EE3211 Modelling Techniques

Lecture 8

Multisample Inference

Example on Pulmonary Disease

- Topic: passive smoking and pulmonary health
- Information on pulmonary function was collected in 6 groups:
  1) Nonsmokers (NS): did not smoke
  2) Passive smokers (PS): in enclosed working area routinely contained tobacco smoke
  3) Non-inhaling smokers (NI): smoked pipes, cigars, or cigarettes (did not inhale)
  4) Light smokers (LS): smoked and inhaled 1-10 cigarettes per day for 20+ years
  5) Moderate smokers (MS): …11-39 cigarettes…..
  6) Heavy smokers (HS)….40+ cigarettes……
- Measured forced mid-expiratory flow (FEF) and compare mean FEF among the 6 groups
- **Q: how can the means of these six groups be compared?**

One-Way ANOVA—Fixed-Effects Model

Suppose: k groups of n_i observations in the ith group.

- y_{ij} : jth observation in the ith group
- Model: $y_{ij} = \mu + \alpha_i + e_{ij}$
  - μ: constant
  - α_i: constant specific to the ith group
  - e_{ij} : error term (normally distributed with mean 0 and variance σ^2)
- A typical observation from the ith group is normally distributed with mean $\mu+\alpha_i$ and variance σ^2

Table 12.1 FEF data for smoking and nonsmoking males

Group number, i	Group name	Mean FEF (L/s)	*sd* FEF (L/s)	n_i
1	NS	3.78	0.79	200
2	PS	3.30	0.77	200
3	NI	3.32	0.86	50
4	LS	3.23	0.78	200
5	MS	2.73	0.81	200
6	HS	2.59	0.82	200

Source: Reprinted by permission of *The New England Journal of Medicine*, *302*(13), 720–723, 1980.

Q: How do you compare the means of the six groups?

One-way analysis of variance (**one-way ANOVA**) model:

- means of an arbitrary number of groups
- each group follows a normal distribution with the same variance
- can determine if the variability in the data comes mostly from variability within groups or can truly be attributed to variability between groups

Interpretation of the parameters of a one-way ANOVA fixed-effects model

1. μ : underlying mean of all groups
2. α_i : difference between mean of the *i*th group and the overall mean
3. e_{ij} : random error about the mean $\mu+\alpha_i$ for an individual observation from *i*th group

Hypothesis Testing in One-Way ANOVA—Fixed-Effects Model

H_0: all $\alpha_i = 0$
vs.
H_1 at least one $\alpha_i \neq 0$

F test for overall comparison of group means

$$y_{ij} - \bar{y} = (y_{ij} - \bar{y}_i) + (\bar{y}_i - \bar{y})$$

$(y_{ij} - \bar{y}_i)$, *within-group variability:* deviation of an individual observation from the group mean for that observation

$(\bar{y}_i - \bar{y})$, *between-group variability:* deviation of a group mean from the overall mean

- if between-group variability is large + within-group variability is small:
  - → *reject H_0:* underlying group means are significantly different
- if between-group variability is small + within-group variability is large:
  - → accept H_0: underlying group means are the same

Squared and summation of the squared deviations:

$$\sum_{i=1}^{k}\sum_{j=1}^{n_i}\left(y_{ij}-\bar{\bar{y}}\right)^2=\sum_{i=1}^{k}\sum_{j=1}^{n_i}\left(y_{ij}-\bar{y}_i\right)^2+\sum_{i=1}^{k}\sum_{j=1}^{n_i}\left(\bar{y}_i-\bar{\bar{y}}\right)^2$$

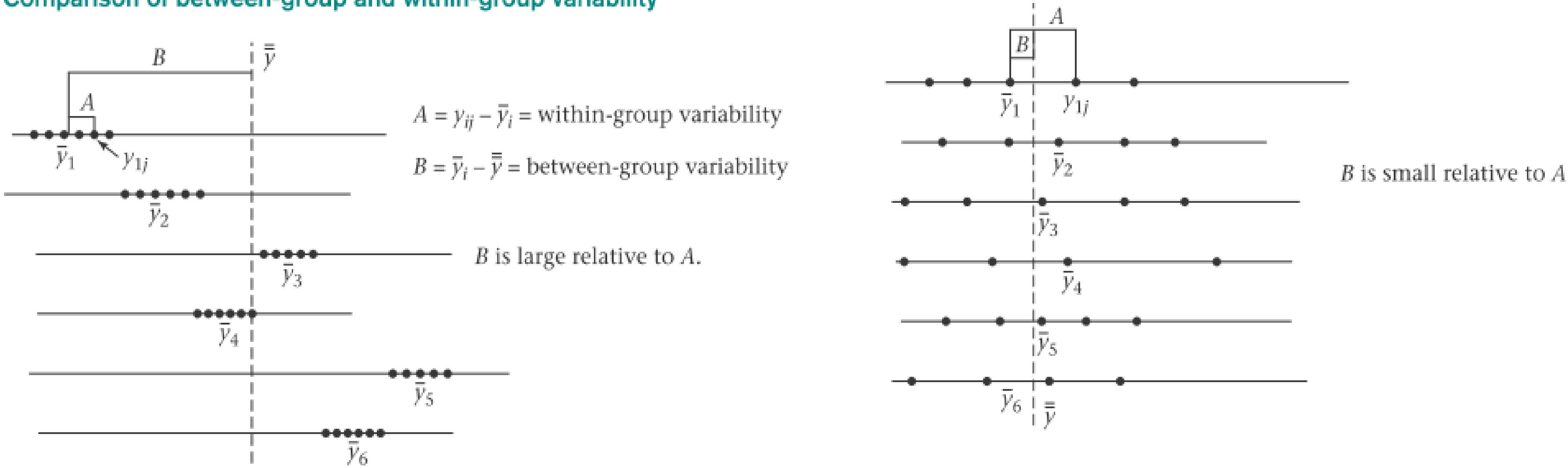
Total Sum of Squares (Total SS): $\sum_{i=1}^{k}\sum_{j=1}^{n_i}\left(y_{ij}-\bar{\bar{y}}\right)^2$

Within Sum of Squares (Within SS): $\sum_{i=1}^{k}\sum_{j=1}^{n_i}\left(y_{ij}-\bar{y}_i\right)^2$

Between Sum of Squares (Between SS): $\sum_{i=1}^{k}\sum_{j=1}^{n_i}\left(\bar{y}_i-\bar{\bar{y}}\right)^2$

Total SS = Between SS + Within SS

Comparison of between-group and within-group variability



Reject H_0 | Accept H_0

Short computational form for the Between SS and Within SS

$$\text{Between SS} = \sum_{i=1}^{k} n_i \bar{y}_i^2 - \frac{\left(\sum_{i=1}^{k} n_i \bar{y}_i\right)^2}{n} = \sum_{i=1}^{k} n_i \bar{y}_i^2 - \frac{y_{..}^2}{n}$$

$$\text{Within SS} = \sum_{i=1}^{k} (n_i - 1) s_i^2$$

- $y_{..}$ = sum of the observations across all groups (grand total of all observations over all groups)
- n = total number of observations over all groups

Between Mean Square = Between MS = Between SS/(k-1)
Within Mean Square = Within MS = Within SS/(n-k)

- Significance test : ratio of Between MS to Within MS
  - If this ratio is large → reject H_0
  - If it is small → accept H_0
  - Under H_0 : the ratio follows an F distribution with $k - 1$(numerator) and $n - k$ (dominator) df

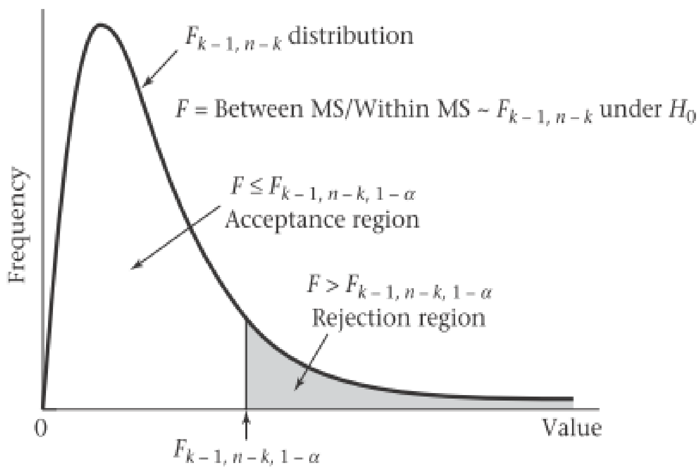
<u>Overall *F* test for One-way ANOVA Procedure</u>

