2024 Summer Institute In Statistics for Clinical & Epidemiological Research

Module 3:

Design, Conduct, and Analysis of Randomized Clinical Trials with Time to Event Primary Endpoints

Lecture 16:

Covariate Adjustment

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Topics

- **Why control for baseline variables in RCT analyses?**
  - Precision vs confounding vs subgroup vs effect modification
- **How to control for baseline variables in RCT design?**
  - Restrict eligibility vs stratified or covariate adaptive randomization
- **How to report distribution of baseline variables in CTR?**
  - Materials / methods vs "conditional confounding"
- **How to model baseline variables in prespecified analyses?**
  - Special case: Change in response vs ANCOVA
  - Stratified vs dummy variables vs linear vs splines
  - Sensitivity of results to *post hoc* adjustment

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Take Home Message 1

- **Why control for baseline variables in RCT analyses?**
  - Precision of inference is the primary issue
    - But mechanism of added precision varies by type of regression
  - Estimation of "within stratum" effect a minor issue with some estimands (odds, hazards)
  - Confounding is in some sense avoided by randomization
    - However, some critics will second guess results in a *post hoc* manner

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Take Home Message 2

- **How to control for baseline variables in RCT design?**
  - Obtain precision by prespecified adjustment for the most important prognostic factors known *a priori*
    - Do not allow data driven selection of adjusted models
  - Restrict eligibility to subset of eventual target population
    - Only if certain no effect modification on efficacy or safety
  - Stratified randomization especially if
    - Want face validity of key prognostic factors in Table 1
    - Interested in prespecified analyses within subgroups
  - Covariate adaptive randomization (minimization) can be avoided
    - Exception if need to attain face validity on many sparse factors

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Take Home Message 3

- **How to report distribution of baseline variables in CTR?**
  - Using Table 1 to describe materials / methods
    - Range, quantiles, means, SD
  - Using Table 1 to <u>second guess</u> comparability of randomized groups
    - Means: arithmetic, geometric, or proportions as appropriate
    - ("Conditional confounding" is a function of means, not medians)

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Take Home Message 4

- **How to model baseline variables in prespecified analyses?**
  - Special case: Change in response (e.g., rates) over course of trial
    - Adjust for baseline measurement in ANCOVA
      - Ideal for balanced group sizes
      - Possible improvements in presence of unequal group sizes
  - Model mis-specification is not generally an important issue
    - I typically model baseline prognostic variables linear continuous
  - Sensitivity of results to *post hoc* adjustment
    - This is invariably "second guessing" pre-specified hypotheses
    - "Randomization imbalance" may decrease our confidence in results, but there are not good statistical foundations for such analyses

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Why Control for Baseline Variables in RCT Analyses?

Regression Analyses

Where am I going?

- It is useful to first consider the operating characteristics of the analyses we will ultimately perform on the RCT data
  - What is the role of confounders, precision variables, and effect modifiers on our inference
- We can be most rigorous with linear regression
  - We can then draw parallels to logistic and proportional hazards regression models

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Regression Models

- According to the parameter compared across groups
  - Means → Linear regression
  - Geom Means → Linear regression on logs
  - Odds → Logistic regression
  - Rates → Poisson regression
  - Hazards → Proportional Hazards regr
  - Quantiles → Parametric (AFT) survival regr

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Regression Models For Time to Event

- Which regression models most relevant for this course?
  - Most often: proportional hazards regression
  - Sometimes: Poisson regression, logistic regression
  - Rarely: linear regression
- The behavior of covariate adjustment in linear regression tends to be the basis for a lot of beliefs about adjusting for baseline variables in RCT
  - PH regression and logistic regression are different from linear regression, and somewhat different from each other
- I will review the properties of each regression model and contrast these differences

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Statistical Analysis Models in RCT

- Consider the distribution of response across groups defined by some "predictor of interest" (POI)
- We choose some summary measure of our response distribution
- We use regression to model our question
  - Simple regression with a binary POI often the standard test
- We estimate a "contrast"
  - Usually difference or ratio across treatment groups
- We operate as distribution-free as possible
  - Frequently: Methods originally derived under strong parametric models are found to be robust in a distribution-free sense

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General Regression Notation

- General notation for variables and parameter

Y_i	Response measured on the ith subject
X_i	Value of the POI for the ith subject
$W_{1i}, W_{2i}, \ldots$	Value of adjustment variables for the ith subject
θ_i	Parameter of distribution of Y_i

- The parameter might be the mean, geometric mean, odds, rate, instantaneous risk of an event (hazard), etc.

