Biost 536 / Epi 536 Categorical Data Analysis in Epidemiology

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Lecture 6:
Matching / Stratification

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Lecture Outline

- Quiz
- Matching / Stratification vs Regression
- Directly Standardized Rates
  - Probability Models for Incidence of Disease
  - Example: Colorectal Cancer Incidence in US Whites

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Quiz (Pre-test and Survey)

U.S. Colorectal Cancer by Country of Birth

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Question 1

- I have data on new cases of colorectal cancer:
  - 62,668 whites known to be born in US
  - 11,026 whites known to be born outside the US
  - 20,746 whites with country of birth not recorded

1) In three (3) words or less, what is the information that is most important to know in order to interpret the above data?

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Question 2

- The data that I have comes from a population based registry of new cases of colorectal cancer diagnosed within a prescribed geographic region during a specified period of time. It reveals new colorectal cancer diagnoses in
  – 62,668 US born whites
  – 11,026 non-US born whites
  – 20,746 whites with country of birth not recorded

2) In three (3) words or less, what is the information that is now most important to know in order to interpret the above data?

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Question 3

- The data that I have comes from a population based registry of new cases of colorectal cancer diagnosed within a prescribed geographic region during a specified period of time. It reveals new colorectal cancer diagnoses in
  – 62,668 US born whites during 225,156,822 person-years of observation
  – 11,026 non-US born whites during 14,444,097 person-years of observation
  – 20,746 whites with country of birth not recorded during 754,295 person-years of observation

3) In three (3) words or less, what is the information that is now most important to know in order to interpret the above data?

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Question 4

- Which of the following was most important in making the decision about how you answered question 3?

  a) Fear that effect modification would make the simple statistics misleading / noninformative

  b) Fear that confounding would make the simple statistics misleading / noninformative

  c) Fear that lack of precision would make the simple statistics misleading / noninformative

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Question 5

- In addition to the data on cancer incidence from the population based registry, I have information on the age, sex, and (most times) the country of birth for each case.
- From US census data I can obtain comparable data for all subjects in the registry catchment area

5) In ten (10) words or less, what single measure would you use to summarize the association between colorectal cancer incidence and country of birth in the US white population?

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Question 6

6) In ten (10) words or less, what statistical analysis model would you use to provide inference about the summary measure of association you chose in Question 5?

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Question 7

- Owing to an impending asteroid collision with the earth, an extraterrestial civilization has commissioned you to gather all land animals and place them in containers according to their family (modern Linnaean classification) and mail them to another planet.

7) What will be the label on the container that requires the greatest postage (i.e., weighs the most)?

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Question 8

- You are given a meter long rod with the following properties:
  - The entire rod weighs one kilogram.
  - Each segment of the rod would weigh in proportion to the length of the segment (e.g., any segment that was half a meter long would weigh 0.5 kg)

8) If you were able to remove all rational numbers (i.e., fractions equal to ratios of integers) thereby leaving only the irrational (numbers such as the square root of 2), how much would the remaining numbers weigh?

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Matching / Stratification vs Regression

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Recall: Adjustment for Covariates

- We "adjust" for other covariates
  - Model effect modification
  - Address confounding
  - Gain precision
- 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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Recall: Comparing models

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

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

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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Recall: 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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Recall: Linear Regression

- Difference in interpretation of slopes

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

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

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

- 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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Recall: 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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Recall: Relationships: True SE

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

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

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

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

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Binary *W* : Notation

- We can use this notation to explore the benefits of matched analyses
- Suppose Y_{1i} measures "cases" having $Z_{1i} = 1$ and $W_{1i} = w_{1i} = 0,1$
  - Suppose n_{11} and n_{10} count the number with $W_{1i} = 1$ and $W_{1i} = 0$, respectively
- Suppose Y_{0i} measures "cases" having $Z_{1i} = 0$ and $W_{1i} = w_{1i} = 0,1$
  - Suppose n_{01} and n_{00} count the number with $W_{0i} = 1$ and $W_{0i} = 0$, respectively
- (Note: In the following I presume homoscedasticity
  - This will not generally be the case with binary data)

