

# Lecture 4

## Extensions of the Logrank Test

Statistics 255 - Survival Analysis

Presented January 21, 2016

Weighted Logrank  
Tests

K-Sample Logrank  
Tests

K-Sample (Tarone)  
Test for Trend

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Tests

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Summary

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# Weighted Logrank Tests

## Logrank and Mantel-Haenzel Test

**M-H Test** Series of (independent) tables at different levels of a confounder  $C$

- ▶ Data at level  $C = k$ :

	D	$\bar{D}$
E	$a_k$	$b_k$
$\bar{E}$	$c_k$	$d_k$

- ▶ M-H test compares  $\Pr[D|E, C = k]$  and  $\Pr[D|\bar{E}, C = k]$  and is designed (most powerful) for the case where the odds ratio,  $\psi_k$  is constant at all levels of  $C$ :

$$\psi_k = \frac{\Pr[D|E, C = k] / \Pr[\bar{D}|E, C = k]}{\Pr[D|\bar{E}, C = k] / \Pr[\bar{D}|\bar{E}, C = k]}$$

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# Weighted Logrank Tests

## Logrank and Mantel-Haenzel Test

**Logrank Test** Series of (dependent) tables at different failure times

- ▶ Data at time  $t_k$ :

	D	$\bar{D}$	Risk Size
E	$d_{0k}$	$y_{0k} - d_{0k}$	$y_{0k}$
$\bar{E}$	$d_{1k}$	$y_{1k} - d_{1k}$	$y_{1k}$
Total	$d_k$	$y_k - d_k$	$y_k$

- ▶ We expect the logrank test to be most powerful when the "odds ratio" over infinitesimal time intervals are constant across time, ie  $\psi_t = \psi$  for all  $t$  where

$$\psi_t = \frac{\Pr[t \leq T < t + \Delta t | E, T \geq t] / \{1 - \Pr[t \leq T < t + \Delta t | E, T \geq t]\}}{\Pr[t \leq T < t + \Delta t | \bar{E}, T \geq t] / \{1 - \Pr[t \leq T < t + \Delta t | \bar{E}, T \geq t]\}}$$

# Weighted Logrank Tests

## Proportional Hazards

- ▶ But, as  $\Delta t \downarrow 0$ 
  - ▶  $1 - \text{Pr}'s \uparrow 1$
  - ▶ Ratio of Pr's  $\rightarrow$  ratio of hazards, ie

$$\psi_t \approx \frac{\lambda(t|E)}{\lambda(t|\bar{E})}$$

- ▶ The logrank test will be most powerful for the case where the hazard ratio remains constant over time. This is called the **proportional hazards** case.

Weighted Logrank Tests

K-Sample Logrank Tests

K-Sample (Tarone) Test for Trend

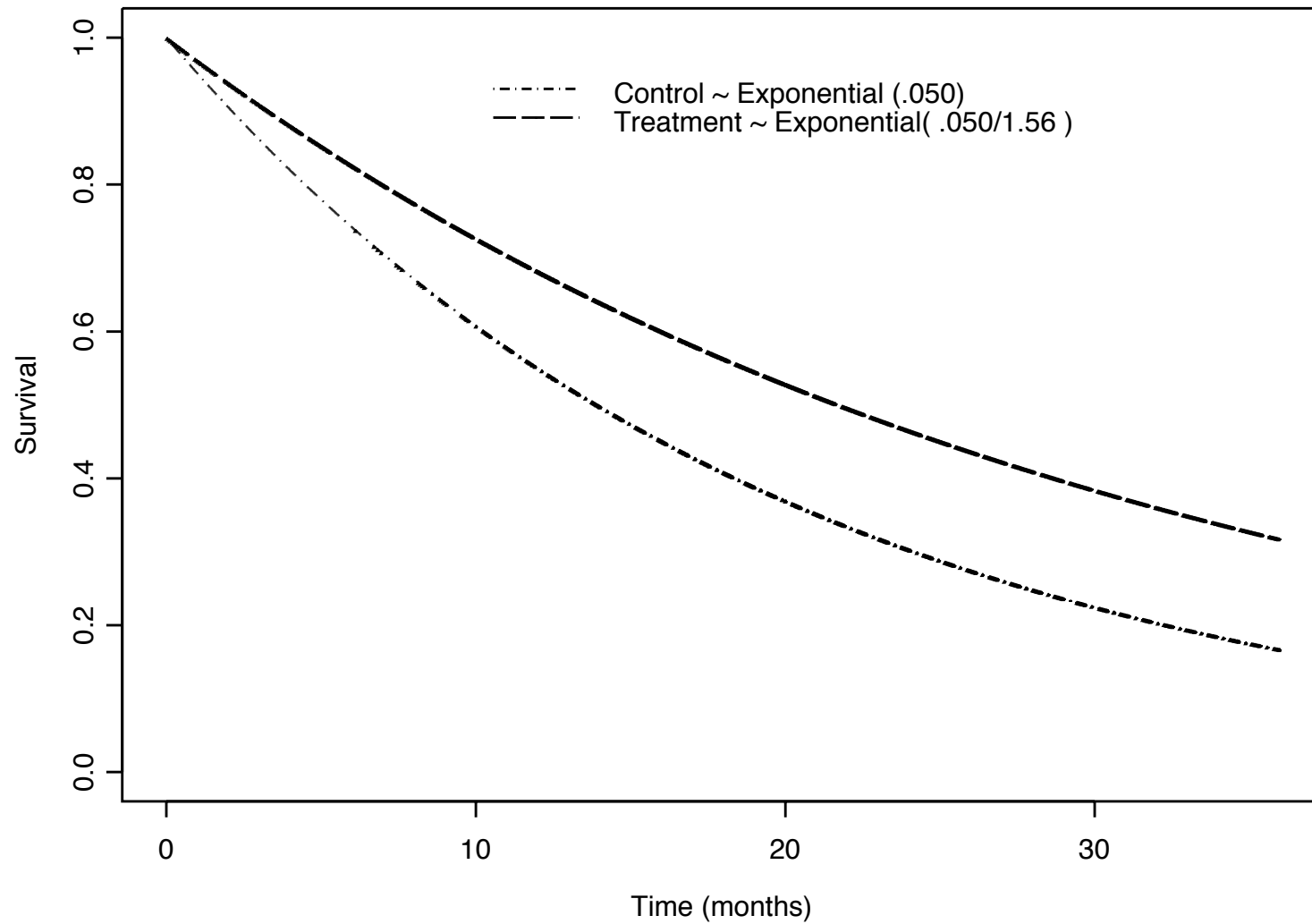
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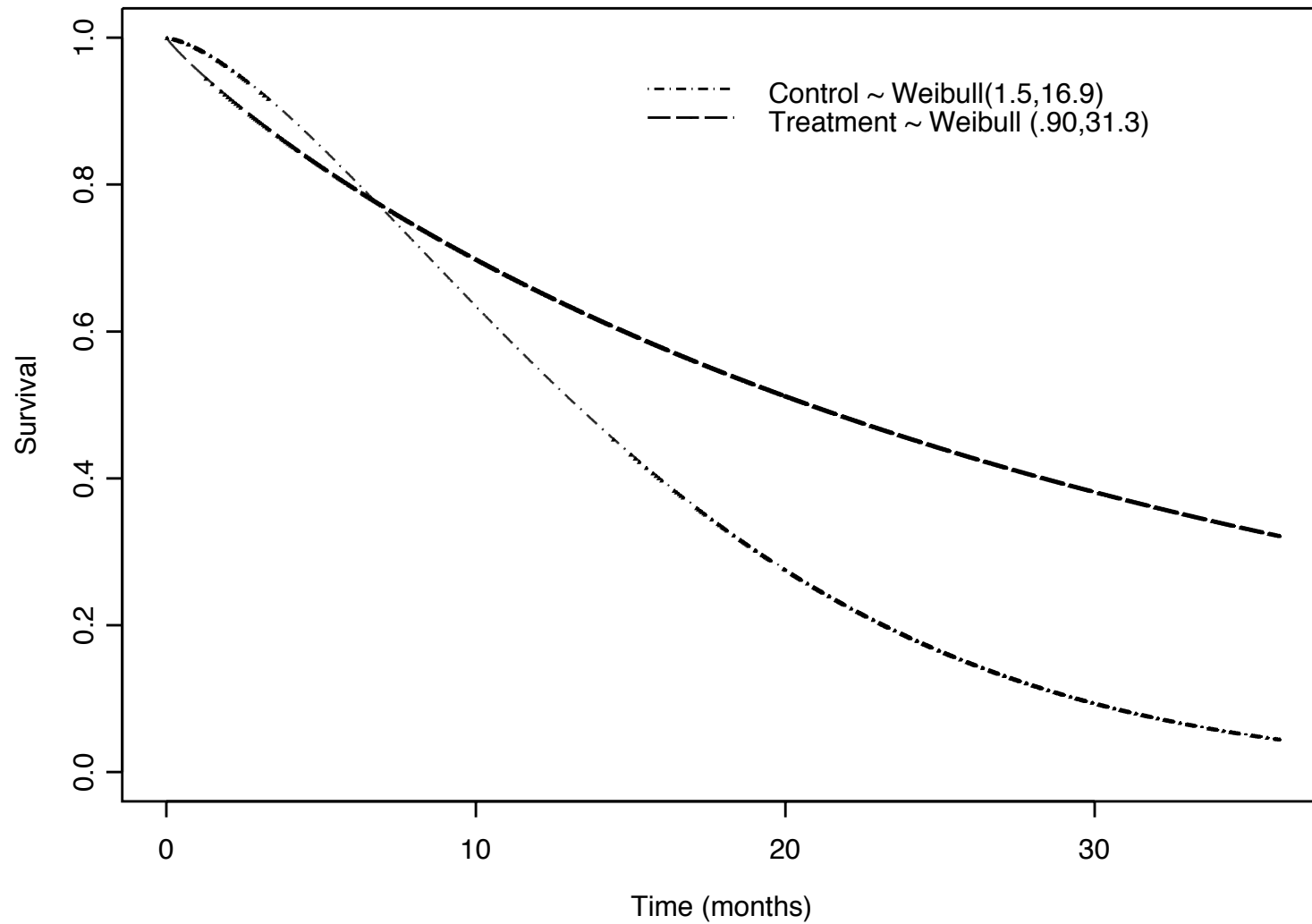
# Weighted Logrank Tests

