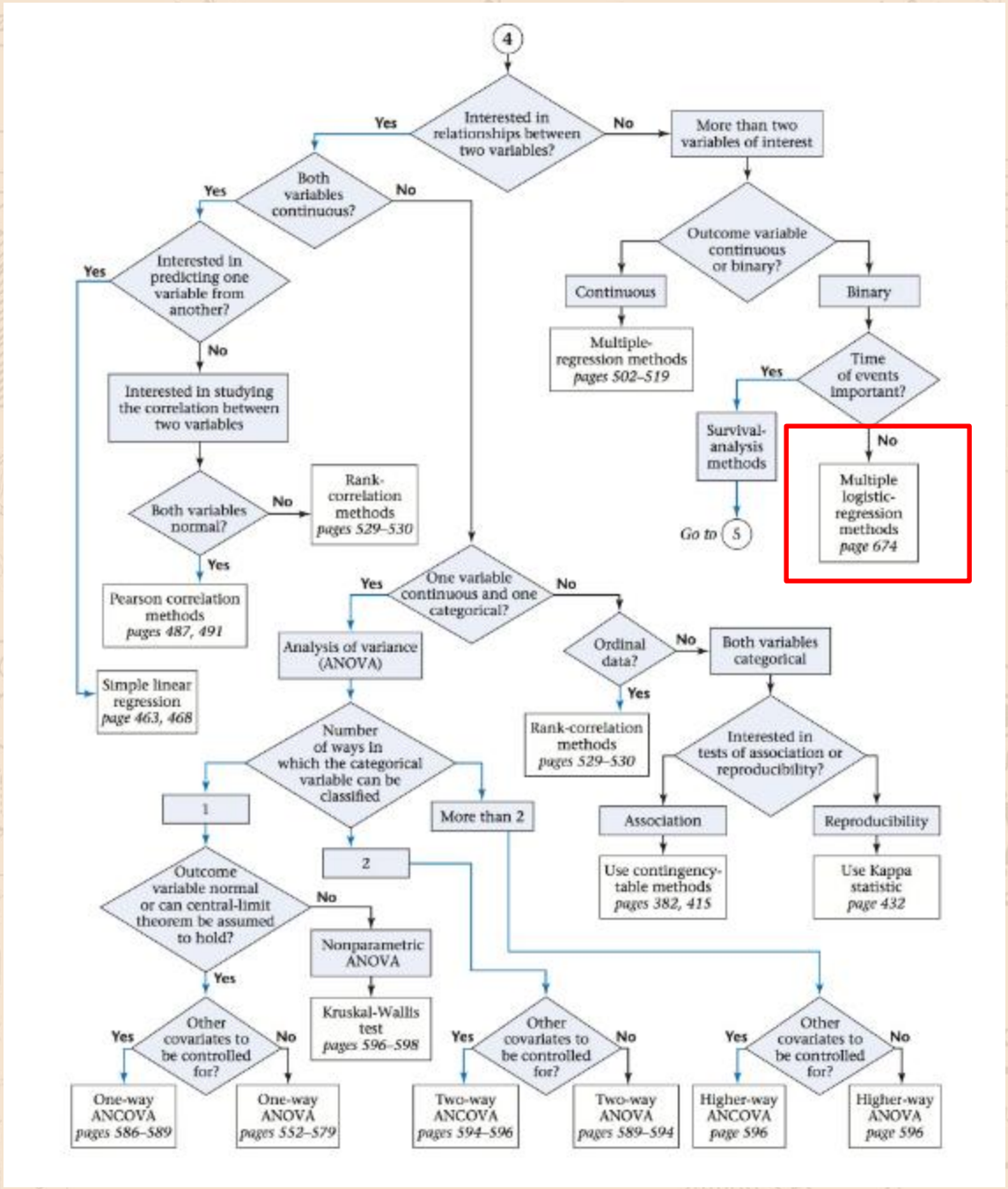
Let *a, b, c, d:* label of the four cells of the 2 × 2 contingency table

Interpretation of OR: $\hat{OR} = \frac{[a/(a+b)] \times [d/(c+d)]}{[c/(c+d)] \times [b/(a+b)]} = \frac{ad}{bc}$

disease-odds ratio: odds in favor of disease for the exposed group divided by the odds in favor of disease for the unexposed group