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Binary *W* : Marginal Distribution

$$\left.\begin{array}{lll} Y_{0i} \mid W_{0i} = 0 & \sim & \left(\gamma_0,\ \sigma^2\right) \\ Y_{0i} \mid W_{0i} = 1 & \sim & \left(\gamma_0 + \gamma_2,\ \sigma^2\right) \end{array}\right\} \Rightarrow$$

$$Y_{0i} \sim \left(\gamma_0 + \frac{n_{01}}{n_{01} + n_{00}} \gamma_2,\ \sigma^2 + \gamma_2^2 \frac{n_{01} n_{00}}{\left(n_{01} + n_{00}\right)^2}\right)$$

$$\left.\begin{array}{lll} Y_{1i} \mid W_{1i} = 0 & \sim & \left(\gamma_0 + \gamma_1,\ \sigma^2\right) \\ Y_{1i} \mid W_{1i} = 1 & \sim & \left(\gamma_0 + \gamma_1 + \gamma_2,\ \sigma^2\right) \end{array}\right\} \Rightarrow$$

$$Y_{1i} \sim \left(\gamma_0 + \gamma_1 + \frac{n_{11}}{n_{11} + n_{10}} \gamma_2,\ \sigma^2 + \gamma_2^2 \frac{n_{11} n_{10}}{\left(n_{11} + n_{10}\right)^2}\right)$$

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Binary W : Unadjusted Analysis

$$Y_{0i} \sim \left(\gamma_0 + \frac{n_{01}}{n_{01}+n_{00}}\gamma_2,\ \sigma^2 + \gamma_2{}^2 \frac{n_{01}n_{00}}{(n_{01}+n_{00})^2}\right)$$

$$Y_{1i} \sim \left(\gamma_0 + \gamma_1 + \frac{n_{11}}{n_{11}+n_{10}}\gamma_2,\ \sigma^2 + \gamma_2{}^2 \frac{n_{11}n_{10}}{(n_{11}+n_{10})^2}\right)$$

$$\bar{Y}_{1\bullet} - \bar{Y}_{0\bullet} \sim \left(\gamma_1 + \frac{n_{11}n_{00} - n_{10}n_{01}}{(n_{11}+n_{10})(n_{01}+n_{00})}\gamma_2,\ \sigma^2 + \gamma_2{}^2\left(\frac{n_{01}n_{00}}{(n_{01}+n_{00})^2} + \frac{n_{11}n_{10}}{(n_{11}+n_{10})^2}\right)\right)$$

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Binary W : Analyses Within Subgroups

$$\left.\begin{array}{l} Y_{1i} \mid W_{1i} = 0 \sim (\gamma_0 + \gamma_1,\ \sigma^2) \\ Y_{0i} \mid W_{0i} = 0 \sim (\gamma_0,\ \sigma^2) \end{array}\right\} \Rightarrow$$

$$\hat{\Delta}_0 = \bar{Y}_{1\bullet} \mid W_{1i} = 0 - \bar{Y}_{0\bullet} \mid W_{0i} = 0 \sim \left(\gamma_1,\ \sigma^2 \frac{n_{10}+n_{00}}{n_{10}n_{00}}\right)$$

$$\left.\begin{array}{l} Y_{1i} \mid W_{1i} = 1 \sim (\gamma_0 + \gamma_1 + \gamma_2,\ \sigma^2) \\ Y_{0i} \mid W_{0i} = 1 \sim (\gamma_0 + \gamma_2,\ \sigma^2) \end{array}\right\} \Rightarrow$$

$$\hat{\Delta}_1 = \bar{Y}_{1\bullet} \mid W_{1i} = 1 - \bar{Y}_{0\bullet} \mid W_{0i} = 1 \sim \left(\gamma_1,\ \sigma^2 \frac{n_{11}+n_{01}}{n_{11}n_{01}}\right)$$