## Ex. Proportional Hazards



# Weighted Logrank Tests

## Ex. Non-Proportional Hazards



## Weighted Logrank Statistics

- ▶ Consider weighting ( $Obs - Exp$ ) differently over time
- ▶ This will enable us to inflate early or late differences
  - Potential for increased power under non-proportional hazards

$$T_W = \frac{\left[ \sum_{k=1}^D w_k (O_k - E_k) \right]^2}{\sum_{k=1}^D w_k^2 V_k} = \frac{\left[ \sum_{k=1}^D w_k U_k \right]^2}{\sum_{k=1}^D w_k^2 V_k}$$

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## Weighted Logrank Statistics

- ▶ Choices for  $w_k$  that have been proposed:
  1.  $w_k = n_k$  gives the **Gehan-Breslow** test (weights equal to the total number of subjects at risk at each failure time). Applies greater weight to early failure times.
  2.  $w_k = \hat{S}_{KM}(t_k-)$  gives the **generalized Wilcoxon** test (weights equal to the pooled estimate of survival just prior to time  $t_k$ ). Applies greater weight to early failure times.
    - ▶ Equivalent to the Wilcoxon rank sum statistic when there is no censoring.
- ▶ The  $G^{\rho, \gamma}$  family (Fleming and Harrington; 1991)
  - ▶  $w_k = \left[ \hat{S}_{KM}(t_k-) \right]^\rho \left[ 1 - \hat{S}_{KM}(t_k-) \right]^\gamma$
  - ▶  $\rho = \gamma = 0$  gives the usual logrank statistic
  - ▶  $\rho = 1$  and  $\gamma = 0$  gives the generalized Wilcoxon test

