

Lecture 11

Hypothesis Testing: Comparing Parameters (Means, Proportions, Incidence Rates) Between More Than 2 Populations With One Test

Section A: (Hypothesis Testing) Comparing Means Between More Than Two Populations: Analysis of Variance (ANOVA)

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Learning Objectives

- In this lecture section you will learn to interpret a p-value from a hypothesis test for (any) mean differences between more than two populations
- The method for getting the p-value is called the Analysis of Variance (frequently called ANOVA)

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Example 1

- Researchers were interested in the relationship between smoking and mid-expiratory flow (FEF), a measure of pulmonary health. The researchers recruited study subjects and classified them into one of six smoking categories¹
 - Nonsmokers (NS)
 - Passive smokers (PS)
 - Non-inhaling smokers (NI)
 - Light smokers (LS)
 - Moderate smokers (MS)
 - Heavy smokers (HS)

¹ White, J.R., Froeb, H.F. Small-Airways Dysfunction in Non-Smokers Chronically Exposed to Tobacco Smoke, *New England Journal of Medicine* 302: 13 (1980)

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Example 1

- To start, the researchers were interested in whether there were any statistically significant differences in pulmonary outcomes (FEV1, FEF, etc..) between the six underlying populations
- One strategy would be to perform lots of two-sample t-tests (for each possible two-group comparison)
- In this example, there would be 15 such comparisons !
 - NS to PS, NS to NI, and so on . . .

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Example 1

- Analysis of Variance (One-Way ANOVA) is an extension of the two-sample (unpaired) t-test to compare means between more than two populations with one test

- General idea behind ANOVA, comparing means for k-groups ($k > 2$):

$$H_0 : \mu_1 = \mu_2 = \dots \mu_k$$

H_A : At least one mean different

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Example 1

- Smoking and FEF
 - From a pool of over 5,200 potential participants, a random sample of 200 men and 200 women was drawn from each smoking group (except for the non-inhalers, where 50 men and 50 women were selected)
 - FEF measurements were taken on each of the subjects

Example 1

- Table 1

Vol. 302 No. 13 SMALL-AIRWAYS DYSFUNCTION IN NONSMOKERS — WHITE AND FROES 721

Table 1. Vital Capacities and Expiratory Flow Rate (Mean ± S.D.) in Male and Female Smokers and Nonsmokers.

Group	No. of Subjects	Age	Height	PVC	FEV ₁	FEF (25-75%)	FEF (50-75%)
1 — Nonsmokers, no smoking environment	200	F 47.7±7.0	162.0±6.58	3.35±0.61	102	2.52±0.61	104
2 — Nonsmokers, smoke exposure	200	M 48.8±7.38	176.3±7.77	4.91±0.73	102	3.72±0.65	103
3 — Smokers not inhaling cigarettes, pipe, or cigars	10	F 46.9±7.10	159±7.08	3.19±0.52	87	2.49±0.74	99
4 — Smokers inhaling 1-10 cigarettes per day > 20 yr	200	F 47.3±6.70	159.77±7.46	3.12±0.59	96	2.40±0.62	98
5 — Smokers inhaling 11-20 cigarettes per day > 20 yr	200	F 45.7±6.67	160±6.98	2.90±0.58*	85	2.13±0.62*	85
6 — Smokers inhaling > 40 cigarettes per day > 20 yr	200	F 45.9±6.73	159.2±6.79	2.91±0.58*	78	2.01±0.64*	80
7 — Smokers inhaling > 40 cigarettes per day > 20 yr	200	M 47.8±7.44	176.53±7.9	3.92±0.73*	82	2.77±0.69*	77
Predictions for age 40-60 yr, height 160-180 cm	1000	F 46.61±6.94	160.3±6.99	3.28	—	2.52	—
Predictions for age 40-60 yr, height 170-175 cm	1000	M 48.33±7.30	175.77±7.34	4.81	—	3.60	—

Example 1

- Data Summary, Males (FEF 25- 75%)

Group	Mean FEF (L/s)	SD FEF (L/s)	n
NS	3.78	0.79	200
PS	3.30	0.77	200
NI	3.32	0.86	50
LS	3.23	0.78	200
MS	2.73	0.81	200
HS	2.59	0.82	200

Example 1

- ANOVA comparing FEF values for males by smoking group

$$H_0: \mu_{NS} = \mu_{PS} = \mu_{NI} = \mu_{LS} = \mu_{MS} = \mu_{HS}$$
$$H_A: \text{At least two groups have different means}$$

- The p-value from ANOVA is very small: $p < 0.01$
 - Conclusion?