H_0: $\alpha_i = 0$ for all i

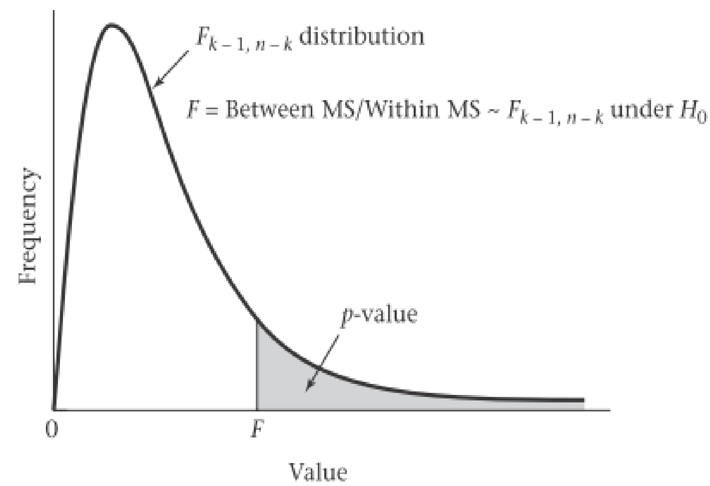
H_1: at least one $\alpha_i \neq 0$

1. Compute Between SS, Between MS, Within SS, and Within MS
2. Compute test statistic F = Between MS/Within MS, which follows an F distribution with k - 1 and $n - k$ *df* under H_0
   - If $F > F_{k-1,n-k,1-\alpha}$ → reject H_0
   - If $F \leq F_{k-1,n-k,1-\alpha}$ → accept H_1
3. Exact p-value = area to the right of F under an $F_{k-1,n-k}$ distribution = $Pr(F_{k-1,n-k} > F)$

Acceptance and rejection regions for the overall F test for one-way ANOVA



Computation of the exact p-value for the overall F test for one-way ANOVA



Display of one-way ANOVA results

Source of variation	SS	*df*	MS	*F* statistic	*p*-value
Between	$\sum_{i=1}^{k} n_i \bar{y}_i^2 - \frac{y_{..}^2}{n} = A$	$k-1$	$\frac{A}{k-1}$	$\frac{A/(k-1)}{B/(n-k)} = F$	$Pr(F_{k-1,n-k} > F)$
Within	$\sum_{i=1}^{k} (n_i - 1)s_i^2 = B$	$n-k$	$\frac{B}{n-k}$		
Total	Between SS + Within SS				

To test whether the mean FEF scores differ significantly among the six groups:

1. Calculate the Between MS and Within MS.
2. Determine F = Between MS/Within MS
3. Find the F value (with the F-table / statistical software)
4. If $p < 0.05$ → reject H_0 (all means are equal) → not all means are equal
5. Conclusion: at least two of the means are significantly different

ANOVA table for FEF data in Table 12.1

	SS	*df*	MS	*F* statistic	*p*-value
Between	184.38	5	36.875	58.0	$p < .001$
Within	663.87	1044	0.636		
Total	848.25				

R commands to perform one-way ANOVA

```
#use aov command
>model=aov(depvar ~ groupvar)
>summary(model)
```

Examples on One-way ANOVA – Pulmonary Disease

- **Question: Compute the Within SS and Between SS for the FEF data in Table 12.1**

TABLE 12.1 FEF data for smoking and nonsmoking males

Group number, i	Group name	Mean FEF (L/s)	*sd* FEF (L/s)	n_i
1	NS	3.78	0.79	200
2	PS	3.30	0.77	200
3	NI	3.32	0.86	50
4	LS	3.23	0.78	200
5	MS	2.73	0.81	200
6	HS	2.59	0.82	200

Source: Based on *The New England Journal of Medicine, 302*(13), 720–723, 1980.

Examples on One-way ANOVA – Pulmonary Disease

Solution:

We calculate the following:

$$Between\ SS = [200(3.78)^2 + 200(3.30)^2 + \cdots + 200(2.59)^2]$$

$$- \frac{[200(3.78) + 200(3.30) + \cdots + 200(2.59)]^2}{1050}$$

$$= 10{,}505.58 - 3292^2/1050$$

$$= 10{,}505.58 - 13{,}321.20$$

$$= 184.38$$

$$\text{Between SS} = \sum_{i=1}^{k} n_i \bar{y}_i^2 - \frac{\left(\sum_{i=1}^{k} n_i \bar{y}_i\right)^2}{n} = \sum_{i=1}^{k} n_i \bar{y}_i^2 - \frac{y_{..}^2}{n}$$

$$\text{Within SS} = \sum_{i=1}^{k} (n_i - 1)s_i^2$$

$$Within\ SS = 199(0.79)^2 + 199(0.77)^2 + 49(0.86)^2 + 199(0.78)^2$$

$$+199(0.81)^2 + 199(0.82)^2$$

$$= 124.20 + 117.99 + 36.24 + 121.07 + 130.56 + 133.81$$

$$= 663.87$$

Examples on One-way ANOVA – Pulmonary Disease

- **Question: Test whether the mean FEF scores differ significantly among the six groups in Table 12.1**

Between Mean Square = Between MS = Between SS/(k-1)
Within Mean Square = Within MS = Within SS/(n-k)

Solution:

Between SS = 184.38 and Within SS = 663.87.

Therefore, because there are 1050 observations combined over all 6 groups, it follows that

Between MS = 184.38 / 5 = 36.875

Within MS = 663.87 / (1050 - 6) = 663.87 / 1044 = 0.636

F = Between MS / Within MS = 36.875 / 0.636 = 58.0 ~ $F_{5,1044}$ under H_0

$F = 58 > F_{5,1044} = 4.10$ → **reject H_0**

Conclusion: at least two of the means are significantly different

TABLE 8 Percentage points of the F distribution ($F_{d_1,d_2,p}$)