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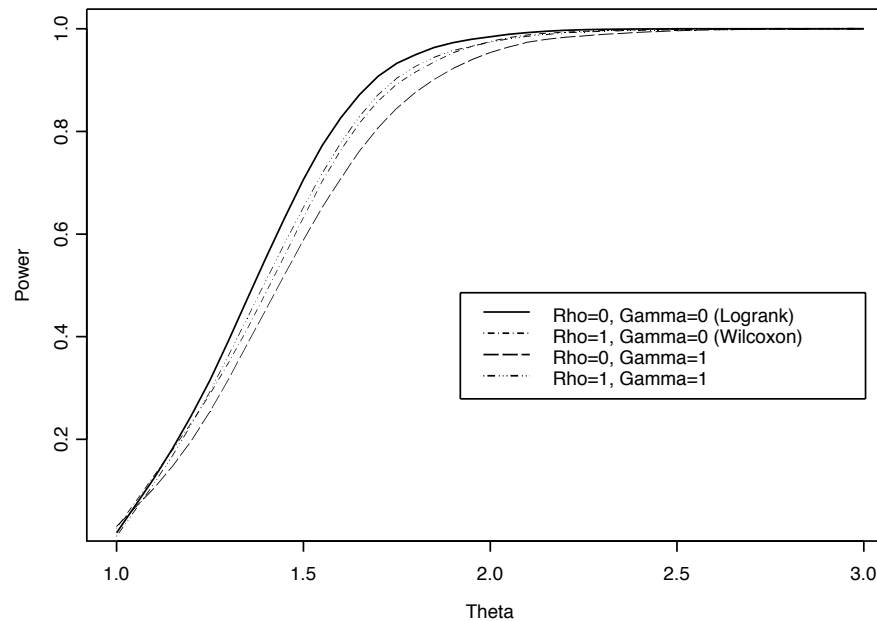
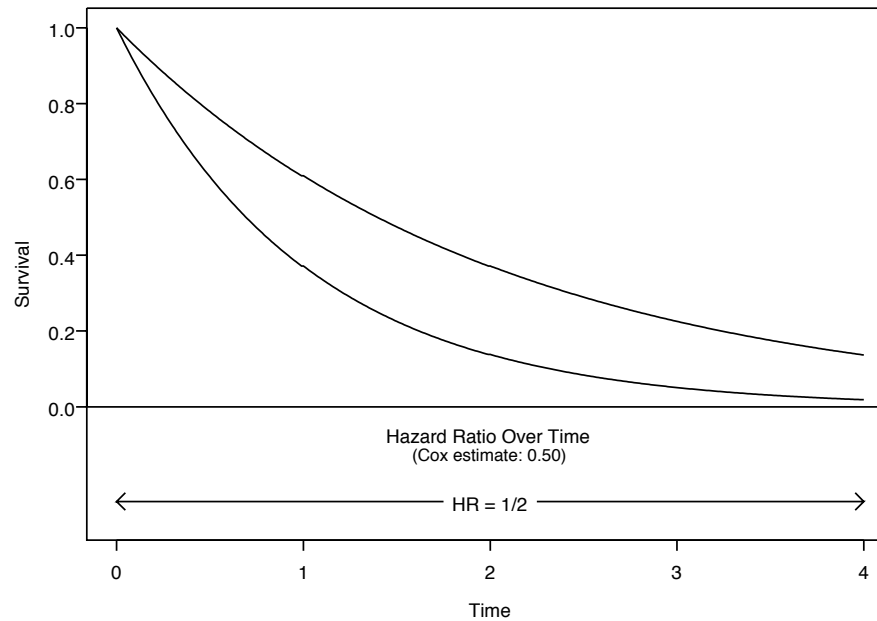
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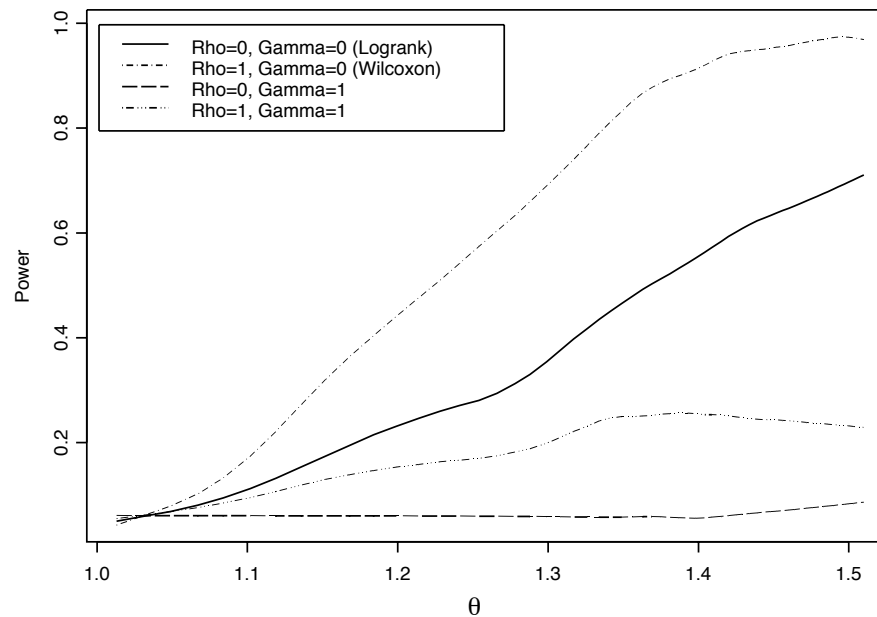
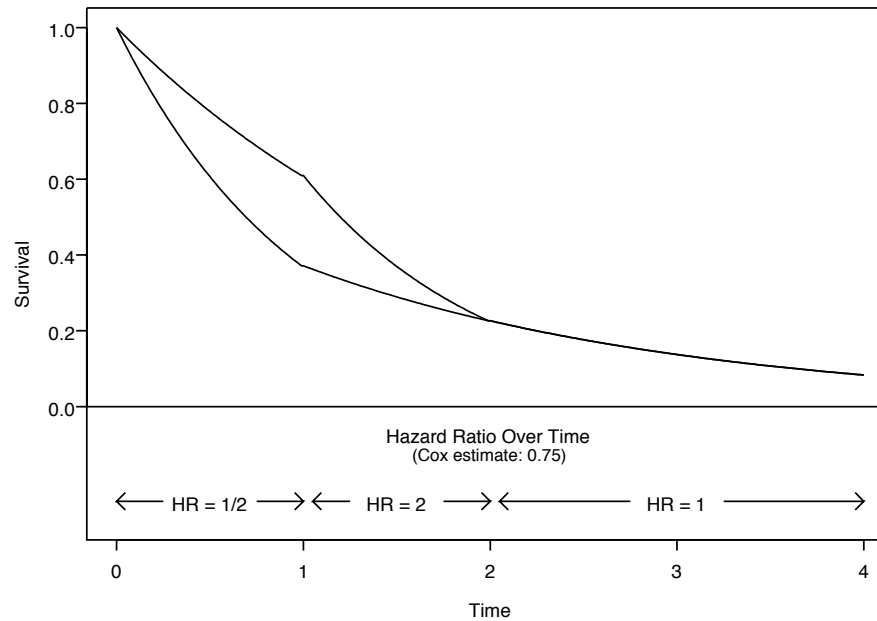
# Weighted Logrank Tests