FIGURE 7.18 Flowchart for appropriate methods of statistical inference




4
Interested in relationships between two variables?
Yes
No
More than two variables of interest
Both variables continuous?
Yes
No
Outcome variable continuous or binary?
Continuous
Binary
Multiple-regression methods pages 502–519
Time of events important?
Yes
No
Survival-analysis methods
Go to 5
Multiple logistic-regression methods page 674
Interested in predicting one variable from another?
Yes
No
Interested in studying the correlation between two variables
Both variables normal?
No
Rank-correlation methods pages 529–530
Yes
Pearson correlation methods pages 487, 491
Simple linear regression page 463, 468
One variable continuous and one categorical?
Yes
No
Analysis of variance (ANOVA)
Ordinal data?
No
Both variables categorical
Yes
Rank-correlation methods pages 529–530
Interested in tests of association or reproducibility?
Association
Reproducibility
Use contingency-table methods pages 382, 415
Use Kappa statistic page 432
Number of ways in which the categorical variable can be classified
1
2
More than 2
Outcome variable normal or can central-limit theorem be assumed to hold?
No
Yes
Nonparametric ANOVA
Kruskal-Wallis test pages 596–598
Other covariates to be controlled for?
Yes
No
One-way ANCOVA pages 586–589
One-way ANOVA pages 552–579
Other covariates to be controlled for?
Yes
No
Two-way ANCOVA pages 594–596
Two-way ANOVA pages 589–594
Other covariates to be controlled for?
Yes
No
Higher-way ANCOVA page 596
Higher-way ANOVA page 596

Example on Relative Risk / Risk Ratio – Cancer

Question: Estimate the RR for breast cancer for women with a late age at first birth (≥ 30) compared with women with a nearly age at first birth(≤ 29) based on the data below.

TABLE 10.1 Data for the international study in Example 10.4 comparing age at first birth in breast-cancer cases with comparable controls

	Age at first birth		
Status	≥30	≤29	Total
Case	683	2537	3220
Control	1498	8747	10,245
Total	2181	11,284	13,465

Source: Based on *WHO Bulletin*, *43*, 209–221, 1970.

Example on Relative Risk / Risk Ratio – Cancer

Solution：
The estimated OR is given by

$$\widehat{OR} = \frac{ad}{bc}$$

$$\widehat{OR} = \frac{683(8747)}{2537(1498)} = 1.57$$

- An estimate of the RR

Multiple Logistic Regression

$$p = \alpha + \beta_1 x_1 + \ldots + \beta_k x_k$$

- p is the probability of disease
- Right hand side: < 0 or > 1 for certain values of $x_1, \ldots, x_k$
  - predicted probabilities < 0 or > 1 → impossible
- logit (logistic) transformation of p is often used as the dependent variable
- The **logit transformation logit(*p*):** logit(p) = ln[p/(1-p)]
- logit transformation: $-\infty$ to $+\infty$)

Multiple Logistic-Regression Model

- $x_1, \ldots, x_k$: independent variables
- y: binomial-outcome variable with probability of success = p

multiple logistic-regression model:

$$\text{logit}(p) = \ln\left(\frac{p}{1-p}\right) = \alpha + \beta_1 x_1 + \cdots + \beta_k x_k$$

Or

$$p = \frac{e^{\alpha+\beta_1 x_1+\cdots+\beta_k x_k}}{1+e^{\alpha+\beta_1 x_1+\cdots+\beta_k x_k}}$$

Interpretation of Logistic-Regression Parameters

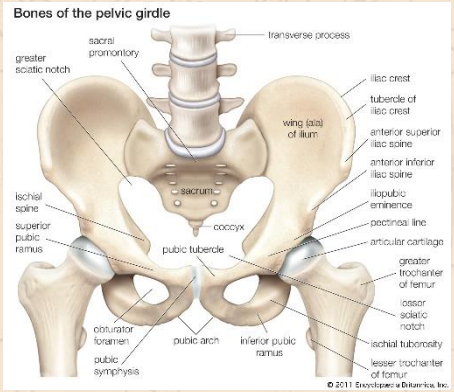
- Multiple logistic regression: analog to multiple linear regression

- Dichotomous exposure variable (xj):1 (if present) and 0 (if absent)
  - OR associates this exposure variable to dependent variable:

$$\hat{OR} = e^{\hat{\beta}j}$$

Example on Infectious Disease

- *Chlamydia trachomatis :* microorganism that has been established as an important cause of nongonococcal urethritis, pelvic inflammatory disease