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Combining Across Subgroups

- Based on the properties of independent, normally distributed estimates

For independent $\hat{\theta}_1 \sim N(\theta_1, se_1^2);\quad \hat{\theta}_2 \sim N(\theta_2, se_2^2)$

$$a\hat{\theta}_1 + b\hat{\theta}_2 \sim N(a\theta_1 + b\theta_2, a^2 se_1^2 + b^2 se_2^2)$$

$$\hat{\theta}_1 - \hat{\theta}_2 \sim N(\theta_1 - \theta_2, se_1^2 + se_2^2)$$

$$\hat{\theta}_1 / \hat{\theta}_2 \sim N\left(\frac{\theta_1}{\theta_2}, \frac{1}{\theta_2^2}\left(se_1^2 + \frac{\theta_1^2}{\theta_2^2} se_2^2\right)\right)$$

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Binary W : Average Across Subgroups

- We can use any weighted average

$$\hat{\Delta}_0 = \bar{Y}_{1\bullet} \mid W_{1i} = 0 - \bar{Y}_{0\bullet} \mid W_{0i} = 0 \sim \left(\gamma_1,\ \sigma^2 \frac{n_{10}+n_{00}}{n_{10}n_{00}}\right)$$

$$\hat{\Delta}_1 = \bar{Y}_{1\bullet} \mid W_{1i} = 1 - \bar{Y}_{0\bullet} \mid W_{0i} = 1 \sim \left(\gamma_1,\ \sigma^2 \frac{n_{11}+n_{01}}{n_{11}n_{01}}\right)$$

$$\hat{\Delta} = w\hat{\Delta}_0 + (1-w)\hat{\Delta}_1 \sim \left(\gamma_1,\ \sigma^2\left(w^2 \frac{n_{10}+n_{00}}{n_{10}n_{00}} + (1-w)^2 \frac{n_{11}+n_{01}}{n_{11}n_{01}}\right)\right)$$

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Binary *W* : Average Across Subgroups

- Optimal choice minimizes variance
  - (Solution would differ when we have heteroscedasticity)

$$\hat{\Delta} = w\hat{\Delta}_0 + (1-w)\hat{\Delta}_1 \quad \sim \quad \left(\gamma_1,\ \sigma^2 \left(w^2 \frac{n_{10}+n_{00}}{n_{10}n_{00}} + (1-w)^2 \frac{n_{11}+n_{01}}{n_{11}n_{01}} \right) \right)$$

$$w = \frac{n_{10}n_{00}(n_{11}+n_{01})}{n_{10}n_{00}(n_{11}+n_{01}) + n_{11}n_{01}(n_{10}+n_{00})}$$

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Example: Mortality by Previous CVD, Sex

- Using inflammatory markers data set
  - Mortality within 4 years is known for everyon
- Descriptive statistics
  - Males: 20.7% if previous CHD; 11.7% if not – RD 0.090
  - Females: 14.7% if previous CHD; 4.9% if not – RD 0.098
- Adjusted analysis could average the subgroup specific RD
  - Weight 50-50? According to M:F ratio in the age range?
  - (Assume no effect modification?)
  - (Average over effect modification?)

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(Frequency) Matching

- We can use this notation to explore the benefits of matched analyses
- Suppose Y_{1i} measures “cases” having $Z_{1i} = 1$ and $W_{1i} = w_{1i} = 0,1$
  - Suppose n_{11} and n_{10} count the number with $W_{1i} = 1$ and $W_{1i} = 0$, respectively
- We then choose “controls” having $Z_{0i} = 0$ and $W_{0i} = w_{1i} = 0,1$ and measure Y_{0i}
  - We will thus have $n_{01} = n_{11}$ and $n_{00} = n_{10}$

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Binary *W* : Frequency Matching

- Optimal choice minimizes variance

$$\hat{\Delta} = w\hat{\Delta}_0 + (1-w)\hat{\Delta}_1 \quad \sim \quad \left(\gamma_1,\ \sigma^2 \left(\frac{n_{10}+n_{00}}{n_{10}n_{00}} \right) \left(w^2 + (1-w)^2 \right) \right)$$

$$w = \frac{n_{10}n_{00}}{n_{10}n_{00} + n_{11}n_{01}}$$

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Generalizations: Stratifications