## Power Comparisons - Proportional Hazards



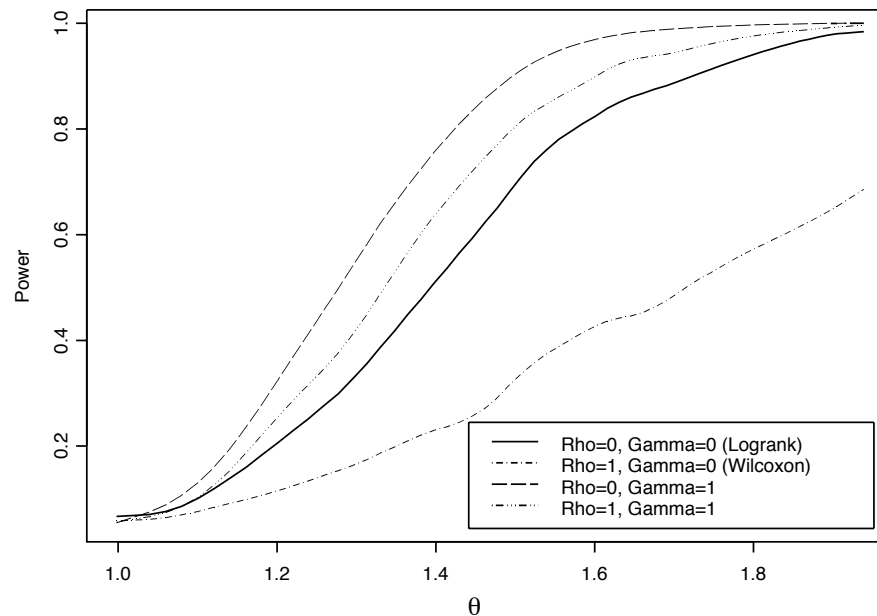
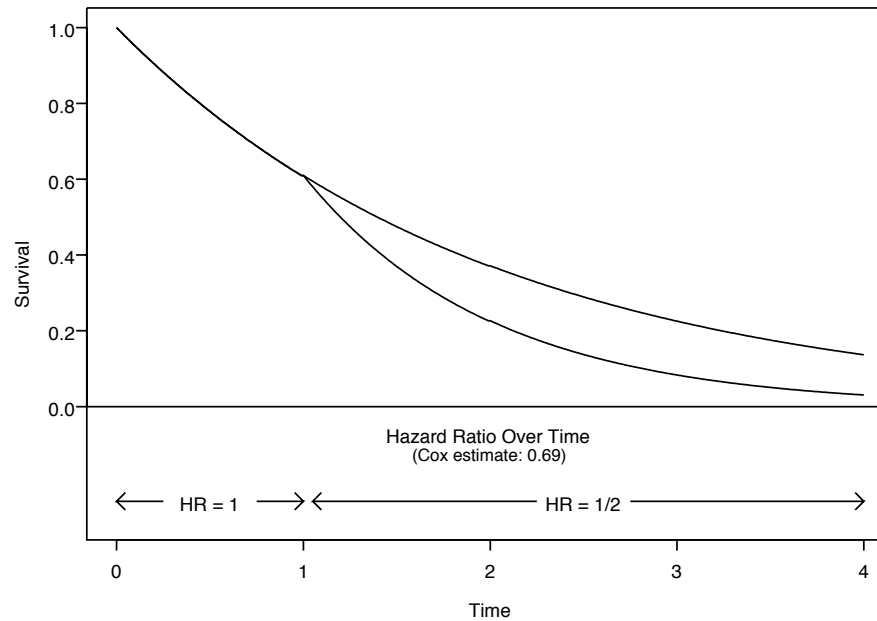
# Weighted Logrank Tests

## Power Comparisons - Early Diverging Hazards



# Weighted Logrank Tests

## Power Comparisons - Late Diverging Hazards



# Weighted Logrank Tests

## Implementation in R - 6MP Example

- ▶ Know that the (unweighted) logrank statistic will be most powerful under proportional hazards
- ▶ How can we (informally) check the proportional hazards assumption?

- ▶ If we have proportional hazards, then

$$\lambda_1(t) = \phi\lambda_0(t)$$

so that

$$\log \Lambda_1(t) = \log(\phi) + \log \Lambda_0(t)$$

- ▶ So, if the log cumulative hazards are roughly parallel, the logrank test will tend to be most powerful

Weighted Logrank Tests

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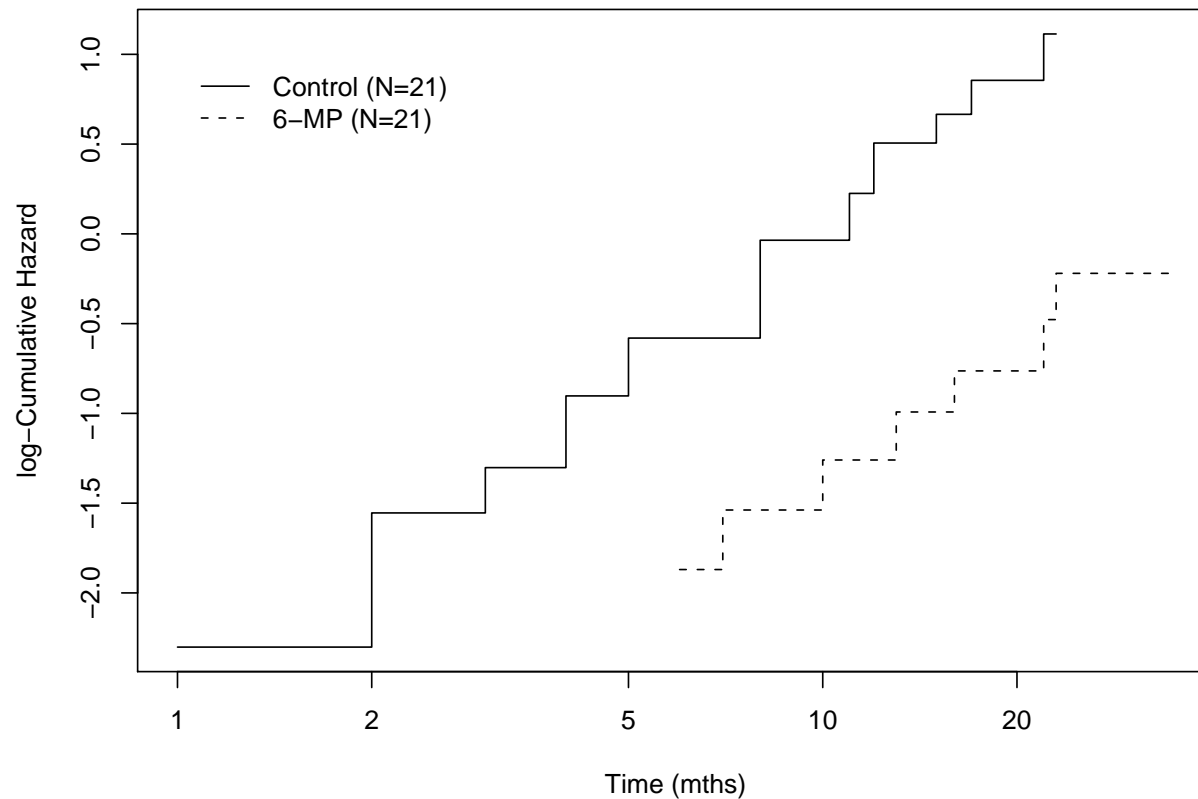
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# Weighted Logrank Tests