- A study of risk factors for *C. trachomatis in* 431 female college students
- Because multiple risk factors may be involved, <u>several risk factors must be controlled for</u> simultaneously in analyzing variables associated with *C. trachomatis*

logit(p_A), logit(p_B): logit of the probability of success for individuals A and B:

$$\text{logit}(p_A) = \alpha + \beta_1 x_1 + \cdots + \beta_{j-1} x_{j-1} + \beta_j (1) + \beta_{j+1} x_{j+1} + \cdots + \beta_k x_k$$
$$\text{logit}(p_B) = \alpha + \beta_1 x_1 + \cdots + \beta_{j-1} x_{j-1} + \beta_j (0) + \beta_{j+1} x_{j+1} + \cdots + \beta_k x_k$$

TABLE 13.18 **Multiple logistic-regression model relating prevalence of *C. trachomatis* to race and number of lifetime sexual partners**

Risk factor	Regression coefficient $(\hat{\beta}_j)$	Standard error $se(\hat{\beta}_j)$	z $[\hat{\beta}_j / se(\hat{\beta}_j)]$
Constant	−1.637		
Black race	+2.242	0.529	+4.24
Lifetime number of sexual partners among users of nonbarrier[a] methods of contraception[b]	+0.102	0.040	+2.55

[a]Barrier methods of contraception include diaphragm, diaphragm and foam, and condom; nonbarrier methods include all other forms of contraception or no contraception.
[b]This variable is defined as 0 for users of barrier methods of contraception.

Source: From McCormack, et al., "Infection with Chlamydia Trachomatis in Female College Students," *American Journal of Epidemiology*, 1985 *121*: 107–115.

Estimation of *ORs* in Multiple Logistic regression for Dichotomous Independent Variables

- x_j*:* dichotomous exposure variable (1 [present] / 0 [absent])
  - OR in multiple logistic-regression model: $\hat{OR} = e^{\hat{\beta}_j}$

    $$\frac{odds\ in\ favor\ of\ success\ if\ xj = 1}{odds\ in\ favor\ of\ success\ if\ xj = 0}$$

    *after controlling for all other variables

  Two-sided 100% × (1-α) CI for the true OR:

$$\left[e^{\hat{\beta}_j - z_{1-\alpha/2}se(\hat{\beta}_j)}, e^{\hat{\beta}_j + z_{1-\alpha/2}se(\hat{\beta}_j)} \right]$$

- Only one risk factor in the model: *E (*1 [exposed] / 0 [unexposed]) and a dichotomous disease variable D

  $\log[p/(1-p)] = \alpha + \beta E$

Example on Multiple Logistic Regression – Infectious Disease

Question: Estimate the odds in favor of infection with C. *trachomatis* for African American women compared with Caucasian women after controlling for previous sexual experience and provide a 95% CI about this estimate.

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Example on Multiple Logistic Regression – Infectious Disease

Solution :

$$\widehat{OR} = e^{2.242} = 9.4$$

Conclusion: odds in favor of infection for African American women are nine times as great as those for Caucasian women after controlling for previous sexual experience.

- because $Z_{1-\alpha/2} = Z_{.975} = 1.96$ and $se(\hat{\beta}_j) = 0.529$
  95% CI for OR is given by:

$$\left[e^{2.242-1.96(0.529)}, e^{2.242+1.96(0.529)}\right] = (e^{1.205}, e^{3.279}) = (3.3, 26.5)$$