df for denominator, d_2	p	df for numerator, d_1: 1	2	3	4	5	6	7	8	12	24	∞
1	.90	39.86	49.50	53.59	55.83	57.24	58.20	58.91	59.44	60.71	62.00	63.33
	.95	161.4	199.5	215.7	224.6	230.2	234.0	236.8	238.9	243.9	249.1	254.3
	.975	647.8	799.5	864.2	899.6	921.8	937.1	948.2	956.7	976.7	997.2	1018.
	.99	4052.	5000.	5403.	5625.	5764.	5859.	5928.	5981.	6106.	6235.	6366.
	.995	16211.	20000.	21615.	22500.	23056.	23437.	23715.	23925.	24426.	24940.	25464.
	.999	405280.	500000.	540380.	562500.	576400.	585940.	592870.	598140.	610670.	623500.	636620.
2	.90	8.53	9.00	9.16	9.24	9.29	9.33	9.35	9.37	9.41	9.45	9.49
	.95	18.51	19.00	19.16	19.25	19.30	19.33	19.35	19.37	19.41	19.45	19.50
	.975	38.51	39.00	39.17	39.25	39.30	39.33	39.36	39.37	39.42	39.46	39.50
	.99	98.50	99.00	99.17	99.25	99.30	99.33	99.36	99.37	99.42	99.46	99.50
	.995	198.5	199.0	199.2	199.2	199.3	199.3	199.4	199.4	199.4	199.5	199.5
	.999	998.5	999.0	999.2	999.2	999.3	999.3	999.4	999.4	999.4	999.5	999.5
3	.90	5.54	5.46	5.39	5.34	5.31	5.28	5.27	5.25	5.22	5.18	5.13
	.95	10.13	9.55	9.28	9.12	9.01	8.94	8.89	8.85	8.74	8.64	8.53
	.975	17.44	16.04	15.44	15.10	14.88	14.74	14.62	14.54	14.34	14.12	13.90
	.99	34.12	30.82	29.46	28.71	28.24	27.91	27.67	27.49	27.05	26.60	26.13
	.995	55.55	49.80	47.47	46.20	45.39	44.84	44.43	44.13	43.39	42.62	41.83
	.999	167.00	148.5	141.1	137.1	134.6	132.8	131.6	130.6	128.3	125.9	123.5
4	.90	4.54	4.32	4.19	4.11	4.05	4.01	3.98	3.95	3.90	3.83	3.76
	.95	7.71	6.94	6.59	6.39	6.26	6.16	6.09	6.04	5.91	5.77	5.63
	.975	12.22	10.65	9.98	9.60	9.36	9.20	9.07	8.98	8.75	8.51	8.26
	.99	21.20	18.00	16.69	15.98	15.52	15.21	14.98	14.80	14.37	13.93	13.46
	.995	31.33	26.28	24.26	23.16	22.46	21.98	21.62	21.35	20.70	20.03	19.32
	.999	74.14	61.25	56.18	53.44	51.71	50.53	49.66	49.00	47.41	45.77	44.05
5	.90	4.06	3.78	3.62	3.52	3.45	3.40	3.37	3.34	3.27	3.19	3.10
	.95	6.61	5.79	5.41	5.19	5.05	4.95	4.88	4.82	4.68	4.53	4.36
	.975	10.01	8.43	7.76	7.39	7.15	6.98	6.85	6.76	6.52	6.28	6.02
	.99	16.26	13.27	12.06	11.39	10.97	10.67	10.46	10.29	9.89	9.47	9.02
	.995	22.78	18.31	16.53	15.56	14.94	14.51	14.20	13.96	13.38	12.78	12.14
	.999	47.18	37.12	33.20	31.09	29.75	28.83	28.16	27.65	26.42	25.13	23.79
6	.90	3.78	3.46	3.29	3.18	3.11	3.05	3.01	2.98	2.90	2.82	2.72
	.95	5.99	5.14	4.76	4.53	4.39	4.28	4.21	4.15	4.00	3.84	3.67
	.975	8.81	7.26	6.60	6.23	5.99	5.82	5.70	5.60	5.37	5.12	4.85
	.99	13.75	10.92	9.78	9.15	8.75	8.47	8.26	8.10	7.72	7.31	6.88
	.995	18.64	14.54	12.92	12.03	11.46	11.07	10.79	10.57	10.03	9.47	8.88
	.999	35.51	27.00	23.70	21.92	20.80	20.03	19.46	19.03	17.99	16.90	15.75
7	.90	3.59	3.26	3.07	2.96	2.88	2.83	2.78	2.75	2.67	2.58	2.47
	.95	5.59	4.74	4.35	4.12	3.97	3.87	3.79	3.73	3.57	3.41	3.23
	.975	8.07	6.54	5.89	5.52	5.29	5.12	4.99	4.90	4.67	4.42	4.14
	.99	12.25	9.55	8.45	7.85	7.46	7.19	6.99	6.84	6.47	6.07	5.65
	.995	16.24	12.40	10.88	10.05	9.52	9.16	8.89	8.68	8.18	7.65	7.08
	.999	29.25	21.69	18.77	17.20	16.21	15.52	15.02	14.63	13.71	12.73	11.70
8	.90	3.46	3.11	2.92	2.81	2.73	2.67	2.62	2.59	2.50	2.40	2.29
	.95	5.32	4.46	4.07	3.84	3.69	3.58	3.50	3.44	3.28	3.12	2.93
	.975	7.57	6.06	5.42	5.05	4.82	4.65	4.53	4.43	4.20	3.95	3.67
	.99	11.26	8.65	7.59	7.01	6.63	6.37	6.18	6.03	5.67	5.28	4.86
	.995	14.69	11.04	9.60	8.81	8.30	7.95	7.69	7.50	7.01	6.50	5.95
	.999	25.42	18.49	15.83	14.39	13.49	12.86	12.40	12.04	11.19	10.30	9.33
9	.90	3.36	3.01	2.81	2.69	2.61	2.55	2.51	2.47	2.38	2.28	2.16
	.95	5.12	4.26	3.86	3.63	3.48	3.37	3.29	3.23	3.07	2.90	2.71
	.975	7.21	5.71	5.08	4.72	4.48	4.32	4.20	4.10	3.87	3.61	3.33
	.99	10.56	8.02	6.99	6.42	6.06	5.80	5.61	5.47	5.11	4.73	4.31
	.995	13.61	10.11	8.72	7.96	7.47	7.13	6.88	6.69	6.23	5.73	5.19
	.999	22.86	16.39	13.90	12.56	11.71	11.13	10.70	10.37	9.57	8.72	7.81
10	.90	3.29	2.92	2.73	2.61	2.52	2.46	2.41	2.38	2.28	2.18	2.06
	.95	4.96	4.10	3.71	3.48	3.33	3.22	3.14	3.07	2.91	2.74	2.54
	.975	6.94	5.46	4.83	4.47	4.24	4.07	3.95	3.85	3.62	3.37	3.08
	.99	10.04	7.56	6.55	5.99	5.64	5.39	5.20	5.06	4.71	4.33	3.91
	.995	12.83	9.43	8.08	7.34	6.87	6.54	6.30	6.12	5.66	5.17	4.64
	.999	21.04	14.91	12.55	11.28	10.48	9.93	9.52	9.20	8.45	7.64	6.76
12	.90	3.18	2.81	2.61	2.48	2.39	2.33	2.28	2.24	2.15	2.04	1.90
	.95	4.75	3.89	3.49	3.26	3.11	3.00	2.91	2.85	2.69	2.51	2.30
	.975	6.55	5.10	4.47	4.12	3.89	3.73	3.61	3.51	3.28	3.02	2.72