Example 1

- Overall summary of pulmonary comparisons, from abstract (based on follow-up two sample comparisons)

($P < 0.005$). When we looked at the extent to which smoke exposure is related to graded abnormality, we found that nonsmokers in smoke-free working environments have the highest scores on the spirometric tests; passive smokers, smokers who do not inhale, and light smokers score similarly and significantly lower; and heavy smokers score the lowest ($P < 0.005$). We conclude that chronic exposure to tobacco smoke in the work environment is deleterious to the nonsmoker and significantly reduces small-airways function. (N Engl J Med. 1980; 302: 720-3.)

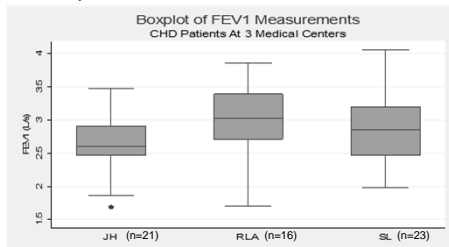
Example 2

- FEV1 and three medical centers²
 - Data was collected on 60 patients with coronary artery disease at 3 difference medical centers (Johns Hopkins, Ranchos Los Amigos Medical Center, St. Louis University School of Medicine)
 - Purpose of study to investigate effects of carbon monoxide exposure on these patients
 - Prior to analyzing CO effects data, researchers wished to compared the respiratory health of these patients across the three medical centers

² Pagano M, Gauvreau K. *Principles of Biostatistics. Second Edition.* Duxbury Press (2000).

Boxplots

■ FEV1 Values by Center



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Boxplots

■ ANOVA

■ Conclusions?

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Example 2

■ ANOVA approach, conceptually

- Assume the null hypothesis is true
- Compute a measure of discrepancy between what was observed in the sample compared to what is expected under the null (in ANOVA this is called a “F-statistic”)
- Compared this measure of discrepancy (F-statistic) to the distribution of such measures because of random sampling variability, when the null is true
- Convert to a p-value

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Example 2

- For this example, the F-statistic is 3.12. To get a p-value, this observed value is compared to a F-distribution with 2 numerator, and 57 denominator degrees of freedom

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Example 2

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Example 3: Academic Physician Salaries³

■ From abstract

Results The mean salary within our cohort was \$167 669 (95% CI, \$158 417–\$176 922) for women and \$200 433 (95% CI, \$194 249–\$206 617) for men. Male gender was associated with higher salary (+\$13 399; $P = .001$) even after adjustment in the final model for specialty, academic rank, leadership positions, publications, and research time. Peters-Belson analysis (use of coefficients derived from regression model for men applied to women) indicated that the expected mean salary for women, if they retained their other measured characteristics but their gender was male, would be \$12 194 higher than observed.

Conclusion Gender differences in salary exist in this select, homogeneous cohort of mid-career academic physicians, even after adjustment for differences in specialty, institutional characteristics, academic productivity, academic rank, work hours, and other factors.

JAMA. 2012;307(22):2410–2417

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³ Jaggi R, et al. Gender Differences in the Salaries of Physician Researchers. *Journal of the American Medical Association* (2012); 307(22); 2410–2417.

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Example 1

- Example: health care indicators by immigrant status¹

TABLE 2—Health Status, Health Care Access, and Health Care Use, by Immigrant Status:
National Survey of America's Families, 1999