## 6MP log-Cumulative Hazards Plot

```
plot( survfit( Surv( time, irelapse ) ~ sixmp, data=sixmpLong ),  
      fun="cloglog", lty=1:2, mark.time=FALSE,  
      xlab="Time (mths)", ylab="log-Cumulative Hazard" )  
legend( 1,1, lty=1:2, legend=c("Control (N=21)", "6-MP (N=21)"),  
       bty="n" )
```



### Weighted Logrank Tests

K-Sample Logrank Tests

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# Weighted Logrank Tests

## Implementation in R - 6MP Example

- ▶ Not too bad...We do not expect the generalized Wilcoxon test to be as powerful as the logrank test in this situation
- ▶ To compute the generalized Wilcoxon, specify the option `rho=1` in the `survdiff()` function
  - ▶ Note: The  $G^{\rho,\gamma}$  statistic is not currently implemented in the `survival` package

```
> #####          Usual (unweight LR test)
> survdiff( Surv( time, irelapse ) ~ sixmp, rho=0, data=sixmpLong )
          N Observed Expected (O-E)^2/E (O-E)^2/V
sixmp=0 21         21      10.7      9.77      16.8
sixmp=1 21          9      19.3      5.46      16.8
```

Chisq= 16.8 on 1 degrees of freedom, p= 4.17e-05

```
> #####          Generalized Wilcoxon test
> survdiff( Surv( time, irelapse ) ~ sixmp, rho=1, data=sixmpLong )
          N Observed Expected (O-E)^2/E (O-E)^2/V
sixmp=0 21      14.55      7.68      6.16      14.5
sixmp=1 21       5.12     12.00      3.94      14.5
```

Chisq= 14.5 on 1 degrees of freedom, p= 0.000143

# Weighted Logrank Tests

## How should weights be chosen?

- ▶ For scientific inference it is not reasonable to look at the survival curves first, then choose weights
- ▶ First, ask whether there is a reason to believe we will have non-proportional hazards
  - ▶ If not, go with the logrank test
  - ▶ If so, consider what survival differences are most meaningful (early vs late)
    - Childhood cancer (late differences)
    - Late stage lung cancer remission (early differences)

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# K-Sample Logrank Tests

## K-Sample Logrank Tests

- ▶ Suppose we have  $K > 2$  groups and we wish to simultaneously compare them with respect to survival time distributions (or equivalently, hazards)

$$H_0 : \quad \lambda_1(t) = \lambda_2(t) = \dots \lambda_K(t), \text{ for all } t > 0$$

(i.e. the survival curves for the all groups are equal everywhere)

- ▶ We are particularly concerned with the alternatives

$$H_A : \quad \lambda_k(t) > \lambda_{k'}(t), \text{ for some } t > 0$$

or

$$\lambda_k(t) < \lambda_{k'}(t), \text{ for some } t > 0$$

for at least some  $k \neq k'$



# K-Sample Logrank Tests

## K-Sample Logrank Tests

- ▶ Test statistic is a generalization of the two sample statistic that depends on the covariance between the  $(O - E)$ 's between each group
- ▶ Consider the data at the  $i^{th}$  observed event time  $t_i$  in the pooled sample:

1	2	...	$k$	...	$K$	Total
$d_{1i}$	$d_{2i}$	...	$d_{ki}$	...	$d_{Ki}$	$d_i$
$y_{1i} - d_{1i}$	$y_{2i} - d_{2i}$	...	$y_{ki} - d_{ki}$	...	$y_{Ki} - d_{Ki}$	$y_i - d_i$

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# K-Sample Logrank Tests

## Ex: Survival in patients with cancer of the larynx (Sect 1.8 in K&M)

- ▶ Time origin: diagnosis with cancer
- ▶ Failure event: death
- ▶ Question of interest: How does survival time from diagnosis to death vary by *stage of disease* at presentation?

```
> larynx[1:10,]
  stage t2death age year death
1     1    0.6  77  76     1
2     1    1.3  53  71     1
3     1    2.4  45  71     1
4     1    2.5  57  78     0
5     1    3.2  58  74     1
6     1    3.2  51  77     0
7     1    3.3  76  74     1
8     1    3.3  63  77     0
9     1    3.5  43  71     1
10    1    3.5  60  73     1
```

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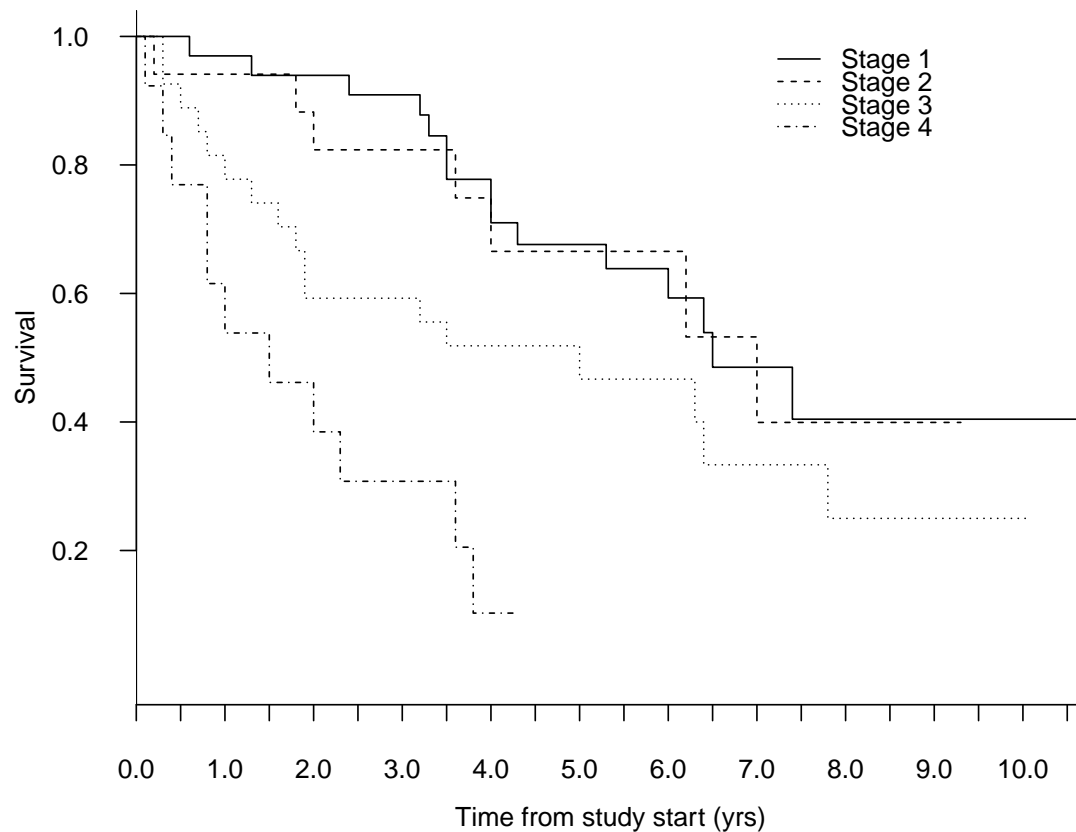
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# K-Sample Logrank Tests