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df for denominator, d_2	*p*	*df* for numerator, d_1										
		1	2	3	4	5	6	7	8	12	24	∞
	.99	9.33	6.93	5.95	5.41	5.06	4.82	4.64	4.50	4.16	3.78	3.36
	.995	11.75	8.51	7.23	6.52	6.07	5.76	5.52	5.35	4.91	4.43	3.90
	.999	18.64	12.97	10.80	9.63	8.89	8.38	8.00	7.71	7.00	6.25	5.42
14	.90	3.10	2.73	2.52	2.39	2.31	2.24	2.19	2.15	2.05	1.94	1.80
	.95	4.60	3.74	3.34	3.11	2.96	2.85	2.76	2.70	2.53	2.35	2.13
	.975	6.30	4.86	4.24	3.89	3.66	3.50	3.38	3.29	3.05	2.79	2.49
	.99	8.86	6.51	5.56	5.04	4.69	4.46	4.28	4.14	3.80	3.43	3.00
	.995	11.06	7.92	6.68	6.00	5.56	5.26	5.03	4.86	4.43	3.96	3.44
	.999	17.14	11.78	9.73	8.62	7.92	7.44	7.08	6.80	6.13	5.41	4.60
16	.90	3.05	2.67	2.46	2.33	2.24	2.18	2.13	2.09	1.99	1.87	1.72
	.95	4.49	3.63	3.24	3.01	2.85	2.74	2.66	2.59	2.42	2.24	2.01
	.975	6.12	4.69	4.08	3.73	3.50	3.34	3.22	3.12	2.89	2.63	2.32
	.99	8.53	6.23	5.29	4.77	4.44	4.20	4.03	3.89	3.55	3.18	2.75
	.995	10.58	7.51	6.30	5.64	5.21	4.91	4.69	4.52	4.10	3.64	3.11
	.999	16.12	10.97	9.01	7.94	7.27	6.80	6.46	6.19	5.55	4.85	4.06
18	.90	3.01	2.62	2.42	2.29	2.20	2.13	2.08	2.04	1.93	1.81	1.66
	.95	4.41	3.55	3.16	2.93	2.77	2.66	2.58	2.51	2.34	2.15	1.92
	.975	5.98	4.56	3.95	3.61	3.38	3.22	3.10	3.01	2.77	2.50	2.19
	.99	8.29	6.01	5.09	4.58	4.25	4.01	3.84	3.71	3.37	3.00	2.57
	.995	10.22	7.21	6.03	5.37	4.96	4.66	4.44	4.28	3.86	3.40	2.87
	.999	15.38	10.39	8.49	7.46	6.81	6.35	6.02	5.76	5.13	4.45	3.67
20	.90	2.97	2.59	2.38	2.25	2.16	2.09	2.04	2.00	1.89	1.77	1.61
	.95	4.35	3.49	3.10	2.87	2.71	2.60	2.51	2.45	2.28	2.08	1.84
	.975	5.87	4.46	3.86	3.51	3.29	3.13	3.01	2.91	2.68	2.41	2.09
	.99	8.10	5.85	4.94	4.43	4.10	3.87	3.70	3.56	3.23	2.86	2.42
	.995	9.94	6.99	5.82	5.17	4.76	4.47	4.26	4.09	3.68	3.22	2.69
	.999	14.82	9.95	8.10	7.10	6.46	6.02	5.69	5.44	4.82	4.15	3.38
30	.90	2.88	2.49	2.28	2.14	2.05	1.98	1.93	1.88	1.77	1.64	1.46
	.95	4.17	3.32	2.92	2.69	2.53	2.42	2.33	2.27	2.09	1.89	1.62
	.975	5.57	4.18	3.59	3.25	3.03	2.87	2.75	2.65	2.41	2.14	1.79
	.99	7.56	5.39	4.51	4.02	3.70	3.47	3.30	3.17	2.84	2.47	2.01
	.995	9.18	6.35	5.24	4.62	4.23	3.95	3.74	3.58	3.18	2.73	2.18
	.999	13.29	8.77	7.05	6.12	5.53	5.12	4.82	4.58	4.00	3.36	2.59
40	.90	2.84	2.44	2.23	2.09	2.00	1.93	1.87	1.83	1.71	1.57	1.38
	.95	4.08	3.23	2.84	2.61	2.45	2.34	2.25	2.18	2.00	1.79	1.51
	.975	5.42	4.05	3.46	3.13	2.90	2.74	2.62	2.53	2.29	2.01	1.64
	.99	7.31	5.18	4.31	3.83	3.51	3.29	3.12	2.99	2.66	2.29	1.80
	.995	8.83	6.07	4.98	4.37	3.99	3.71	3.51	3.35	2.95	2.50	1.93
	.999	12.61	8.25	6.59	5.70	5.13	4.73	4.44	4.21	3.64	3.01	2.23
60	.90	2.79	2.39	2.18	2.04	1.95	1.87	1.82	1.77	1.66	1.51	1.29
	.95	4.00	3.15	2.76	2.53	2.37	2.25	2.17	2.10	1.92	1.70	1.39
	.975	5.29	3.93	3.34	3.01	2.79	2.63	2.51	2.41	2.17	1.88	1.48
	.99	7.08	4.98	4.13	3.65	3.34	3.12	2.95	2.82	2.50	2.12	1.60
	.995	8.49	5.80	4.73	4.14	3.76	3.49	3.29	3.13	2.74	2.29	1.69
	.999	11.97	7.77	6.17	5.31	4.76	4.37	4.09	3.86	3.32	2.69	1.89
120	.90	2.75	2.35	2.13	1.99	1.90	1.82	1.77	1.72	1.60	1.45	1.19
	.95	3.92	3.07	2.68	2.45	2.29	2.17	2.09	2.02	1.83	1.61	1.25
	.975	5.15	3.80	3.23	2.89	2.67	2.52	2.39	2.30	2.05	1.76	1.31
	.99	6.85	4.79	3.95	3.48	3.17	2.96	2.79	2.66	2.34	1.95	1.38
	.995	8.18	5.54	4.50	3.92	3.55	3.28	3.09	2.93	2.54	2.09	1.43
	.999	11.38	7.32	5.78	4.95	4.42	4.04	3.77	3.55	3.02	2.40	1.54
∞	.90	2.71	2.30	2.08	1.94	1.85	1.77	1.72	1.67	1.55	1.38	1.00
	.95	3.84	3.00	2.60	2.37	2.21	2.10	2.01	1.94	1.75	1.52	1.00
	.975	5.02	3.69	3.12	2.79	2.57	2.41	2.29	2.19	1.94	1.64	1.00
	.99	6.63	4.61	3.78	3.32	3.02	2.80	2.64	2.51	2.18	1.79	1.00
	.995	7.88	5.30	4.28	3.72	3.35	3.09	2.90	2.74	2.36	1.90	1.00
	.999	10.83	6.91	5.42	4.62	$\boxed{4.10}$	3.74	3.47	3.27	2.74	2.13	1.00

Comparisons of Specific Groups in One-Way ANOVA

- H_0: all group means are equal
  H_1: at least two group means are different
  - Do not know which of the groups have means that differ from each other
  - Overall F test: if reject H_0 → compare the specific groups

<u>*t* Test for Comparison of Pairs of Groups</u>

- test whether groups 1 and 2 have means that are significantly different from each other
- Under either hypothesis:
  - $\overline{Y}_1$ is normally distributed with mean $\mu+\alpha_1$ and variance σ^2/n_1
  - $\overline{Y}_2$ is normally distributed with mean $\mu+\alpha_2$ and variance σ^2/n_2
- The difference of the sample means $(\overline{y}_1 - \overline{y}_2)$ will be used as a test criterion:

$$\overline{Y}_1 - \overline{Y}_2 \sim N\left[\alpha_1 - \alpha_2, \sigma^2\left(\frac{1}{n_1} + \frac{1}{n_2}\right)\right]$$

- Reduce to:

$$\boxed{\overline{Y}_1 - \overline{Y}_2 \sim N\left[0, \sigma^2\left(\frac{1}{n_1} + \frac{1}{n_2}\right)\right]}$$

- If σ^2 known, dividing by the standard error:

$$\boxed{Z = \frac{\overline{Y}_1 - \overline{Y}_2}{\sqrt{\sigma^2\left(\frac{1}{n_1} + \frac{1}{n_2}\right)}}}$$

- $Z \sim N(0,1)$ distribution under H_0
  - Because σ^2 is unknown and can be estimated by s^2

    The test statistic becomes:

$$S^2 = [(n_1-1)s_1^2 + (n_2-1)s_2^2]/(n_1+n_2-2)$$

- One-way ANOVA:
  - k sample variances
  - Estimate σ^2 by computing a weighted average of k individual sample variances
  - Weights are the df in each of k samples

    (degree of freedom: max. no. of logically independent values; values that have freedom to vary)

$$s^2 = \sum_{i=1}^{k}(n_i-1)s_i^2 \Big/ \sum_{i=1}^{k}(n_i-1) = \left[\sum_{i=1}^{k}(n_i-1)s_i^2\right] \Big/ (n-k) = \text{Within MS}$$

- Pooled estimate of the variance for one-way ANOVA

t Test for the Comparison of Pairs of Groups in One-Way ANOVA (LSD Procedure)

- Goal: suppose we wish to compare two specific groups (group 1 and group 2) among *k* groups
- H_0: $\alpha_1 = \alpha_2$ vs. H_1: $\alpha_1 \neq \alpha_2$

1.Compute the pooled estimate of variance s^2 = within MS from one way ANOVA

$$t = \frac{\bar{y}_1 - \bar{y}_2}{\sqrt{s^2\left(\frac{1}{n_1} + \frac{1}{n_2}\right)}}$$

2. Compute the test statistic:

- which follows a t_{n-k} distribution under H_0

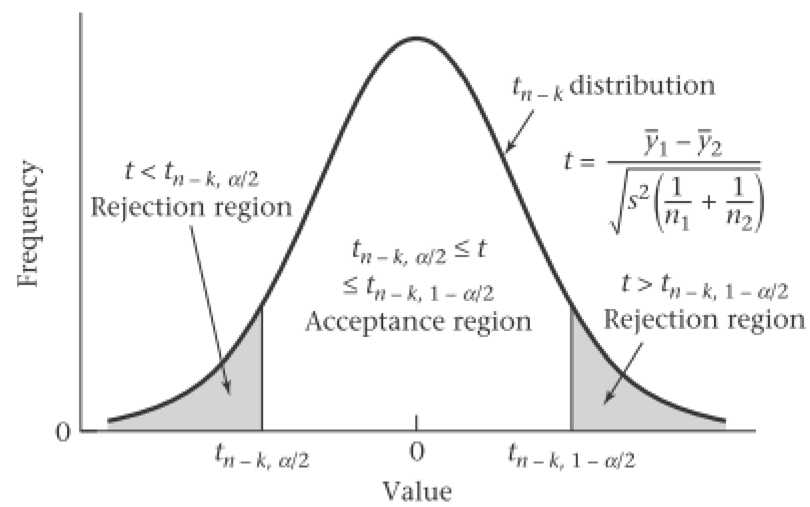
3. Two-sided level α test:

- reject H_0: if $t > t_{n-k,1-\alpha/2}$ or $t < t_{n-k,\alpha/2}$
- accept H_0 if $t_{n-k,\alpha/2} \leq t \leq t_{n-k,1-\alpha/2}$

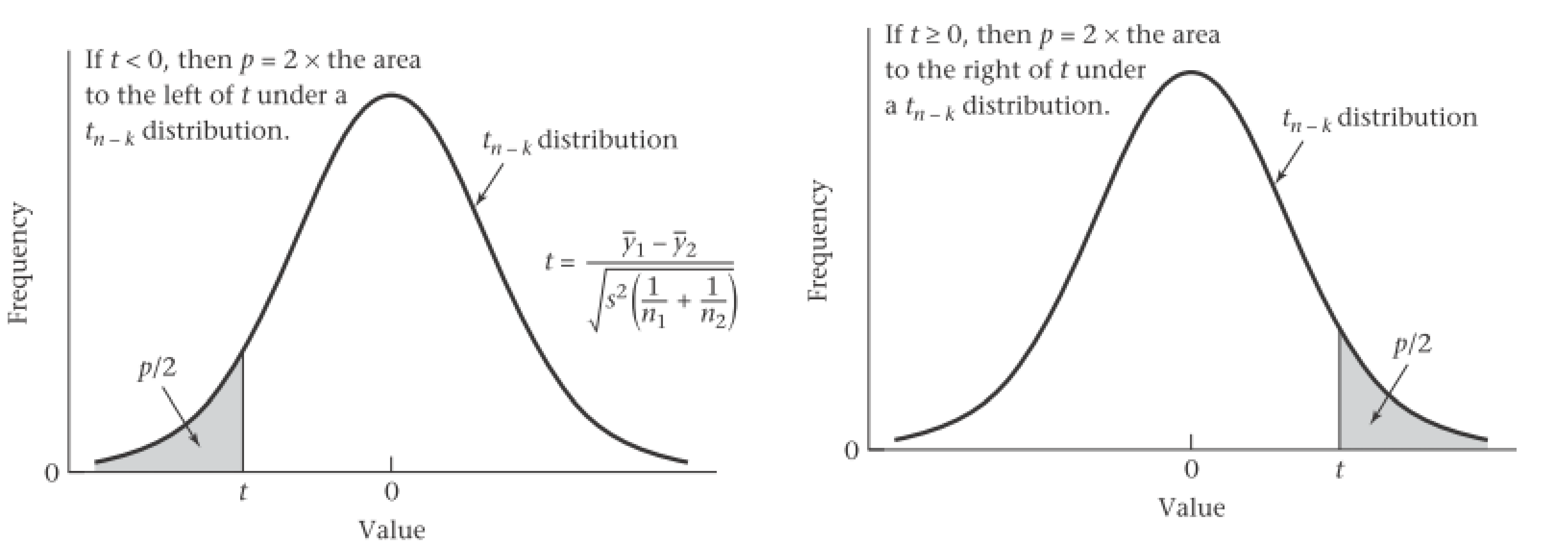
4. Exact *p*-value:

- $p = 2 \times$ the area to the left of t under a t_{n-k} distribution if $t < 0$
  $= 2 \times Pr(t_{n-k} < t)$
- $p = 2 \times$ the areas to the right of t under a t_{n-k} distribution if $t \geq 0$
  $= 2 \times Pr(t_{n-k} > t)$

Acceptance and rejection regions for the *t* test for the comparison of pairs of groups in one-way ANOVA (LSD approach)



Computation of the exact *p*-value for the *t* test for the comparison of pairs of groups in one-way ANOVA (LSD approach)



Example on Comparison of Specific Group(s) in One-way ANOVA: Pulmonary Disease

- **Question: Compare each pair of groups for the FEF data in Table 12.1, and report any significant differences.**

Solution:

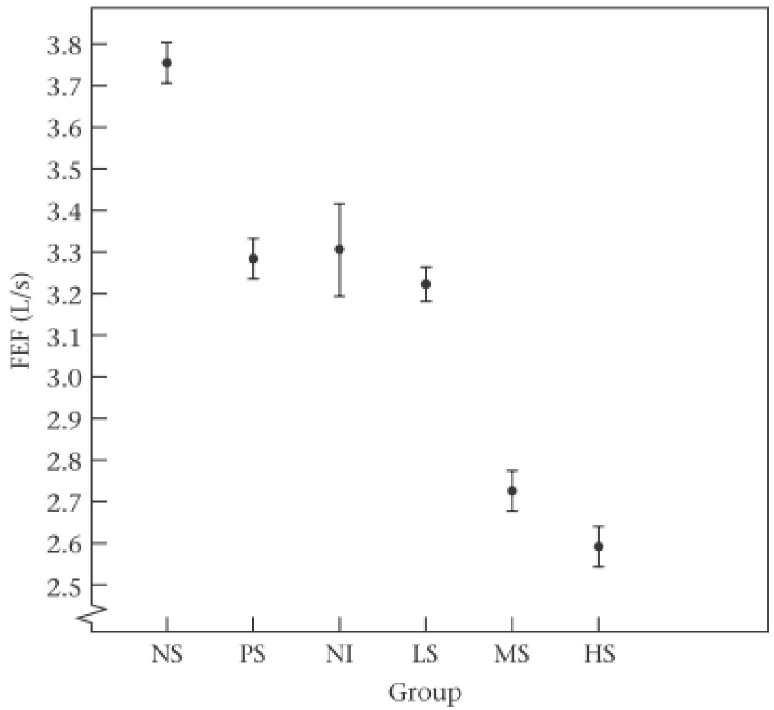
- First plot the mean ± *se* of the FEF values for each of the six groups in Figure 12.6 to obtain some idea of the magnitude of the differences between groups.

- The standard error for an individual group mean is estimated by $s/\sqrt{n_i}$, where s^2 = within MS.

- Notice that the nonsmokers, and light smokers have about the same pulmonary function and are worse off than the nonsmokers; and the moderate and heavy smokers have the poorest pulmonary function.

Example on Comparison of Specific Group(s) in One-way ANOVA: Pulmonary Disease

Figure 12.6 Mean ± *se* for FEF for each of six smoking groups



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correct

Frequent error in performing the *t* test (compare groups 1 and 2):

- use sample variances to estimate σ^2 from *these two groups (vs.* from *all k groups)*
- If former situation: different estimates of σ^2 obtained for each pair of groups considered
- not reasonable (all the groups are assumed to have the same underlying variance σ^2)

Example on Comparison of Specific Group(s) in One-way ANOVA: Pulmonary Disease

- Note also that the standard error bars are wider for the non-inhaling smokers than for the other groups because this group has only 50 people compared with 200 for all other groups.

- Are the observer differences in the figure statistically significant as assessed by the LSD procedure in Equation 12.12? The results are presented in Table 12.4.

Table 12.4 Comparisons of specific pairs of groups for the FEF data in Table 12.1 using the LSD t test approach

Groups compared	Test statistic	p-value
NS, PS	$t=\dfrac{3.78-3.30}{\sqrt{0.636\left(\dfrac{1}{200}+\dfrac{1}{200}\right)}}=\dfrac{0.48}{0.08}=6.02^{a}$	< .001
NS, NI	$t=\dfrac{3.78-3.32}{\sqrt{0.636\left(\dfrac{1}{200}+\dfrac{1}{50}\right)}}=\dfrac{0.46}{0.126}=3.65$	< .001
NS, LS	$t=\dfrac{3.78-3.23}{\sqrt{0.636\left(\dfrac{1}{200}+\dfrac{1}{200}\right)}}=\dfrac{0.55}{0.08}=6.90$	< .001
NS, MS	$t=\dfrac{3.78-2.73}{0.080}=\dfrac{1.05}{0.08}=13.17$	< .001
NS, HS	$t=\dfrac{3.78-2.59}{0.080}=\dfrac{1.19}{0.08}=14.92$	< .001
PS, NI	$t=\dfrac{3.30-3.32}{0.126}=\dfrac{-0.02}{0.126}=-0.16$	NS
PS, LS	$t=\dfrac{3.30-3.23}{0.080}=\dfrac{0.07}{0.08}=0.88$	NS
PS, MS	$t=\dfrac{3.30-2.73}{0.080}=\dfrac{0.57}{0.08}=7.15$	< .001
PS, HS	$t=\dfrac{3.30-2.59}{0.080}=\dfrac{0.71}{0.08}=8.90$	< .001
NI, LS	$t=\dfrac{3.32-3.23}{0.126}=\dfrac{0.09}{0.126}=0.71$	NS
NI, MS	$t=\dfrac{3.32-2.73}{0.126}=\dfrac{0.59}{0.126}=4.68$	< .001
NI, HS	$t=\dfrac{3.32-2.59}{0.126}=\dfrac{0.73}{0.126}=5.79$	< .001
LS, MS	$t=\dfrac{3.23-2.73}{0.08}=\dfrac{0.50}{0.08}=6.27$	< .001
LS, HS	$t=\dfrac{3.23-2.59}{0.08}=\dfrac{0.64}{0.08}=8.03$	< .001
MS, HS	$t=\dfrac{2.73-2.59}{0.08}=\dfrac{0.14}{0.08}=1.76$	NS

[a]All test statistics follow a t_{1044} distribution under H_0.