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Multiple Regression

- General notation for multiple regression model

$$g(\theta_i) = \beta_0 + \beta_1 \times X_i + \beta_2 \times W_{1i} + \beta_3 \times W_{2i} + \cdots$$

$g(\ )$	"link" function used for modeling
β_0	"Intercept"
β_1	"Slope for Pred of Interest X"
β_j	"Slope for covariate W_{j-1}"

- The link function is usually either
  - none (difference of means), or
  - log (ratio of means, geom means, odds, hazards, quantiles)

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Comparison of Models

- The major difference between regression models is interpretation of the parameters
  - Summary: Mean, geometric mean, odds, hazards
  - Comparison of groups: Difference, ratio
- Issues related to inclusion of covariates remain the same
  - Address the scientific question
    - Predictor of interest (sometimes modeled with multiple variables)
    - Effect modifiers
  - Address confounding
  - Increase precision

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Adjustment for Covariates

- We "adjust" for other covariates
- Define groups according to
  - Predictor of interest, and
  - Other covariates
- Compare the distribution of response across groups which
  - differ with respect to the Predictor of Interest, but
  - are the same with respect to the other covariates
    - "holding other variables constant"

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Unadjusted vs Adjusted Models

- Adjustment for covariates changes the scientific question
- Unadjusted models
  - Slope compares parameters across groups differing by 1 unit in the modeled predictor
    - Groups may also differ with respect to other variables
- Adjusted models
  - Slope compares parameters across groups differing by 1 unit in the modeled predictor but similar with respect to other modeled covariates
- (In RCT investigating a difference in means, the two questions may have similar numeric answers due to double expectation)

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Interpretation of Slopes

- Difference in interpretation of slopes

$$\text{Unadj Model}: \quad g[\theta \mid X_i] = \beta_0 + \beta_1 \times X_i$$

  - β_1 = Compares θ for groups differing by 1 unit in X
    - (The distribution of W might differ across groups being compared)

$$\text{Adj Model}: \quad g[\theta \mid X_i, W_i] = \gamma_0 + \gamma_1 \times X_i + \gamma_2 \times W_i$$

  - γ_1 = Compares θ for groups differing by 1 unit in X, but agreeing in their values of W

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Comparing models

Unadjusted $g[\theta | X_i] = \beta_0 + \beta_1 \times X_i$

Adjusted $g[\theta | X_i, W_i] = \gamma_0 + \gamma_1 \times X_i + \gamma_2 \times W_i$

Science: When is $\gamma_1 = \beta_1$?

When is $\hat{\gamma}_1 = \hat{\beta}_1$?

Statistics: When is $se(\hat{\gamma}_1) = se(\hat{\beta}_1)$?

When is $\hat{se}(\hat{\gamma}_1) = \hat{se}(\hat{\beta}_1)$?

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General Results

- These questions can not be answered precisely in the general case
- However, in linear regression we can derive exact results
- These will serve as a basis for later examination of
  - Logistic regression
  - Poisson regression
  - Proportional hazards regression

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Linear Regression

- Difference in interpretation of slopes

$$\text{Unadjusted Model}: \quad E[Y_i \mid X_i] = \beta_0 + \beta_1 \times X_i$$

  – β_1 = Diff in mean Y for groups differing by 1 unit in X
    - (The distribution of W might differ across groups being compared)

$$\text{Adjusted Model}: \quad E[Y_i \mid X_i, W_i] = \gamma_0 + \gamma_1 \times X_i + \gamma_2 \times W_i$$

  – γ_1 = Diff in mean Y for groups differing by 1 unit in X, but agreeing in their values of W

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Relationships: True Slopes

- The slope of the unadjusted model will tend to be

$$\beta_1 = \gamma_1 + \rho_{XW} \frac{\sigma_W}{\sigma_X} \gamma_2$$

- Hence, true adjusted and unadjusted slopes for X are estimating the same quantity only if

  – $\rho_{XW} = 0$ (X and W are truly uncorrelated), OR

  – $\gamma_2 = 0$ (no association between W and Y after adjusting for X)

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Relationships: Estimated Slopes