TABLE 3 The normal distribution

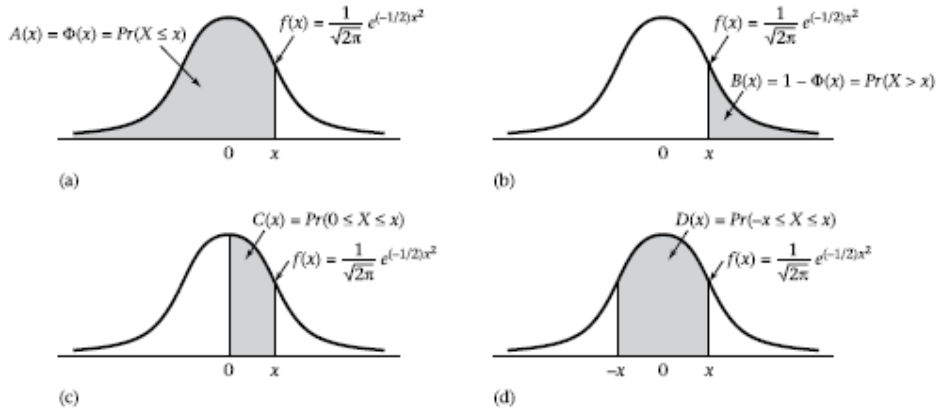

TABLE 3 The normal distribution *(continued)*

x	A[a]	B[b]	C[c]	D[d]
1.82	.9656	.0344	.4656	.9312
1.83	.9664	.0336	.4664	.9327
1.84	.9671	.0329	.4671	.9342
1.85	.9678	.0322	.4678	.9357
1.86	.9686	.0314	.4686	.9371
1.87	.9693	.0307	.4693	.9385
1.88	.9699	.0301	.4699	.9399
1.89	.9706	.0294	.4706	.9412
1.90	.9713	.0287	.4713	.9426
1.91	.9719	.0281	.4719	.9439
1.92	.9726	.0274	.4726	.9451
1.93	.9732	.0268	.4732	.9464
1.94	.9738	.0262	.4738	.9476
1.95	.9744	.0256	.4744	.9488
1.96	.9750	.0250	.4750	.9500
1.97	.9756	.0244	.4756	.9512
1.98	.9761	.0239	.4761	.9523
1.99	.9767	.0233	.4767	.9534
2.00	.9772	.0228	.4772	.9545
2.01	.9778	.0222	.4778	.9556
2.02	.9783	.0217	.4783	.9566
2.03	.9788	.0212	.4788	.9576
2.04	.9793	.0207	.4793	.9586
2.05	.9798	.0202	.4798	.9596
2.06	.9803	.0197	.4803	.9606
2.07	.9808	.0192	.4808	.9615
2.08	.9812	.0188	.4812	.9625
2.09	.9817	.0183	.4817	.9634
2.10	.9821	.0179	.4821	.9643
2.11	.9826	.0174	.4826	.9651
2.12	.9830	.0170	.4830	.9660
2.13	.9834	.0166	.4834	.9668
2.14	.9838	.0162	.4838	.9676
2.15	.9842	.0158	.4842	.9684
2.16	.9846	.0154	.4846	.9692
2.17	.9850	.0150	.4850	.9700
2.18	.9854	.0146	.4854	.9707
2.19	.9857	.0143	.4857	.9715
2.20	.9861	.0139	.4861	.9722
2.21	.9864	.0136	.4864	.9729
2.22	.9868	.0132	.4868	.9736
2.23	.9871	.0129	.4871	.9743
2.24	.9875	.0125	.4875	.9749
2.25	.9878	.0122	.4878	.9756
2.26	.9881	.0119	.4881	.9762
2.27	.9884	.0116	.4884	.9768
2.28	.9887	.0113	.4887	.9774
2.29	.9890	.0110	.4890	.9780
2.30	.9893	.0107	.4893	.9786
2.31	.9896	.0104	.4896	.9791
2.32	.9898	.0102	.4898	.9797
2.33	.9901	.0099	.4901	.9802
2.34	.9904	.0096	.4904	.9807
2.35	.9906	.0094	.4906	.9812
2.36	.9909	.0091	.4909	.9817
2.37	.9911	.0089	.4911	.9822
2.38	.9913	.0087	.4913	.9827

Summary

- Main epidemiological study designs and relevant effect estimates:

Study Design	Prospective cohort study	Case and Control
Effect Estimate	Relative Risk/ Risk Ratio	Odds ratio

- **Multiple logistic regression:** $p = \alpha + \beta_1 x_1 + \ldots + \beta_k x_k$

$$\text{logit}(p) = \ln\left(\frac{p}{1-p}\right) = \alpha + \beta_1 x_1 + \cdots + \beta_k x_k$$

- OR: links exposure variable to the dependent variable: $\hat{OR} = e^{\hat{\beta}_j}$

  95% CI for OR: $\left[e^{\hat{\beta}_j - z_{1-\alpha/2}\text{se}(\hat{\beta}_j)}, e^{\hat{\beta}_j + z_{1-\alpha/2}\text{se}(\hat{\beta}_j)}\right]$