TABLE 5 Percentage points of the t distribution ($t_{d,u}$)*

Degrees of freedom, d	u = .75	.80	.85	.90	.95	.975	.99	.995	.9995
1	1.000	1.376	1.963	3.078	6.314	12.706	31.821	63.657	636.619
2	0.816	1.061	1.386	1.886	2.920	4.303	6.965	9.925	31.598
3	0.765	0.978	1.250	1.638	2.353	3.182	4.541	5.841	12.924
4	0.741	0.941	1.190	1.533	2.132	2.776	3.747	4.604	8.610
5	0.727	0.920	1.156	1.476	2.015	2.571	3.365	4.032	6.869
6	0.718	0.906	1.134	1.440	1.943	2.447	3.143	3.707	5.959
7	0.711	0.896	1.119	1.415	1.895	2.365	2.998	3.499	5.408
8	0.706	0.889	1.108	1.397	1.860	2.306	2.896	3.355	5.041
9	0.703	0.883	1.100	1.383	1.833	2.262	2.821	3.250	4.781
10	0.700	0.879	1.093	1.372	1.812	2.228	2.764	3.169	4.587
11	0.697	0.876	1.088	1.363	1.796	2.201	2.718	3.106	4.437
12	0.695	0.873	1.083	1.356	1.782	2.179	2.681	3.055	4.318
13	0.694	0.870	1.079	1.350	1.771	2.160	2.650	3.012	4.221
14	0.692	0.868	1.076	1.345	1.761	2.145	2.624	2.977	4.140
15	0.691	0.866	1.074	1.341	1.753	2.131	2.602	2.947	4.073
16	0.690	0.865	1.071	1.337	1.746	2.120	2.583	2.921	4.015
17	0.689	0.863	1.069	1.333	1.740	2.110	2.567	2.898	3.965
18	0.688	0.862	1.067	1.330	1.734	2.101	2.552	2.878	3.922
19	0.688	0.861	1.066	1.328	1.729	2.093	2.539	2.861	3.883
20	0.687	0.860	1.064	1.325	1.725	2.086	2.528	2.845	3.850
21	0.686	0.859	1.063	1.323	1.721	2.080	2.518	2.831	3.819
22	0.686	0.858	1.061	1.321	1.717	2.074	2.508	2.819	3.792
23	0.685	0.858	1.060	1.319	1.714	2.069	2.500	2.807	3.767
24	0.685	0.857	1.059	1.318	1.711	2.064	2.492	2.797	3.745
25	0.684	0.856	1.058	1.316	1.708	2.060	2.485	2.787	3.725
26	0.684	0.856	1.058	1.315	1.706	2.056	2.479	2.779	3.707
27	0.684	0.855	1.057	1.314	1.703	2.052	2.473	2.771	3.690
28	0.683	0.855	1.056	1.313	1.701	2.048	2.467	2.763	3.674
29	0.683	0.854	1.055	1.311	1.699	2.045	2.462	2.756	3.659
30	0.683	0.854	1.055	1.310	1.697	2.042	2.457	2.750	3.646
40	0.681	0.851	1.050	1.303	1.684	2.021	2.423	2.704	3.551
60	0.679	0.848	1.046	1.296	1.671	2.000	2.390	2.660	3.460
120	0.677	0.845	1.041	1.289	1.658	1.980	2.358	2.617	3.373
∞	0.674	0.842	1.036	1.282	1.645	1.960	2.326	2.576	3.291

Example on Comparison of Specific Group(s) in One-way ANOVA: Pulmonary Disease

Solution:

- There are very highly significant differences:
  (1) between the nonsmokers and all other groups
  (2) between the passive smokers and the moderate and heavy smokers
  (3) between the non-inhaling and the moderate and heavy smokers
  (4) between the light smokers and the moderate and heavy smokers.

- There are no significant differences between the passive smokers, non-inhalers, and light smokers and no significant differences between the moderate and heavy smokers
  - there is a trend toward significance with the latter comparison.

Multiple Comparisons

- Comparisons are made before looking at the data → t test procedure is appropriate
- Comparisons are made after looking at the data

  → large no. of comparisons

  → some significant differences may be found by chance (false significant difference)

Multiple Comparisons—Bonferroni Approach

- Avoid too many falsely significant difference
- Overall probability of declaring any significant differences between all possible pairs of groups is maintained at some fixed significance level
- Simplest : *Bonferroni adjustment*

Suppose we want to compare two specific groups (group 1 and group 2) among k groups.

H_0: $\alpha_1 = \alpha_2$ vs. H_1: $\alpha_1 \neq \alpha_2$

<u>Bonferroni multiple-comparisons procedure</u>:

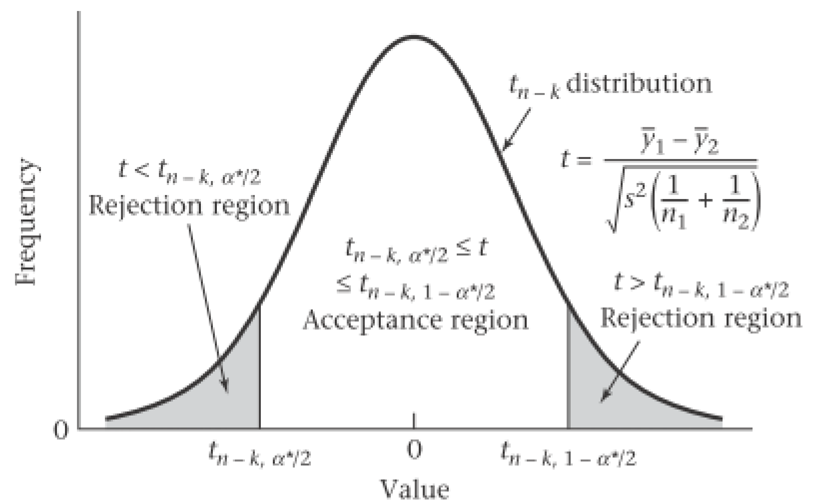
1. Compute pooled estimate of the variance s^2 = Within MS from the one-way ANOVA.

2. Compute test statistic: $\boxed{t = \dfrac{\bar{y}_1 - \bar{y}_2}{\sqrt{s^2\left(\dfrac{1}{n_1} + \dfrac{1}{n_2}\right)}}}$

3. Two-sided level α test, let $\alpha^* = \alpha/\binom{k}{2}$
   - reject H_0: if $t > t_{n-k,1-\alpha^*/2}$ or $t < t_{n-k,\alpha^*/2}$
   - accept H_0: if $t > t_{n-k,\alpha^*/2} \leq t \leq t_{n-k,1-\alpha^*/2}$

$$\boxed{no.of\ test = \binom{k}{2} = \frac{k!}{2!\,(k-2)!}}$$

Figure 12.7 Acceptance and rejection regions for the comparison of pairs of groups in one-way ANOVA (Bonferroni approach)



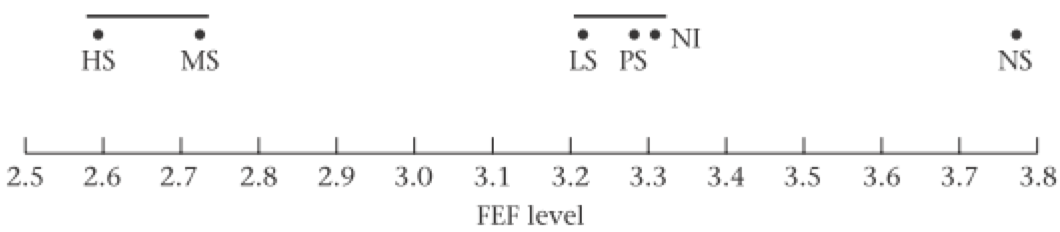
k groups:

- ($^{k}{}_{2}$) possible two-group comparisons
- each two-group comparison at the α^* level of significance.
- Let E be the event that at least one of the two-group comparisons is statistically significant

Pr(E) = Pr(none of the two-group comparisons is statistically significant)
= 1- α

- each of the two-group comparisons were independent
  from the multiplication law of probability: *Pr(E)* = (1- α*)^{c} where c = ($^{k}{}_{2}$)
  1- α = (1-α*)^{c}

Figure 12.8 Display of results of Bonferroni multiple-comparisons procedure on FEF data in Table 12.1



Line drawn between the names or numbers of each pair of means that is not significantly different

- Visually summarize the results of many comparisons of pairs of means
- Multiple-comparisons procedures are more strict than ordinary t tests (compare more than two means)
- As k increases, c = $\binom{k}{2}$ increases and therefore $\alpha^* = \alpha/c$ decreases
- The critical value, $t_{n-k,1-\alpha^*/2}$, therefore increases
  - As k increases, the df (n-k) decreases and the percentile 1- $\alpha^*/2$ increases
  - Both lead to larger critical value

When is multiple-comparisons procedure used over LSD procedure?

- Multiple-comparisons procedures should be used if there are many groups and not all comparisons between individual groups are planned
- Relatively few groups and only specific comparisons of interest are intended, then use ordinary t tests (i.e., the LSD procedure)
- Multiple-comparisons procedure is applicable for comparing pairs of means

Example on Bonferroni Correction – Pulmonary Disease

- **Question: Apply the Bonferroni multiple-comparisons procedure to the FEF data in Table 12.1**

$\binom{6}{2} = \frac{6!}{2!(6-2)!} = \frac{6*5*\cancel{4*3*2*1}}{2*\cancel{(4*3*2*1)}}$

Solution:

- Experiment-wise type I error = .05
- n = 1050 subjects and k = 6 groups

→ $n - k = 1044$ and $c = \binom{6}{2} = 15$

$\alpha^* = .05/15 = .0033$ level of significance

- critical value for each of these t tests is $t_{1044,1\ -\ .0033/2} = t_{1044,.99833}$. We will approximate a t distribution with 1044 *df* by an N (0,1)distribution or, $t_{1044,.99833} \approx z_{.99833}$
- $z_{.99833} = 2.93$
- Table 12.4 which provides the *t* statistics for each two-group comparison

TABLE 3 The normal distribution *(continued)*

x	A[a]	B[b]	C[c]	D[d]	x	A	B	C	D
1.82	.9656	.0344	.4656	.9312	2.39	.9916	.0084	.4916	.9832
1.83	.9664	.0336	.4664	.9327	2.40	.9918	.0082	.4918	.9836
1.84	.9671	.0329	.4671	.9342	2.41	.9920	.0080	.4920	.9840
1.85	.9678	.0322	.4678	.9357	2.42	.9922	.0078	.4922	.9845
1.86	.9686	.0314	.4686	.9371	2.43	.9925	.0075	.4925	.9849
1.87	.9693	.0307	.4693	.9385	2.44	.9927	.0073	.4927	.9853
1.88	.9699	.0301	.4699	.9399	2.45	.9929	.0071	.4929	.9857
1.89	.9706	.0294	.4706	.9412	2.46	.9931	.0069	.4931	.9861
1.90	.9713	.0287	.4713	.9426	2.47	.9932	.0068	.4932	.9865
1.91	.9719	.0281	.4719	.9439	2.48	.9934	.0066	.4934	.9869
1.92	.9726	.0274	.4726	.9451	2.49	.9936	.0064	.4936	.9872
1.93	.9732	.0268	.4732	.9464	2.50	.9938	.0062	.4938	.9876
1.94	.9738	.0262	.4738	.9476	2.51	.9940	.0060	.4940	.9879
1.95	.9744	.0256	.4744	.9488	2.52	.9941	.0059	.4941	.9883
1.96	.9750	.0250	.4750	.9500	2.53	.9943	.0057	.4943	.9886
1.97	.9756	.0244	.4756	.9512	2.54	.9945	.0055	.4945	.9889
1.98	.9761	.0239	.4761	.9523	2.55	.9946	.0054	.4946	.9892
1.99	.9767	.0233	.4767	.9534	2.56	.9948	.0052	.4948	.9895
2.00	.9772	.0228	.4772	.9545	2.57	.9949	.0051	.4949	.9898
2.01	.9778	.0222	.4778	.9556	2.58	.9951	.0049	.4951	.9901
2.02	.9783	.0217	.4783	.9566	2.59	.9952	.0048	.4952	.9904
2.03	.9788	.0212	.4788	.9576	2.60	.9953	.0047	.4953	.9907
2.04	.9793	.0207	.4793	.9586	2.61	.9955	.0045	.4955	.9909
2.05	.9798	.0202	.4798	.9596	2.62	.9956	.0044	.4956	.9912
2.06	.9803	.0197	.4803	.9606	2.63	.9957	.0043	.4957	.9915
2.07	.9808	.0192	.4808	.9615	2.64	.9959	.0041	.4959	.9917
2.08	.9812	.0188	.4812	.9625	2.65	.9960	.0040	.4960	.9920
2.09	.9817	.0183	.4817	.9634	2.66	.9961	.0039	.4961	.9922
2.10	.9821	.0179	.4821	.9643	2.67	.9962	.0038	.4962	.9924
2.11	.9826	.0174	.4826	.9651	2.68	.9963	.0037	.4963	.9926
2.12	.9830	.0170	.4830	.9660	2.69	.9964	.0036	.4964	.9929
2.13	.9834	.0166	.4834	.9668	2.70	.9965	.0035	.4965	.9931
2.14	.9838	.0162	.4838	.9676	2.71	.9966	.0034	.4966	.9933
2.15	.9842	.0158	.4842	.9684	2.72	.9967	.0033	.4967	.9935
2.16	.9846	.0154	.4846	.9692	2.73	.9968	.0032	.4968	.9937
2.17	.9850	.0150	.4850	.9700	2.74	.9969	.0031	.4969	.9939
2.18	.9854	.0146	.4854	.9707	2.75	.9970	.0030	.4970	.9940
2.19	.9857	.0143	.4857	.9715	2.76	.9971	.0029	.4971	.9942
2.20	.9861	.0139	.4861	.9722	2.77	.9972	.0028	.4972	.9944
2.21	.9864	.0136	.4864	.9729	2.78	.9973	.0027	.4973	.9946
2.22	.9868	.0132	.4868	.9736	2.79	.9974	.0026	.4974	.9947
2.23	.9871	.0129	.4871	.9743	2.80	.9974	.0026	.4974	.9949
2.24	.9875	.0125	.4875	.9749	2.81	.9975	.0025	.4975	.9950
2.25	.9878	.0122	.4878	.9756	2.82	.9976	.0024	.4976	.9952
2.26	.9881	.0119	.4881	.9762	2.83	.9977	.0023	.4977	.9953
2.27	.9884	.0116	.4884	.9768	2.84	.9977	.0023	.4977	.9955
2.28	.9887	.0113	.4887	.9774	2.85	.9978	.0022	.4978	.9956
2.29	.9890	.0110	.4890	.9780	2.86	.9979	.0021	.4979	.9958
2.30	.9893	.0107	.4893	.9786	2.87	.9979	.0021	.4979	.9959
2.31	.9896	.0104	.4896	.9791	2.88	.9980	.0020	.4980	.9960
2.32	.9898	.0102	.4898	.9797	2.89	.9981	.0019	.4981	.9961
2.33	.9901	.0099	.4901	.9802	2.90	.9981	.0019	.4981	.9963
2.34	.9904	.0096	.4904	.9807	2.91	.9982	.0018	.4982	.9964
2.35	.9906	.0094	.4906	.9812	2.92	.9982	.0018	.4982	.9965
2.36	.9909	.0091	.4909	.9817	2.93	.9983	.0017	.4983	.9966
2.37	.9911	.0089	.4911	.9822	2.94	.9984	.0016	.4984	.9967
2.38	.9913	.0087	.4913	.9827	2.95	.9984	.0016	.4984	.9968