- Stratified analyses:
  - Analyze within each subgroup
  - Average the results across subgroups
- When averaging across subgroups
  - If there is no effect modification, then we are free to choose weights to minimize variance (maximize precision)
  - If there is effect modification, we will get different answers according to which weights we use
    - Often we use population based weights so our answer will be relevant to some population of interest

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Generalizations: Matching

- Frequency matching
  - We ensure that the marginal distribution of each covariate is the same across POI groups
  - Matching on fixed effects
- Individual matching
  - We ensure that the joint distribution (including interactions) of the matching variables are the same across POI groups
  - Matching on fixed effects or random effects
    - Fixed effects: e.g., age, sex, height, weight, smoking behavior
    - Random effects: e.g., hospital, family, community of residence

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Comparison to Regression

- We use regression to
  - Borrow information across groups
  - Form contrasts (e.g., slope) measuring associations
- As a rule, we can perform stratified analyses within regression
  - Fit dummy variables for each stratum
    - Does not borrow information across strata
  - May have to weight strata appropriately in a weighted regression
  - May have to consider how variances are estimated
    - Only within subgroups, or
    - Borrow information about variance across groups
  - (With binary response variables, issues about variance will also have to consider mean-variance relationships and adequacy of model)

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  - Males: 20.7% if previous CHD; 11.7% if not – RD 0.090
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```
. regress deadin4 male prevdis m_prevdis
             |          Robust
     deadin4 |  Coef.  Std. Err.    t    P>|t|     [95% Conf. Interval]
        male |  .0675   .0094     7.16   0.000      .0491    .0860
     prevdis |  .0979   .0158     6.18   0.000      .0669    .1289
   m_prevdis | -.0080   .0243    -0.33   0.742     -.0557    .0397
       _cons |  .0492   .0045    11.04   0.000      .0404    .0579