Ex: Survival in patients with cancer of the larynx (Sect 1.8 in K&M)



Stage 1	33 (0)	23 (7)	6 (14)	1 (15)
Stage 2	17 (0)	11 (3)	3 (7)	0 (7)
Stage 3	27 (0)	14 (13)	4 (16)	0 (17)
Stage 4	13 (0)	3 (9)	0 (11)	0 (11)
Total	90 (0)	51 (32)	13 (48)	1 (50)

# K-Sample Logrank Tests

## Ex: Survival in patients with cancer of the larynx (Sect 1.8 in K&M)

- ▶ `survfit()` can be used to test differences in  $K$ -samples as before

```
> survdiff( Surv(t2death,death) ~ stage, data=larynx )  
Call:  
survdiff(formula = Surv(t2death, death) ~ stage, data = larynx)
```

	N	Observed	Expected	(O-E)^2/E	(O-E)^2/V
stage=1	33	15	22.57	2.537	4.741
stage=2	17	7	10.01	0.906	1.152
stage=3	27	17	14.08	0.603	0.856
stage=4	13	11	3.34	17.590	19.827

```
Chisq= 22.8 on 3 degrees of freedom, p= 4.53e-05
```

**Conclusion:** The hypothesis that all four survival curves are equal is clearly rejected. We conclude that at least one group is different with respect to survival

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# K-Sample Logrank Tests

## Ex: Survival in patients with cancer of the larynx (Sect 1.8 in K&M)

- ▶ Additional Notes:
- ▶ The  $G^\rho$  family of weighted logrank statistics can be extended to  $K$ -samples by specifying the `rho` value in `survfit()`
- ▶ These tests say nothing about *how* the groups differ; which one is worst, best, etc. (though the sum of ranks gives a clue). That can be further explored with a trend test or regression modeling...
- ▶ For now, we could also think about testing for *trend* since stage is *ordinal*

# K-Sample (Tarone) Test for Trend

## Larynx Cancer Example

- ▶ Recall that there were 4 stages of disease recorded at baseline (the origin)
- ▶ The 4 stage of disease groups can be ordered in a meaningful way
- ▶ Suppose we wish to examine the hypothesis that the survival experience by stage of disease is **either** *progressively worse* **or** *progressively better* by stage of disease
- ▶ That is, we wish to take advantage of the *ordinal* nature of the stage of disease variable `stagedx`

# K-Sample (Tarone) Test for Trend

## Larynx Cancer Example

- ▶ Formally, for  $K$  ordered groups with dose vector  $s_1, \dots, s_K$  (could be  $s_1 = 1, \dots, s_K = K$ ), we want to test the hypothesis

$$H_0 : \lambda_1(t) = \lambda_2(t) = \dots = \lambda_K(t), \text{ for all } t > 0$$

(\*Note: Same  $H_0$  as the general  $K$ -sample problem!)

vs.

$$H_A : \phi^{s_1} \lambda_1(t) = \phi^{s_2} \lambda_2(t) = \dots = \phi^{s_K} \lambda_K(t), \\ \text{for } \phi \neq 1 \text{ and for all } t > 0$$

- ▶ What is the general form of this alternative in terms of survival curves?

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# K-Sample (Tarone) Test for Trend

## Formulation of the test

- ▶ Recall the log-rank test is:

$$X^2 = \frac{U^2}{V} \sim \chi_1^2$$

where

$$U \equiv U_1 \equiv \sum_j (\text{obs}_{(j)1} - \text{exp}_{(j)1}) = \sum_j U_{(j)1}$$

is the “observed” – “expected” discrepancy for group 1,  
and

$$V \equiv V_1 \equiv \text{Var}[U_1] = \sum_j V_{(j)1}$$

is the variance of  $U_1$  under  $H_0$



# K-Sample (Tarone) Test for Trend

## Formulation of the test

- ▶ Suppose group 1 (e.g. treatment) being compared to group 0 (e.g. placebo). Could similarly define

$$U_0 = \sum_j (\text{obs}_{(j)0} - \text{exp}_{(j)0}) = \sum_j U_{(j)0}$$

and write

$$U = 1 \times U_1 + 0 \times U_0 = U_1$$

assigning “scores” 1 and 0 to the two groups

# K-Sample (Tarone) Test for Trend

## Formulation of the test

- ▶ For  $K$ -samples, assign scores  $s_1, s_2, \dots, s_K$  and compute

$$U_T = s_1 \times U_1 + s_2 \times U_2 + \dots + s_K \times U_K = \sum_{k=1}^K s_k (O_k - E_k)$$

- ▶ Then  $U_T$  will be *large* (positive or negative) if the  $U_k$ s increase (or decrease) with  $s_k$
- ▶  $V_T$  is computed using the variance-covariance matrix of  $(U_1, U_2, \dots, U_K)$ :

$$V_T = \sum_{k=1}^K s_k^2 V_{kk} + 2 \sum_{k < k'} s_k s_{k'} V_{kk'}$$

# K-Sample (Tarone) Test for Trend

## Formulation of the test

- ▶ So our test statistic is

$$X_T^2 = \frac{U_T^2}{V_T} \sim \chi_1^2$$

- ▶ Why 1-degree of freedom?

→ Test is really a regression of  $\log \lambda_k(t)$  on  $s_k$

# K-Sample (Tarone) Test for Trend

## Larynx Cancer Example

- ▶ There is no dedicated function for the trend test in R, but I have written the function `survtrend()` and posted it on the course webpage for this purpose

```
> survtrend( Surv(t2death,death) ~ stage, data=larynx )
      N Observed Expected
stage=1 33      15  22.5660
stage=2 17       7  10.0117
stage=3 27      17  14.0845
stage=4 13      11   3.3377
```

```
Logrank Test : Chi(3) = 22.763, p-value = 4.5252e-05
```

```
Tarone Test Trend : Chi(1) = 13.815, p-value = 0.00020169
```

Conclusion: Reject the hypothesis that all four survival curves are equal and conclude that stage is positively associated with the hazard for death

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# K-Sample (Tarone) Test for Trend

## Comments

- ▶ The trend test depends on the order of the covariate being tested while the general  $K$ -sample test does not
- ▶ Why use a trend test (on 1 df) vs. a general  $K$ -sample test (on  $K - 1$  df)?
  - ▶ If effects are monotonically ordered it will be more *sensitive*
    - ▶ The general  $K$ -sample test has less power because it does not take advantage of the ordinal nature of the data
  - ▶ It seeks to detect a more *specific* alternative
    - ▶ If survival curves differ, but differences are not ordered, trend test less likely to reject
- ▶ The trend test is essentially a regression of the hazard on the covariate of interest

# Stratified Logrank Tests

## Confounding

- ▶ One definition: A **confounder** is a variable that is associated with the predictor of interest ( $X$ ) *and* causally related to the outcome of interest ( $Y$ ).