- The estimated slope of the unadjusted model will be

$$\hat{\beta}_1 = \hat{\gamma}_1 \left(1 + \hat{\gamma}_2 r_{XW} \left[\frac{s_W}{s_X \left(r_{YX} - r_{YW} r_{XW} \right)} \right] \right)$$

- Hence, estimated adjusted and unadjusted slopes for X are equal only if
  - $r_{XW} = 0$ (X and W are uncorrelated in the sample, which can be arranged by experimental design), OR
  - $\hat{\gamma}_2 = 0$ (which cannot be predetermined, because Y is random)
  - $s_W = 0$ (*W* is controlled at a single value in which case $r_{XW} = 0$)

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Relationships: True SE

Unadjusted Model $\left[se\left(\hat{\beta}_1\right) \right]^2 = \dfrac{Var\left(Y \mid X\right)}{nVar\left(X\right)}$

Adjusted Model $\left[se\left(\hat{\gamma}_1\right) \right]^2 = \dfrac{Var\left(Y \mid X, W\right)}{nVar\left(X\right)\left(1 - r_{XW}^2\right)}$

$$Var\left(Y \mid X\right) = \gamma_2^2 Var\left(W \mid X\right) + Var\left(Y \mid X, W\right)$$

$$\sigma_{Y|X}^2 = \gamma_2^2 \sigma_{W|X}^2 + \sigma_{Y|X,W}^2$$

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Relationships: True SE

Unadjusted Model $\left[se\left(\hat{\beta}_1\right)\right]^2 = \frac{Var\left(Y|X\right)}{nVar\left(X\right)}$

Adjusted Model $\left[se\left(\hat{\gamma}_1\right)\right]^2 = \frac{Var\left(Y|X,W\right)}{nVar\left(X\right)\left(1-r_{XW}^2\right)}$

$$Var\left(Y \mid X\right) = \gamma_2^2 Var\left(W \mid X\right) + Var\left(Y \mid X,W\right)$$

Thus, $se\left(\hat{\beta}_1\right) = se\left(\hat{\gamma}_1\right)$ if

$r_{XW} = 0$

AND

$\gamma_2 = 0$ OR $Var\left(W \mid X\right) = 0$

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Relationships: Estimated SE

Unadjusted Model $\left[s\hat{e}\left(\hat{\beta}_1\right)\right]^2 = \frac{SSE\left(Y|X\right)/(n-2)}{(n-1)s_X^2}$

Adjusted Model $\left[s\hat{e}\left(\hat{\gamma}_1\right)\right]^2 = \frac{SSE\left(Y|X,W\right)/(n-3)}{(n-1)s_X^2\left(1-r_{XW}^2\right)}$

Thus, $s\hat{e}\left(\hat{\beta}_1\right) = s\hat{e}\left(\hat{\gamma}_1\right)$ if

$r_{XW} = 0$

AND

$SSE\left(Y|X\right)/(n-2) = SSE\left(Y|X,W\right)/(n-3)$

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Special Cases

- Behavior of unadjusted and adjusted models according to whether
  - *X* and *W* are uncorrelated (no association in means)
  - *W* is associated with *Y* after adjustment for *X*

	$r_{XW} = 0$	$r_{XW} \neq 0$
$\gamma_2 \neq 0$	Precision	Confounding
$\gamma_2 = 0$	Irrelevant	Var Inflation

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Simulations

- Unadjusted and adjusted estimates of effect of binary POI as a function of
  - Effect of a covariate on summary of outcome (mean, odds, …)
  - Sampling scheme: Association between covariate and POI
    - Difference in mean covariate
    - Difference in median covariate

$$\text{Sampling} \quad : \quad E\left[W_i \,|\, X_i\right] = \alpha_0 + \alpha_1 \times X_i$$

$$\hat{\alpha}_1 = r_{XW} \frac{s_W}{s_X} = \overline{W}_{X=1} - \overline{W}_{X=0}$$

$$\text{Unadjusted}: \quad g\left[\theta \,|\, X_i\right] = \beta_0 + \beta_1 \times X_i$$

$$\text{Adjusted} \quad : \; g\left[\theta \,|\, X_i, W_i\right] = \gamma_0 + \gamma_1 \times X_i + \gamma_2 \times W_i$$