	US Born, % (SE)		Foreign Born, % (SE)	
	Citizen Parents	Noncitizen Parents	Citizen (Naturalized)	Noncitizen
Health and well-being				
Had good current health status	3.9 (0.22)	3.5 (0.30)	4.2 (0.48)	3.2 (0.39)
Regular behavior at ages 5-17 y	6.4 (0.30)	6.3 (0.38)	3.7 (0.30)	2.9 (0.39)
Regular behavior at ages 12-17 y	7.9 (0.42)	3.9 (0.30)	5.1 (0.38)	6.4 (0.47)
Nondevelopment in children at ages 5-17 y	16.7 (0.55)	12.4 (0.29)	10.7 (0.47)	29.3 (0.59)
Health insurance coverage and health care use and access				
Lack of medical insurance at any time in past 12 mo	15.34 (0.55)	34.37 (2.62)	12.86 (3.68)	52.3 (2.77)
No usual source of care other than ER	5.78 (0.27)	18.21 (1.93)	12.19 (4.18)	27.93 (2.63)
At least one doctor visit in past year	77.03 (0.54)	65.43 (2.28)	77.04 (5.38)	51.75 (2.48)
ER visit in past year	25.43 (0.47)	23.47 (1.96)	11.59 (3.62)	12.45 (1.72)
At least one visit to dentist in past year (>=3 y old)	80.47 (0.44)	62.73 (2.81)	84.65 (3.42)	55.59 (2.81)
Visit to mental health specialist in past year (>=3 y old)	7.17 (0.32)	2.83 (0.89)	5.55 (1.86)	1.77 (0.46)
Subtotal of those reported specifically for diabetes visit				
Insurance at or before 2005: 40%				
Lack of medical insurance at any time in past 12 mo	26.66 (1.32)	36.76 (3.29)	32.19 (10.56)	66.96 (5.96)
Current Medicaid/SCHIP rate, coverage	45.66 (0.59)	46.63 (0.36)	63.26 (0.46)	19.97 (2.59)
Access of specific SCHIP programs	50.25 (0.29)	46.93 (0.34)	48.43 (1.74)	38.71 (1.56)
Access of Medicaid programs	88.85 (0.72)	85.83 (1.27)	80.95 (1.26)	80.79 (3.12)

Note. ER = emergency room; FPL = federal poverty level; SCHIP = State Child Health Insurance Program. All χ^2 P s were less than .05.

¹ Huang, Z., et al. Health Status and Health Service Access and Use Among Children in U.S. Immigrant Families, *American Journal of Public Health* 96: 4 (2006)

Example 1

- Zoom in

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Example 1

- Chi Square Approach

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Example 2

- Out of pocket spending, medication adherence: dialysis patients, 12 countries²

ABSTRACT: Few studies have examined drug costs and adherence in similar patient cohorts across countries. Using representative samples of hemodialysis patients from twelve countries, we examined out-of-pocket medication spending and cost-related nonadherence. Mean monthly spending ranged from \$8 in the United Kingdom to \$114 in the United States. The proportion of patients reporting nonadherence because of cost ranged from 3 percent in Japan to 29 percent in the United States. Out-of-pocket spending was related to national pharmaceutical financing policies and predicted national nonadherence rates. However, inconsistencies in the relationship between patient costs and nonadherence suggested that other social or policy factors also matter. [*Health Affairs* 27, no. 1 (2008): 89-102; 10.1377/hlthaff.27.1.89]

² Hirth R, et al. Out-Of-Pocket Spending And Medication Adherence Among Dialysis Patients In Twelve Countries. *Health Affairs* (2008). 27 (1).

Example 2

- Characteristics of dialysis patients, 12 countries (six shown)

EXHIBIT 1
Descriptive Measures Of The Prevalent Cross-Sectional Patient Sample, Dialysis Patients In Twelve Countries, 2002-2004

	A/NZ (n = 543)	REL (n = 468)	CAN (n = 503)	FRA (n = 481)	GER (n = 524)	ITA (n = 540)
Mean age (years)	59.9 (4.7)	66.2 (3.4)	62.1 (4.7)	64.1 (4.9)	61.7 (4.1)	64.1 (3.7)
Minority ^a	23.5%	5.3%	10.7%	7.3%	0.4%	6.4%
Income (\$US)						
<\$20,000	85.0%	73.4%	71.8%	67.0%	59.7%	70.3%
\$20,000-\$39,999	9.1	17.9	20.6	21.6	27.1	17.4
\$40,000+	5.9	9.1	7.4	11.2	13.1	4.2
Insurance type						
National only	69.8%	74.2%	79.6%	45.5%	95.4%	99.6%
Private only	5.4	0.4	0.2	0.2	2.9	0.0
Mean number of comorbid conditions ^b	3.7 (2)	3.9 (2.1)	4.1 (2.1)	3.1 (1.9)	3.4 (2.1)	2.7 (1.9)
Mean number of prescribed medications	6.7 (3.4)	9.9 (4.1)	12.6 (4.8)	7.7 (3.5)	9.7 (3.5)	6.4 (3.6)