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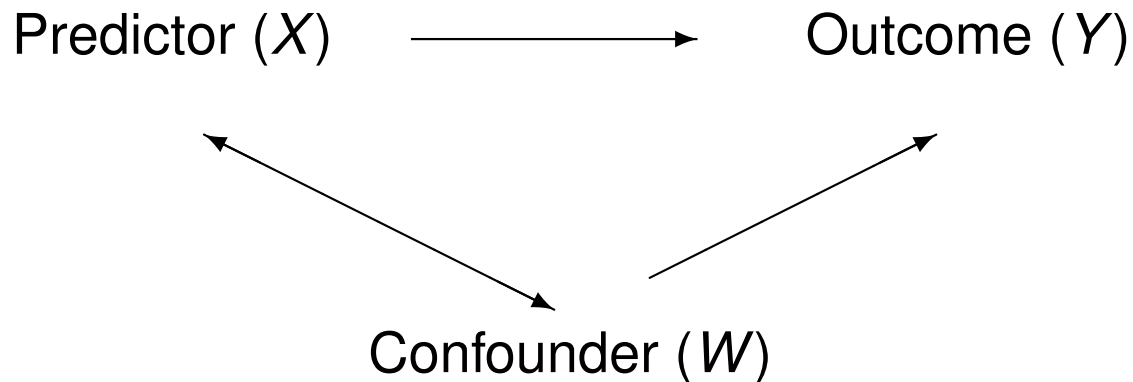
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# Stratified Logrank Tests

## Confounding

- ▶ Example: Weight may be a confounder in the relationship between diabetes and blood pressure:
  - ▶ Diabetics tend to be heavier than non-diabetics
  - ▶ Increased weight is associated with higher blood pressure
- ▶ Note: When considering potential confounders, need to carefully consider whether or not the potential confounder lies in the *causal pathway* of the association of interest



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# Stratified Logrank Tests

## Confounding

- ▶ How do we deal with confounding? Adjust for the confounder
- ▶ Adjustment involves the assumption that the effect of interest is *similar across all strata* of the potential confounder
- ▶ What if we want to test for differences in risk (ie survival data) after adjustment for a potential confounding factor?
  - One solution is to **stratify** the sample

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# Stratified Logrank Tests

## Set-up and Notation

- ▶ Suppose the variable we wish to stratify on has  $J$  levels
- ▶ Consider testing the hypothesis

$$H_0 : \quad \lambda_{j1}(t) = \lambda_{j0}(t), \text{ for } j = 1, \dots, J \text{ and } t > 0$$

$$H_A : \quad \lambda_{j1}(t) = \phi \lambda_{j0}(t), \text{ for } j = 1, \dots, J \text{ and } t > 0, \phi \neq 1$$

- ▶ Notes:

1.  $\lambda_{j1}(t)$  can differ from  $\lambda_{j'1}(t)$  for two strata  $j$  and  $j'$ , as can  $\lambda_{j0}(t)$  and  $\lambda_{j'0}(t)$
2. Testing whether, on average across *strata*  $j = 1, \dots, J$  and across *time*  $t$ , the *within-stratum hazard*  $\lambda_{j1}(t)$  greater (or less) than  $\lambda_{j0}(t)$ ?
3. Testing for *similar (proportional hazards) effects* across time and strata

# Stratified Logrank Tests

## Set-up and Notation

- ▶ Suppose that, *for the  $j$ th stratum*

$n_{i(j)}$  = the number at risk at time  $t_{i(j)}$

$d_{i(j)}$  = the number failing at time  $t_{i(j)}$

- ▶ Define

$n_{i(j)1}$  = the number at risk *in group 1*  
and stratum  $j$  at time  $t_{i(j)}$

$d_{i(j)1}$  = the number failing *in group 1*  
and stratum  $j$  at time  $t_{i(j)}$

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# Stratified Logrank Tests

## Set-up and Notation

- ▶ Recall: the **log-rank test** for the  $j$ th stratum only would compare “observed” to “expected”:

$$\begin{aligned} U_j &= \sum_i (\text{obs}_{i(j)} - \text{exp}_{i(j)}) = \sum_i U_{i(j)} \\ &= \sum_i \left\{ d_{i(j)1} - n_{i(j)1} \left( \frac{d_{i(j)}}{n_{i(j)}} \right) \right\} \end{aligned}$$

using the variance

$$V_j = \text{Var}[U_j] = \sum_i v_{i(j)}$$

- ▶ If  $U_j$  is large (positive or negative), then the test will reject within the  $j$ th stratum

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# Stratified Logrank Tests

## Set-up and Notation

- ▶ The **stratified log-rank test** sums (averages) over strata just as the log-rank test sums (averages) over times:

$$U_S = \sum_j U_j = \sum_j \sum_i U_{i(j)}$$

and

$$V_S = \text{Var}[U_S] = \sum_j V_j = \sum_j \sum_i v_{i(j)}$$

- ▶ Under  $H_0$

$$X_S^2 = \frac{U_S^2}{V_S} \sim \chi_1^2$$

- ▶ The **stratified log-rank test** statistic  $U_S$  is a weighted average of the within-stratum log-rank test statistics  $U_i$

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# Stratified Logrank Tests

## Back to the larynx cancer example...

- ▶ Let's consider adjustment for age as a potential confounding factor in the relationship between stage of disease and time to death
- ▶ Specifically, consider age discretized into 3 groups

```
> ##
> ##### Consider potential confounding by age
> ##
> summary(larynx$age)
  Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
  41.0   57.0   65.0   64.6   72.0   86.0
> round( quantile( larynx$age, c(0, .33, .66, 1) ) )
  0%  33%  66% 100%
  41   60   70   86
> larynx$agegrp <- cut( larynx$age, c(41, 60, 70, 86),
                        include.lowest=TRUE )
> summary( larynx$agegrp )
 [41,60] (60,70] (70,86]
      30      32      28
```

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# Stratified Logrank Tests

## Back to the larynx cancer example...

- ▶ Let's consider first whether or not age is likely to meet the definition of a confounder...

```
> ##  
> ##### Does age meet the definition of a confounder? (not really...)  
> ##  
> chisq.test( table( larynx$stage, larynx$agegrp ) )
```

Pearson's Chi-squared test

```
data: table(larynx$stage, larynx$agegrp)  
X-squared = 4.7134, df = 6, p-value = 0.5811
```

```
> survdiff( Surv(t2death, death) ~ agegrp, data=larynx )  
Call:  
survdiff(formula = Surv(t2death, death) ~ agegrp, data = larynx)
```