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Linear Regression

- Simulation results

	Truth					Avg Estimates (SE)	
	ΔMdn	α_1	r_{XW}	γ_2	γ_1	β_1	γ_1
Irrelevant	0.0	0.0	0.00	0.0	0.0	0.0 (0.20)	0.0 (0.20)
Precision	0.0	0.0	0.00	1.0	0.0	0.0 (0.28)	0.0 (0.19)
Precision	- 0.3	0.0	0.00	1.0	0.0	0.0 (0.28)	0.0 (0.20)
Precision	0.0	0.0	0.00	1.0	1.0	1.0 (0.28)	1.0 (0.20)
Confound	0.3	0.3	0.15	1.0	0.0	0.3 (0.28)	0.0 (0.21)
Confound	0.0	0.3	0.15	1.0	0.0	0.3 (0.29)	0.0 (0.21)
Var Inflatn	0.0	1.0	0.45	0.0	0.0	0.0 (0.20)	0.0 (0.22)

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Linear Regression

- Simulation results

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Linear Regression

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Linear Regr Take Home: Estimate

- The magnitude of confounding is a product of
  - Magnitude of association between covariate and response AND
  - Difference of mean covariate value across POI groups
    - If adjustment would be linear, mean (not median, etc) matters
- If POI and covariate independent, adjusted and unadjusted estimates will tend to be equal
  - Randomization will lead to such independence
- If POI and covariate orthogonal, adjusted and unadjusted estimates will be exactly equal
  - Stratified, blocked randomization will lead to such orthogonality

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Linear Regr Take Home: Std Err

- Adjusting for a confounder, precision of estimates for response-POI association can be larger or smaller than unadjusted analysis
- Association between covariate and response will tend to decrease SE in adjusted model
  - Thus some increased precision from modeling important prognostic variable in RCT
- Difference in mean covariate across treatment groups in sample will tend to increase SE in adjusted model
  - But in RCT, any such difference in means will tend to be small in large sample sizes or with stratified blocked randomization
  - And covariate adaptive minimization could attempt to minimize difference in means

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Noncollapsibility

- In logistic regression and proportional hazards regression, the differences between unadjusted and adjusted analyses is also affected by "noncollapsibility"
  - Double expectation formula does not protect us
- Even in the absence of confounding, the odds ratio computed when combining two strata can differ from the stratum specific odds ratios
  - And the hazard ratios behave similarly to the odds ratios
- We can consider l'Abbe plots

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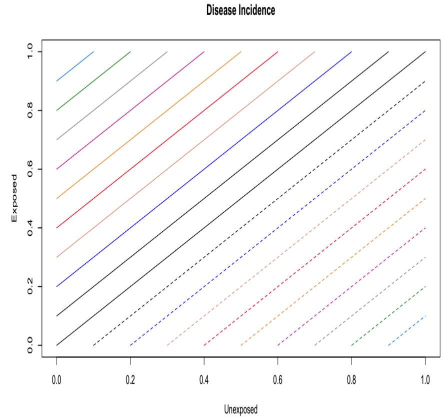
Contours: Equal Risk Difference (RD)

- Graph of all possible values for disease incidences
  - Two strata having the same RD will lie on the same line
  - Owing to the double expectation formula, with no confounding, the RD for the combined strata will also be on that same line



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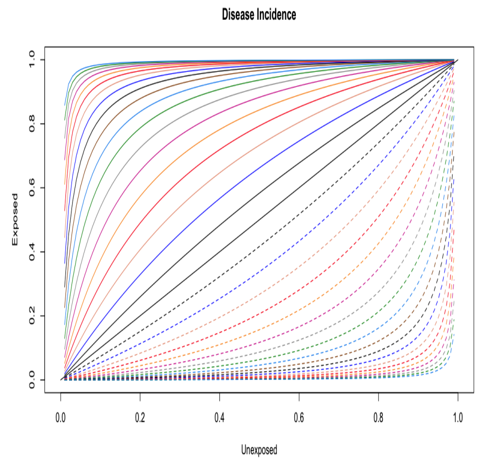
Contours: Equal Odds Ratio (OR)

- Graph of all possible values for disease incidences
  - Two strata having the same OR will lie on the same line