. regress deadin4 male prevdis, robust
             |               Robust
     deadin4 |   Coef. Std. Err.    t    P>|t|     [95% Conf. Interval]
        male |   .0656   .0090     7.33   0.000      .0481    .0832
     prevdis |   .0940   .0121     7.75   0.000      .0702    .1177
       _cons |   .0499   .0046    10.84   0.000      .0409    .0589
```

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Probability Models for Incidence of Disease

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Risk Sets

- Most often, we recognize that the probability of an event depends in some way upon time
- In many cases, that time dependence is something we merely want to adjust for as we compare different groups
  - It is not as important to contrast the event probability over time
- We thus find it convenient to couch many of our analyses of binary data in terms that also consider "time to event"

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Incidence and Mortality Rates (Hazards)

- We are often interested in the rate (over time) at which individuals convert from being "event-free" to having had the event
  - Time can be calendar time, age, study time …
  - (They differ in what we call time zero)
- At each point in time, we essentially compute a proportion
  - Denominator: Individuals who are currently "event-free"
  - Numerator: Among those in the denominator, who converts in the next instant
- Referred to as
  - Epidemiology: incidence and mortality rates, force of mortality
  - Statistics and probability: hazard function

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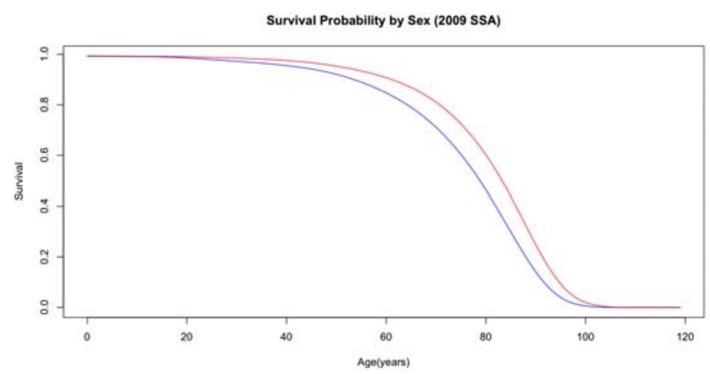
Age Effects on Mortality



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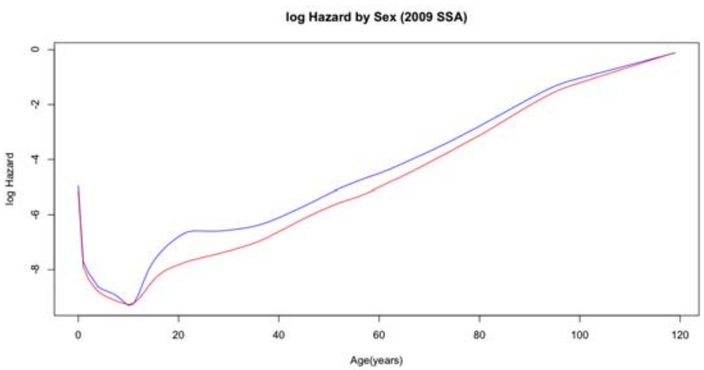
Age Effects on Mortality



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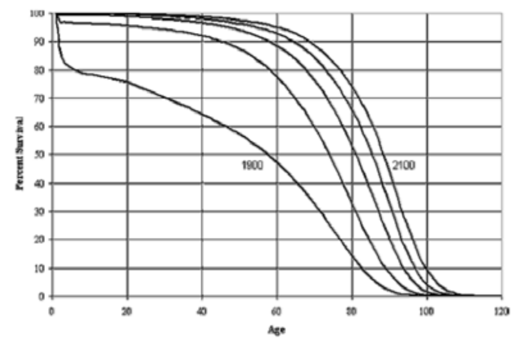
Birth Cohort Effects on Mortality

- Survival curves 1900 to 2100 by 50 year increments



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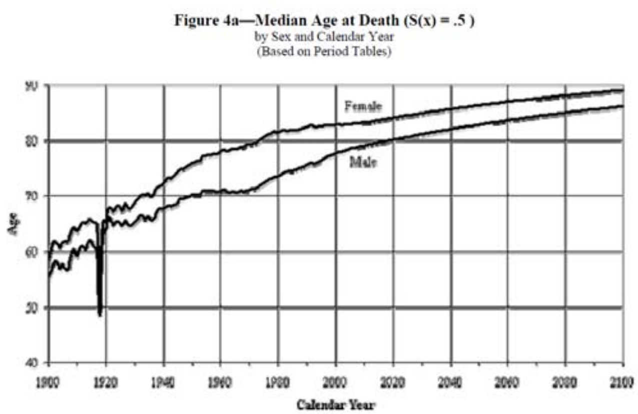
Calendar Year Effects on Mortality



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Hazard Function Notation

- For each individual in some group of interest, *T* measures the time the event will occur
  - *Y(t)* is thus an indicator that the event has occurred prior to *t*
  - *T* might be infinity

Hazard function (continuous T) : for very small Δt

$$\lambda(t) = \Pr(t \le T < t + \Delta t \mid t \le T)$$
$$= \frac{\Pr(t \le T < t + \Delta t)}{\Pr(t \le T)} = \frac{f(t)}{1 - F(t)}$$

$F(t)$ is cumulative distribution function

$f(t)$ is density

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Hazard Rate Based Inference

- When the changing conversion rate is just a nuisance to our primary question, we still have to worry that time might be
  - An effect modifier and/or
  - A confounder and/or
  - A precision variable.
- Most often we choose some way to adjust for those roles by
  - Using weighted averages of the hazard (e.g., standardized rates)
  - Adjusting in a regression model
    - Poisson models adjusting for person-time at risk
    - Proportional hazards regression models
    - Parametric regression models

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(Cumulative) Incidence and Mortality

- Sometimes we choose a specific interval of time of greatest interest
  - E.g., incidence of cancer within one year, teenage mortality
- Usually estimated with a simple proportion
  - Denominator: Individuals who are "event-free" at time *a*
  - Numerator: Individuals experiencing event between *a* and *b*
- It does relate to the hazard

(Cumulative) incidence between times *a* and *b*

$$\Pr(a \le T < b \mid a \le T) = 1 - e^{-\int_a^b \lambda(u)\,du}$$

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(Cumulative) Incidence Based Inference