(continued on next page)

Table 12.4 Comparisons of specific pairs of groups for the FEF data in Table 12.1 using the LSD t test approach

Groups compared	Test statistic	p-value
NS, PS	$t = \frac{3.78 - 3.30}{\sqrt{0.636\left(\frac{1}{200} + \frac{1}{200}\right)}} = \frac{0.48}{0.08} = 6.02^{a}$	< .001
NS, NI	$t = \frac{3.78 - 3.32}{\sqrt{0.636\left(\frac{1}{200} + \frac{1}{50}\right)}} = \frac{0.46}{0.126} = 3.65$	< .001
NS, LS	$t = \frac{3.78 - 3.23}{\sqrt{0.636\left(\frac{1}{200} + \frac{1}{200}\right)}} = \frac{0.55}{0.08} = 6.90$	< .001
NS, MS	$t = \frac{3.78 - 2.73}{0.080} = \frac{1.05}{0.08} = 13.17$	< .001
NS, HS	$t = \frac{3.78 - 2.59}{0.080} = \frac{1.19}{0.08} = 14.92$	< .001
PS, NI	$t = \frac{3.30 - 3.32}{0.126} = \frac{-0.02}{0.126} = -0.16$	NS
PS, LS	$t = \frac{3.30 - 3.23}{0.080} = \frac{0.07}{0.08} = 0.88$	NS
PS, MS	$t = \frac{3.30 - 2.73}{0.080} = \frac{0.57}{0.08} = 7.15$	< .001
PS, HS	$t = \frac{3.30 - 2.59}{0.080} = \frac{0.71}{0.08} = 8.90$	< .001
NI, LS	$t = \frac{3.32 - 3.23}{0.126} = \frac{0.09}{0.126} = 0.71$	NS
NI, MS	$t = \frac{3.32 - 2.73}{0.126} = \frac{0.59}{0.126} = 4.68$	< .001
NI, HS	$t = \frac{3.32 - 2.59}{0.126} = \frac{0.73}{0.126} = 5.79$	< .001
LS, MS	$t = \frac{3.23 - 2.73}{0.08} = \frac{0.50}{0.08} = 6.27$	< .001
LS, HS	$t = \frac{3.23 - 2.59}{0.08} = \frac{0.64}{0.08} = 8.03$	< .001
MS, HS	$t = \frac{2.73 - 2.59}{0.08} = \frac{0.14}{0.08} = 1.76$	NS

[a] All test statistics follow a t_{1044} distribution under H_0.

Example on Bonferroni Correction – Pulmonary Disease

Solution:

- Absolute value of all t statistics for two-group comparisons that were statistically significant using the LSD approach are ≥ 3.65

  (3.65 ≥ 2.935 → remain statistically significant under the Bonferroni procedure)
- Comparisons that were not statistically significant with the LSD procedure are also not significant under the Bonferroni procedure

  *must be the case because the Bonferroni procedure is more conservative than the LSD procedure.

  *critical region using the LSD procedure with a two-sided test (α = .05) is $t < -1.96$ or $t > 1.96$, whereas the comparable critical region using the Bonferroni procedure is $t < -2.935$ or $t > 2.935$
- The Bonferroni-corrected p-value for comparison of the NS vs. the PS group = 6(5) Pr[N(0,l) > 6.02]

=no. of test * 2 *Pr[N(0,l) > 6.02]

$= \frac{6*5}{2}$ * 2 *Pr[N(0,l) > 6.0

The False Discovery Rate

- Genetic studies with many hypotheses: control of the experiment-wise type I error does not seem a reasonable approach to control for multiple comparisons (very conservative inferential procedures)
- FDR: developed by Benjamini and Hochberg
  - Goal: control the proportion of false-positive results among reported statistically significant results

False-Discovery-Rate (FDR) Testing Procedure

1. k separate tests with p-values = $p_1, \ldots, p_k$
2. Renumber the tests : $p_1 \leq p_2 \leq \ldots \leq p_k$
3. Define $q_i = kp_i/i$, $i = 1,\ldots,k$
   - i = rank of the p-values among the k tests
4. Let FDRi = false-discovery rate for the ith test be defined by min $(q_i, \ldots, q_k)$
5. Find the largest i such that $FDR_i < FDR_0$ = critical level for the FDR (usually 0.05).
6. Reject H_0 for the hypotheses 1, …, i, and accept H_0 for the remaining hypotheses.

no more than 5% of the reported positive results will be false positives

<u>*less conservative*</u>

Example on FDR – Cardiovascular Disease, Genetics

- A subsample of 520 cases of cardiovascular disease (CVD) and 1100 controls was obtained among men in a prospective cohort study **nested case-control study**
- Baseline blood samples were obtained from men in the subsample and analyzed for 50 candidate single-nucleotide polymorphisms (SNPs).
- Each SNP was coded as 0 if homozygous wild type (the most common), 1 if heterozygote, and 2 if homozygous mutant. The association of each SNP with CVD was assessed using contingency-table methods.
- A chi-square test for trend was run for each SNP. This yielded 50 separate p-values. If the Bonferroni approach in Equation 12.14 were used, then $\alpha^* = .05/50 = .001$. With such a low value for α^* it is likely that very few of the hypotheses would be rejected, resulting in a great loss in power.
- Instead, an alternative approach based on the **false-discovery rate (FDR)** was used to control for the problem of multiple testing.

Figure 12.10 *p*-Values from tests of 50 SNPs

```
Stem Leaf                      #  Boxplot
   9 013                       3     |
   8 7                         1     |
   8 01                        2     |
   7                                 |
   7 0                         1     |
   6 5789                      4     |
   6 112                       3  +-----+
   5 67                        2  |     |
   5 114                       3  |     |
   4 5689                      4  |     |
   4 0144                      4  *--+--*
   3 58                        2  |     |
   3 24                        2  |     |
   2 89                        2  |     |
   2 234                       3  |     |
   1                              |     |
   1 3                         1  |     |
   0 5699                      4  +-----+
   0 012222334                 9     |
     ----+----+----+----+
 Multiply Stem.Leaf by 10**-1
```

Stem-and-leaf plot and box plot of the p-values from the tests of 50 SNPs.

Example on FDR – Cardiovascular Disease, Genetics

Question: Apply the FDR approach to the genetics data

Solution:

- Stem-and-leaf plot and box plot of the p-values from the tests of each of the 50 SNPs
- The p-values for the nominally significant genes:

Table 12.5 Ordered *p*-values for 10 most significant SNPs

	SNP	*p*-Value
1	gene30	<.0001
2	gene20	.011
3	gene48	.017
4	gene50	.017
5	gene4	.018
6	gene40	.019
7	gene7	.026
8	gene14	.034
9	gene26	.042
10	gene47	.048

- Note that 10 of the genes are statistically significant, with nominal p-values ranging from <.0001 to .048

Example on FDR –
Cardiovascular Disease, Genetics

Solution:

- The "Bonferroni p-value" = min {50 x nominal p-value, 1.0} (third column)
  → the level of significance at which the results for a specific SNP would be just statistically significant if a Bonferroni correction were made
- q_i are not necessarily in the same order as the original nominal p-values

Table 12.6 Use of the FDR approach to analyzing the CVD data qi = B p-value / rank

min (rank k ~ rank n)

	SNP	Naïve *p*-value	Bonferroni *p*-value	q_i	FDR_i
1	gene30	<.0001	.0035	.0035	.0035
2	gene20	.011	.54	.28	.16
3	gene48	.017	.86	.28	.16
4	gene50	.017	.87	.22	.16
5	gene4	.018	.92	.18	.16
6	gene40	.019	.94	.16	.16
7	gene7	.026	1.00	.18	.18
8	gene14	.034	1.00	.21	.21
9	gene26	.042	1.00	.23	.23
10	gene47	.048	1.00	.24	.24

Summary

- One-way ANOVA methods: relate a normally distributed outcome variable to the levels of a single categorical independent variable

  -Fixed-effects model: the levels of categorical variable are determined in advance

  → test the hypothesis that the mean level of the dependent variable is different for different groups defined by the categorical variable

- Methods to adjust for multiple comparisons: Bonferroni correction and false-discovery rate