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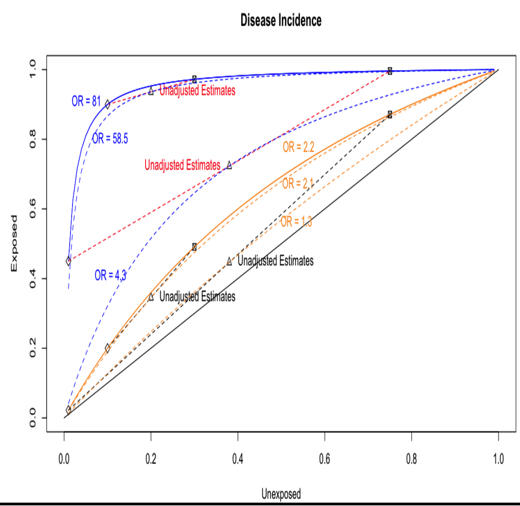
Deattenuation of OR

- When "collapsing strata", the OR will lie on a different contour
  - Amount of attenuation will depend on prognostic strength



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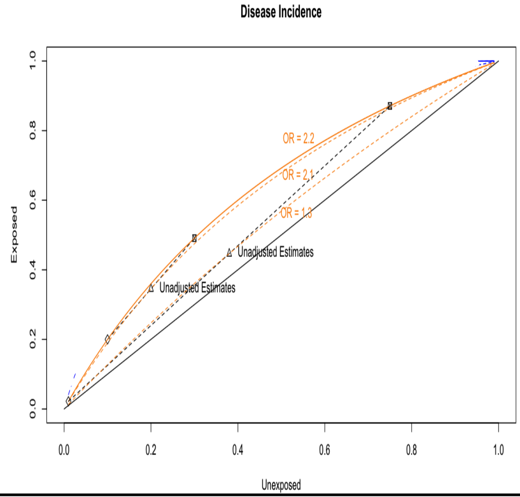

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Deattenuation of OR

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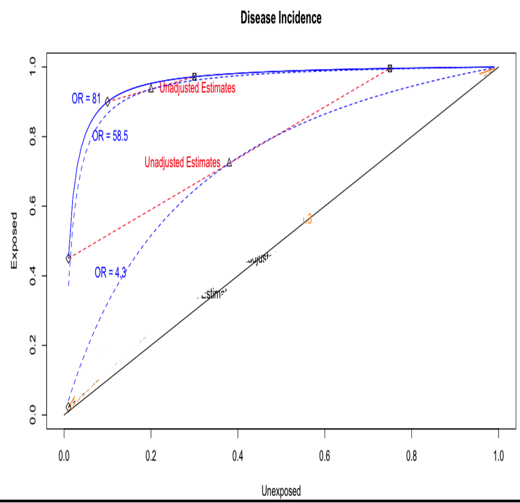

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Aside: Deattenuation of HR in PH

- Recall the connections between logistic regression and PH regression
  - The score test in logistic regression on a saturated model is related to the Cochran-Mantel-Haenszel statistic
  - The log rank test was originally proposed as an application of CMH to analyses stratifying on failure times
  - The log rank statistic is the score test in PH regression on binary outcomes
- While HR statistics do not easily lend themselves to display on a l'Abbe plot, we might expect that the same behavior will obtain

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Logistic Regression

- Simulation results

	Truth					Avg Estimates (SE)	
	ΔMdn	α_1	r_{XW}	γ_2	γ_1	β_1	γ_1
Irrelevant	0.0	0.0	0.00	0.0	0.0	0.0 (0.42)	0.0 (0.42)
Precision	0.0	0.0	0.00	1.0	0.0	0.0 (0.40)	0.0 (0.42)
Precision	- 0.3	0.0	0.00	1.0	0.0	0.0 (0.42)	0.0 (0.43)
Precision	0.0	0.0	0.00	1.0	1.0	0.8 (0.43)	1.0 (0.49)
Confound	0.3	0.3	0.15	1.0	0.0	0.3 (0.43)	0.0 (0.48)
Confound	0.0	0.3	0.15	1.0	0.0	0.2 (0.41)	0.0 (0.47)
Var Inflatn	0.0	1.0	0.45	0.0	0.0	0.0 (0.41)	0.0 (0.47)

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Logist Regr Take Home: Estimate

- The magnitude of confounding is primarily a function of
  - Magnitude of association between covariate and response AND
  - Difference of mean covariate value across POI groups
    - If adjustment would be linear, mean (not median, etc) matters most
- Even if no confounding, adjusted and unadjusted estimates will be different if new covariate (conditionally) associated with response
  - Adjusting for a precision variable will "deattenuate" OR (and estimate)
  - The amount of "deattenuation" depends on
    - The strength of association between the added covariate and the response, and
    - The adjusted strength of association between the POI and the response