	N	Observed	Expected	(O-E) <sup>2</sup> /E	(O-E) <sup>2</sup> /V
agegrp=[41,60]	30	14	15.9	0.221	0.330
agegrp=(60,70]	32	16	20.8	1.103	1.938
agegrp=(70,86]	28	20	13.3	3.325	4.615

Chisq= 4.7 on 2 degrees of freedom, p= 0.0937

Weighted Logrank Tests

K-Sample Logrank Tests

K-Sample (Tarone) Test for Trend

Stratified Logrank Tests

Matched Tests

Summary

# Stratified Logrank Tests

## Back to the larynx cancer example...

- ▶ From the above, age is not significantly associated with stage or with time to death (in the dataset)
- ▶ The implication of this is that adjustment for age is unlikely to have any impact on the conclusions of our analysis (we will lose some efficiency though...)
  - ▶ In a real setting, when testing a well-defined hypothesis we should decide upon adjustment for age before assessing the data in order to avoid data-driven inflation of the type 1 error rate!

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## Back to the larynx cancer example...

- ▶ Let's stratify by age here as an example... To do this, use the `strata()` function in the formula statement of `survdiff()`

```
> ##  
> ##### LR test of association between stage and t2death,  
> ##### stratified by agegrp  
> ##  
> survdiff(Surv(t2death,death) ~ stage + strata(agegrp), data=larynx)  
Call:  
survdiff(formula = Surv(t2death, death) ~ stage + strata(agegrp),  
          data = larynx)
```

	N	Observed	Expected	(O-E)^2/E	(O-E)^2/V
stage=1	33	15	23.60	3.134	6.430
stage=2	17	7	9.38	0.602	0.763
stage=3	27	17	13.23	1.074	1.547
stage=4	13	11	3.79	13.686	16.182

Chisq= 20.1 on 3 degrees of freedom, p= 0.00016

Weighted Logrank  
Tests

K-Sample Logrank  
Tests

K-Sample (Tarone)  
Test for Trend

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Summary



# Stratified Logrank Tests

## Conclusions

- ▶ Stage of disease at diagnosis is positively related to the risk of death
- ▶ This relationship still holds after adjusting for the effect of age
- ▶ The association is not due to any (positive or negative) association of age with stage of disease and / or age with risk of death
- ▶ The association is not due to any **confounding** effect of age

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## Matching

- ▶ When explicit control for confounders will be difficult, comparative studies are sometime performed on samples of *matched pairs*:
  - ▶ one member of pair is exposed or treated and the other is not (or gets placebo)
  - ▶ matching on: age  $\times$  sex, neighborhood, clinic, etc.
  - ▶ twins
  - ▶ matched pairs like many strata of size 2

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## Matching

- ▶ To account for matching in the sampling scheme, we can:
  1. stratify on the matching set,
  2. compare outcomes within that strata, then
  3. combine the results across (independent) strata
- ▶ As an example, consider the 6-MP data where subjects were actually matched by remission status and hospital
  - ▶ One member randomized to 6-MP (vs. placebo) maintenance therapy

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Summary

# Matched Tests

## Ex: 6-MP data

- ▶ A proper analysis should account for the correlation induced by matching...

```
> ##
> #####          Matched analysis of the 6-MP data
> ##
> sixmp <- read.table( "http://www.ics.uci.edu/~dgillen/
                        STAT255/Data/sixmp.txt" )

> sixmp[1:5,]
  pairid tpbo t6mp irelapse
1      1     1   10         1
2      2    22    7         1
3      3     3   32         0
4      4    12   23         1
5      5     8   22         1

> ##
> #####          Transform data to long format
> ##
> sixmpLong <- cbind( rep(sixmp$pairid, 2), c(sixmp$tpbo, sixmp$t6mp),
+                    rep(0:1, each=21), c( rep(1,21), sixmp$irelapse ) )
> sixmpLong <- as.data.frame( sixmpLong )
> names( sixmpLong ) <- c( "pairid", "time", "sixmp", "irelapse" )
```

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# Matched Tests

## Ex: 6-MP data

```
> ##
> #####          Matched analysis stratifying by pairid
> ##
> survdiff(Surv(time, irelapse)~sixmp+strata(pairid), data=sixmpLong)
Call:
survdiff(formula = Surv(time, irelapse) ~ sixmp + strata(pairid),
          data = sixmpLong)

              N Observed Expected (O-E)^2/E (O-E)^2/V
sixmp=0  21      21      13.5      4.17      10.7
sixmp=1  21       9      16.5      3.41      10.7

Chisq= 10.7  on 1 degrees of freedom, p= 0.00106
```

Conclusion: After accounting for correlation induced by matching on remission status and hospital, we conclude that there is a difference in time-to-relapse between the 6-MP arm and the control arm using a level .05 test

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# Stratified Analyses

## Summary

1. Analyses by separate strata, stratified tests and adjustment are statistical activities, but . . .
  - ▶ . . . the identification of confounders and the decision to adjust for them are extra-statistical considerations
  - ▶ . . . they involve (1) the scientific question of interest and (2) possible chains of causality
2. If the *study design* is stratified or matched, always adjust
3. Stratified tests will have good power for alternatives that are in the same direction in each stratum
4. When effects are different by stratum (*interaction or effect modification*), analyses are better performed and reported separately on each stratum

# Stratified Analyses

## Summary

5. Weighted,  $K$ -sample and  $K$ -sample trend test versions of the stratified log-rank test exist
6. Strata can be quite small for adjustment (but not for within-stratum analyses)
7. When data are in the form of matched pairs (or small sets), think of them as many small strata
8. Stratified log-rank test on matched pairs is the censored data analogue of the the signed-rank test for paired data

Weighted Logrank Tests

$K$ -Sample Logrank Tests

$K$ -Sample (Tarone) Test for Trend

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Summary

# Stratified Analyses

## Analogous Methods For Binomial Data

	Proportions	Survival Data
1. Description	$\hat{p}, \hat{RR}$ $\hat{OR}$	$\hat{S}, \hat{\Lambda},$ $\hat{\lambda}, \hat{RR}$
2. Two-sample test	Z test/ $\chi^2$ test	Logrank test
3. Stratified two-sample test	Mantel-Haenzel test	Stratified logrank test
4. <i>K</i> -sample heterogeneity test	<i>K</i> -sample heterogeneity test	<i>K</i> -sample logrank test
5. <i>K</i> -sample trend test	Cochran-Armitage trend test	Tarone trend test
6. Regression models	Logistic regression	Cox regression

Weighted Logrank Tests

*K*-Sample Logrank Tests

*K*-Sample (Tarone) Test for Trend

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Summary