- Note that if the hazard function is (nearly) constant over some small period of time then

(Cumulative) incidence between times *a* and *b*

$$\Pr(a \le T < b \mid a \le T) = 1 - e^{-\int_a^b \lambda(u)\,du} = 1 - e^{-\int_a^b \lambda\,du} = 1 - e^{-\lambda(b-a)}$$

- This "piecewise exponential" model is often used as a basis for inference
  - The "exponential distribution" has a constant hazard
  - The exponential distribution is "memorylessness"
    - Independent intervals are independent
      - Within or between individuals
  - Also be thought of as Poisson approximation to binomial and/or times between events in Poisson process

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Person-year Based Analyses

- We divide time into small intervals
  - Small age intervals will have common risk
  - Small follow-up time intervals
- We estimate person-years of observation
  - Each person may contribute to several categories
  - Sum across individuals for each category
- Estimate risk within those intervals
- Compare risk ratio across POI groups

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Directly Standardized Rates

- Stratum specific weights chosen based on population

$$Y_i \mid X_i = x \quad \sim \quad P(\lambda_x t_i) \doteq N(\lambda_x t_i, \lambda_x t_i)$$

$$\hat{\lambda}_x = \frac{\sum_{i:X_i=x} Y_i}{\sum_{i:X_i=x} t_i} \quad \dot{\sim} \quad N\left(\lambda_x, \frac{\lambda_x}{\sum_{i:X_i=x} t_i}\right)$$

$$\hat{\lambda} = \frac{\sum_x w_x \hat{\lambda}_x}{\sum_x w_x}$$

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Quiz Answers

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Question 1

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1) In three (3) words or less, what is the information that is most important to know in order to interpret the above data?

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Study design

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Question 2

- The data that I have comes from a population based registry of new cases of colorectal cancer diagnosed within a prescribed geographic region during a specified period of time. It reveals new colorectal cancer diagnoses in
  - 62,668 US born whites
  - 11,026 non-US born whites
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2) In three (3) words or less, what is the information that is now most important to know in order to interpret the above data?

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Question 2

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Denominator data

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Question 3

- The data that I have comes from a population based registry of new cases of colorectal cancer diagnosed within a prescribed geographic region during a specified period of time. It reveals new colorectal cancer diagnoses in
  - 62,668 US born whites during 225,156,822 person-years of observation
  - 11,026 non-US born whites during 14,444,097 person-years of observation
  - 20,746 whites with country of birth not recorded during 754,295 person-years of observation

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3) In three (3) words or less, what is the information that is now most important to know in order to interpret the above data?

Age distribution

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Question 4

- Which of the following was most important in making the decision about how you answered question 3?

a) Fear that effect modification would make the simple statistics misleading / noninformative

b) Fear that confounding would make the simple statistics misleading / noninformative

c) Fear that lack of precision would make the simple statistics misleading / noninformative

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Question 4