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Logist Regr Take Home: Std Err

- Standard errors of estimated OR measuring POI – response association are largely driven by the mean-variance relationship
  - SE of odds behaves like 1 / p(1-p)
  - Greater homogeneity of groups leads to p closer to 0 or 1
  - Usually statistical significance of the POI – response association is affected very little by adjustment for a "precision" variable unless it is <u>very</u> strongly associated with response
- Note that if we persist in estimating the population OR instead of the adjusted OR, we do gain precision by adjustment
  - We do have to take a weighted average, however
  - See Tangen & Koch, *Stat Med*, 2000

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Proportional Hazards Regression

- Simulation results

	Truth					Avg Estimates (SE)	
	ΔMdn	α_1	r_{XW}	γ_2	γ_1	β_1	γ_1
Irrelevant	0.0	0.0	0.00	0.0	0.0	0.0 (0.20)	0.0 (0.20)
Precision	0.0	0.0	0.00	1.0	0.0	0.0 (0.21)	0.0 (0.22)
Precision	- 0.3	0.0	0.00	1.0	0.0	0.0 (0.21)	0.0 (0.21)
Precision	0.0	0.0	0.00	1.0	1.0	0.7 (0.21)	1.0 (0.22)
Confound	0.3	0.3	0.15	1.0	0.0	0.2 (0.21)	0.0 (0.21)
Confound	0.0	0.3	0.15	1.0	0.0	0.1 (0.20)	0.0 (0.22)
Var Inflatn	0.0	1.0	0.45	0.0	0.0	0.0 (0.20)	0.0 (0.23)

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Next

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PH Regr Take Home: Estimate

- The magnitude of confounding is primarily a function of
  - Magnitude of association between covariate and response AND
  - Difference of mean covariate value across POI groups
    - If adjustment would be linear, mean (not median, etc) matters most
- Even if no confounding, adjusted and unadjusted estimates will be different if new covariate (conditionally) associated with response (PH regression is related to logistic regression)
  - Adjusting for a precision variable will "deattenuate" HR (and estimate)
  - The amount of "deattenuation" depends on
    - The strength of association between the added covariate and the response, and
    - The adjusted strength of association between the POI and the response

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PH Regr Take Home: Std Err

- Standard errors of estimated HR measuring POI – response association are largely driven by the mean-variance relationship of the sample size ratios
  - Unless there is a very strong association, the SE tends to be fairly constant for a range of different HRs
- Holding the SE constant, we will obtain a lower p value with a deattenuated HR

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Precision: Linear Regression

- E.g., X, W independent in population (or completely randomized experiment) AND W associated with Y independent of X

$$\rho_{XW} = 0 \qquad \gamma_2 \neq 0$$

	True Value	Estimates
Slopes	$\beta_1 = \gamma_1$	$\hat{\beta}_1 \approx \hat{\gamma}_1$
Std Errs	$se(\hat{\beta}_1) > se(\hat{\gamma}_1)$	$s\hat{e}(\hat{\beta}_1) > s\hat{e}(\hat{\gamma}_1)$

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Precision: Logistic Regression

- Adjusting for a precision variable
  - Deattenuates slope away from the null
  - Standard errors reflect mean-variance relationship
    - Substantially increased power only in extreme cases
      - » (OR > 5 for equal samples sizes of binary W)

		True Value	Estimates
Slopes	$\beta_1 > 0:$	$0 < \beta_1 < \gamma_1$	$0 < \hat{\beta}_1 < \hat{\gamma}_1$
	$\beta_1 < 0:$	$0 > \beta_1 > \gamma_1$	$0 > \hat{\beta}_1 > \hat{\gamma}_1$
Std Errs		$se(\hat{\beta}_1) < se(\hat{\gamma}_1)$	$\hat{se}(\hat{\beta}_1) < \hat{se}(\hat{\gamma}_1)$

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Precision: Poisson Regression

- Adjusting for a precision variable (with robust SE)
  - No effect on the slope (similar to linear regression)
    - log ratios are linear in log means
  - Standard errors reflect mean-variance relationship
    - Virtually no effect on power