Example 2

- Percentage of minorities, compared across the 12 countries (only 6 countries shown)

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Mean age (years)	59.9 (14.7)	66.2 (13.4)	62.1 (14.7)	64.1 (14.5)	61.7 (14.1)	64 (13.7)
Minority ^a	21.5%	5.3%	18.7%	7.3%	0.4%	0.4%
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<\$20,000	85.0%	73.4%	71.8%	67.0%	59.7%	78.3%
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Private only	5.4	0.4	0.2	0.2	2.9	0.0
Mean number of comorbid conditions ^b	3.7 (2)	3.9 (2.1)	4.1 (2.1)	3.1 (1.9)	3.4 (2.1)	2.7 (1.9)
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Example 2

- Distribution of income categories

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Example 2

- ANOVA as well (previously lecture section infiltration!)

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Example 3: Academic Physician Salaries³

- From abstract

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JAMA. 2012;307(2):2410-2417 www.jama.com

³ Jaggi R, et al. Gender Differences in the Salaries of Physician Researchers. *Journal of the American Medical Association* (2012); 307(22); 2410-2417.

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Example 3: Academic Physician Salaries³

- Table: characteristics of physicians by sex

Table 1. Characteristics of the Analytic Sample by Gender (N = 800)

Characteristic	Women	Men	P Value
Race			
White	189 (76.9)	415 (75.1)	
Asian/Pacific Islander	38 (15.4)	98 (17.7)	.70
Black/African American	4 (1.6)	5 (0.9)	
Other	16 (6.5)	33 (6.0)	
Unknown	0	2 (0.4)	
Age, mean (SD), y	46.3 (3.9)	46.0 (3.9)	.27
Children			
Yes	208 (84.2)	404 (89.3)	
No	39 (15.8)	57 (10.3)	.03
Unknown	0	2 (0.4)	
Marital status			
Married	215 (87.0)	500 (91.0)	
Divorced/never married	13 (5.3)	34 (6.2)	.02
Singly/never married	17 (6.9)	15 (2.7)	
Unknown	2 (0.8)	1 (0.2)	

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White	189 (76.9)	415 (75.1)	
Asian/Pacific Islander	38 (15.4)	98 (17.7)	.70
Black/African American	4 (1.6)	5 (0.9)	
Other	16 (6.5)	33 (6.0)	
Unknown	0	2 (0.4)	
Age, mean (SD), y	46.3 (3.9)	46.0 (3.9)	.27
Children			
Yes	208 (84.2)	404 (89.3)	
No	39 (15.8)	57 (10.3)	.03
Unknown	0	2 (0.4)	
Marital status			
Married	215 (87.0)	500 (91.0)	
Divorced/never married	13 (5.3)	34 (6.2)	.02
Singly/never married	17 (6.9)	15 (2.7)	
Unknown	2 (0.8)	1 (0.2)	

Summary

Section C: (Hypothesis Testing) Comparing Survival Curves Between More Than Two Populations: Log-rank Tests

Learning Objectives

- In this lecture set you will learn interpret a p-value for a hypothesis test comparing survival curves (and hence incidence rates) between more than two populations
- The method for getting the p-value is an extension of the log rank test shown in lecture 10, and is also called a log rank test

Example 1¹

■ Maternal Vitamin Supplementation and Infant Mortality

$$IR \hat{R}_{vitA} = \frac{IR_{vitA}}{IR_{placebo}} = \frac{0.00041 \text{ deaths/day}}{0.00039 \text{ deaths/day}} \approx 1.05$$

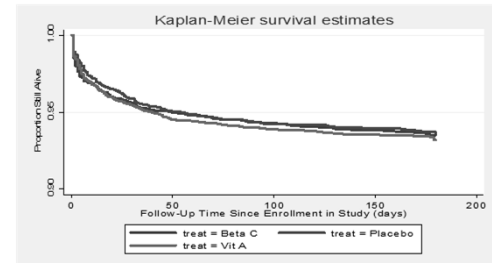
$$IR \hat{R}_{BC} = \frac{IR_{BC}}{IR_{placebo}} = \frac{0.00039 \text{ deaths/day}}{0.00039 \text{ deaths/day}} \approx 1.00$$

¹ Katz J, West K et al. Maternal low-dose vitamin A or B-carotene supplementation has no effect on fetal loss and early infant mortality: a randomized cluster trial in Nepal. *American Journal of Clinical Nutrition* (2000) Vol. 71, No. 6, 1570-1576.