	True Value	Estimates
Slopes	$\beta_1 = \gamma_1$	$\hat{\beta}_1 \approx \hat{\gamma}_1$
Std Errs	$se(\hat{\beta}_1) > se(\hat{\gamma}_1)$	$\hat{se}(\hat{\beta}_1) > \hat{se}(\hat{\gamma}_1)$

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Precision: PH Regression

- Adjusting for a precision variable
  - Deattenuates slope away from the null
  - Standard errors stay fairly constant
    - (Complicated result of binomial mean-variance)

		True Value	Estimates
Slopes	$\beta_1 > 0:$	$0 < \beta_1 < \gamma_1$	$0 < \hat{\beta}_1 < \hat{\gamma}_1$
	$\beta_1 < 0:$	$0 > \beta_1 > \gamma_1$	$0 > \hat{\beta}_1 > \hat{\gamma}_1$
Std Errs		$se(\hat{\beta}_1) \approx se(\hat{\gamma}_1)$	$s\hat{e}(\hat{\beta}_1) \approx s\hat{e}(\hat{\gamma}_1)$

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Lin Reg: Stratified Randomization

- Stratified (orthogonal) randomization in a designed experiment
  - Also when designing observational study with matching
- Unless we adjust for the stratification variables, we estimate the true standard errors incorrectly

$$r_{XW} = 0 \qquad \gamma_2 \neq 0$$

	True Value	Estimates
Slopes	$\beta_1 = \gamma_1$	$\hat{\beta}_1 = \hat{\gamma}_1$
Std Errs	$se(\hat{\beta}_1) = se(\hat{\gamma}_1)$	$s\hat{e}(\hat{\beta}_1) > s\hat{e}(\hat{\gamma}_1)$

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Treatment of Variables

- Measure and compare distribution across groups
  - Response variable in regression
- Vary systematically (intervention)
- Control at a single level (fixed effects)
- Control at multiple levels (fixed or random effects)
  - Stratified (blocked) randomization
- Measure and adjust (fixed or random effects)
- Treat as "error"

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Key Message re PH Regression

- In the presence of a **strongly** prognostic baseline covariate, any treatment effect will appear strongest when we compare "apples to apples"
  - This is not an artefact of the statistical analysis, but instead a "truth" in the real world
- We can realize this stronger effect by
  - Restricting accrual to a single stratum defined by the prognostic variable, or
  - Performing adjusted (stratified?) analyses based on the prognostic variable
- Precision in a PH regression model comes almost exclusively from deattenuation of the HR estimate
  - Standard errors of regression parameters are largely unchanged

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Take Home Message 1

- **Why control for baseline variables in RCT analyses?**
  - Precision of inference is the primary issue
    - But mechanism of added precision varies by type of regression
  - Estimation of "within stratum" effect a minor issue with some estimands (odds, hazards)
  - Confounding is in some sense avoided by randomization
    - However, some critics will second guess results in a *post hoc* manner

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Take Home Message 2

- **How to control for baseline variables in RCT design?**
  - Obtain precision by prespecified adjustment for the most important prognostic factors known *a priori*
    - Do not allow data driven selection of adjusted models
  - Restrict eligibility to subset of eventual target population
    - Only if certain no effect modification on efficacy or safety
  - Stratified randomization especially if
    - Want face validity of key prognostic factors in Table 1
    - Interested in prespecified analyses within subgroups
  - Covariate adaptive randomization (minimization) can be avoided
    - Exception if need to attain face validity on many sparse factors

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Take Home Message 3

- **How to report distribution of baseline variables in CTR?**
  - Using Table 1 to describe materials / methods
    - Range, quantiles, means, SD
  - Using Table 1 to second guess comparability of randomized groups
    - Means: arithmetic, geometric, or proportions as appropriate
    - ("Conditional confounding" is a function of means, not medians)

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Take Home Message 4

- **How to model baseline variables in prespecified analyses?**
  - Special case: Change in response (e.g., rates) over course of trial
    - Adjust for baseline measurement in ANCOVA
      - Ideal for balanced group sizes
      - Possible improvements in presence of unequal group sizes
  - Model mis-specification is not generally an important issue
    - I typically model baseline prognostic variables linear continuous
  - Sensitivity of results to *post hoc* adjustment
    - This is invariably "second guessing" pre-specified hypotheses
    - "Randomization imbalance" may decrease our confidence in results, but there are not good statistical foundations for such analyses

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