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Example 1

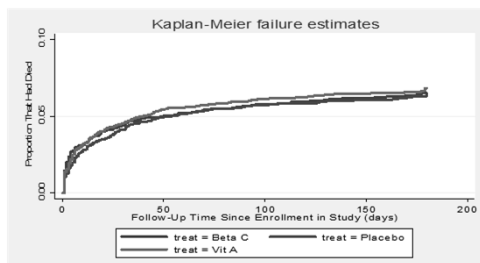
■ Maternal Vitamin Supplementation and Infant Mortality



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Example 1

■ Maternal Vitamin Supplementation and Infant Mortality



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Example 1

■ Log rank test

■ Interpretation?

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Examples 2

■ Return to Work Following Injury: The Role of Economic, Social, and Job-Related Factors²

“The main dependent variable in the analysis is the time (in days) from injury to the first time the study patient returned to work. Kaplan-Meier estimates of the cumulative proportion of patients returning to work were computed. These estimates take into account how long patients were followed as well as when they returned to work. A log-rank test was used to test the association between the cumulative probability of RTW and each of the risk factors considered one at a time”

² MacKenzie E, et al Return to Work Following Injury: The Role of Economic, Social, and Job-Related Factors *America Journal of Public Health* 88; 11 (1998)

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Example 2

■ Kaplan Meier estimates of $1 - \hat{S}(t)$

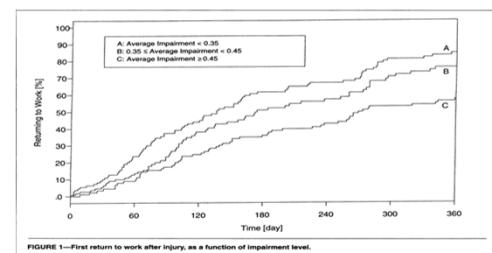


FIGURE 1—First return to work after injury, as a function of impairment level.

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Example 3

- Post partum ART therapy for children born to HIV positive women³

BACKGROUND
The safety and efficacy of adding antiretroviral drugs to standard zidovudine prophylaxis in infants of mothers with human immunodeficiency virus (HIV) infection who did not receive antenatal antiretroviral therapy (ART) because of late identification are unclear. We evaluated three ART regimens in such infants.

METHODS
Within 48 hours after their birth, we randomly assigned formula-fed infants born to women with a peripartum diagnosis of HIV type 1 (HIV-1) infection to one of three regimens: zidovudine for 6 weeks (zidovudine-alone group), zidovudine for 6 weeks plus three doses of nevirapine during the first 8 days of life (two-drug group), or zidovudine for 6 weeks plus nevirapine and lamivudine for 2 weeks (three-drug group). The primary outcome was HIV-1 infection at 3 months in infants uninfected at birth.

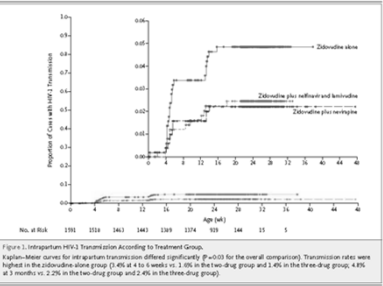
RESULTS

3 Nielson-Saines K, et al. Three Postpartum Antiretroviral Regimens to Prevent Intrapartum HIV Infection. *New England Journal of Medicine* (2012). 366 (25).

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Example 3

- Post partum ART therapy for children born to HIV positive women



"Kaplan-Meier curves for intrapartum transmission differed significantly ($P = 0.03$ for the overall comparison). Transmission rates were highest in the zidovudine-alone group (3.4% at 4 to 6 weeks vs. 1.6% in the two-drug group and 1.4% in the three-drug group; 4.8% at 3 months vs. 2.2% in the two-drug group and 2.4% in the three-drug group)."

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Example 3

- Post partum ART therapy for children born to HIV positive women

CONCLUSIONS
In neonates whose mothers did not receive ART during pregnancy, prophylaxis with a two- or three-drug ART regimen is superior to zidovudine alone for the prevention of intrapartum HIV transmission; the two-drug regimen has less toxicity than the three-drug regimen. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development [NICHD] and others; ClinicalTrials.gov number: NCT00699359.)

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Summary

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