- Which of the following was most important in making the decision about how you answered question 3?

a) Fear that effect modification would make the simple statistics misleading / noninformative

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Question 5

- In addition to the data on cancer incidence from the population based registry, I have information on the age, sex, and (most times) the country of birth for each case.
- From US census data I can obtain comparable data for all subjects in the registry catchment area

5) In ten (10) words or less, what single measure would you use to summarize the association between colorectal cancer incidence and country of birth in the US white population?

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Question 5

- In addition to the data on cancer incidence from the population based registry, I have information on the age, sex, and (most times) the country of birth for each case.
- From US census data I can obtain comparable data for all subjects in the registry catchment area

5) In ten (10) words or less, what single measure would you use to summarize the association between colorectal cancer incidence and country of birth in the US white population?

Average incidence ratio across birthplace groups adjusted for sex, age

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Question 6

6) In ten (10) words or less, what statistical analysis model would you use to provide inference about the summary measure of association you chose in Question 5?

Directly standardized rates and/or Poisson regression

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Question 7

- Owing to an impending asteroid collision with the earth, an extraterrestial civilization has commissioned you to gather all land animals and place them in containers according to their family (modern Linnaean classification) and mail them to another planet.

7) What will be the label on the container that requires the greatest postage (i.e., weighs the most)?

Ants

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Question 8

- You are given a meter long rod with the following properties:
  - The entire rod weighs one kilogram.
  - Each segment of the rod would weigh in proportion to the length of the segment (e.g., any segment that was half a meter long would weigh 0.5 kg)

8) If you were able to remove all rational numbers (i.e., fractions equal to ratios of integers) thereby leaving only the irrational (numbers such as the square root of 2), how much would the remaining numbers weigh?

1 kg

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Example: Incidence of Colorectal Cancer by Birthplace

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Example

- We are interested in exploring the incidence of colorectal cancer by birthplace among whites in the US
- Cases identified through the SEER registry 1973-1987
- Available data
  - US, 25 non-US, unknown
  - Age in 5 year groups
  - Sex
- Denominator data from US census data

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Analysis Model

- Effect modification in question?
- Potential confounding?
  - Variables causally associated with cancer incidence
  - Variable associated with birthplace in sample
- Precision?

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Analysis Model

- Effect modification in question?
  - Analysis within sex subgroups?
- Potential confounding?
  - Variables causally associated with cancer incidence
  - Variable associated with birthplace in sample
  - Age?
- Precision?

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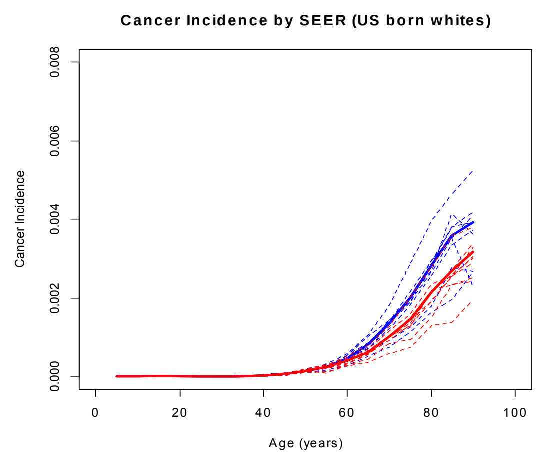
Associations with SEER



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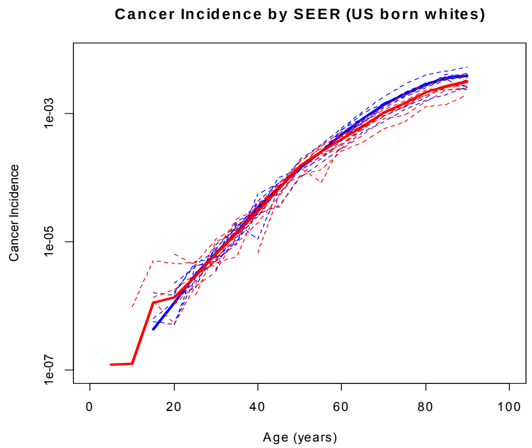
Associations with Response (log)



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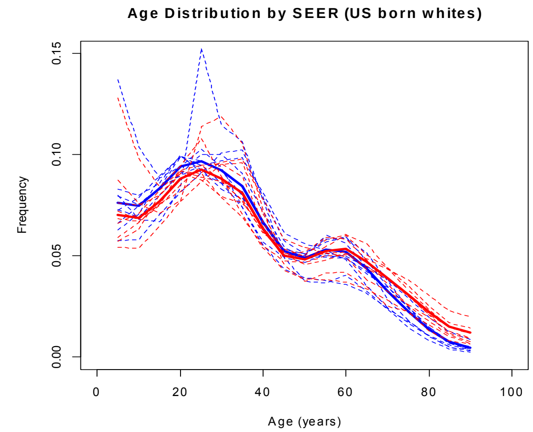
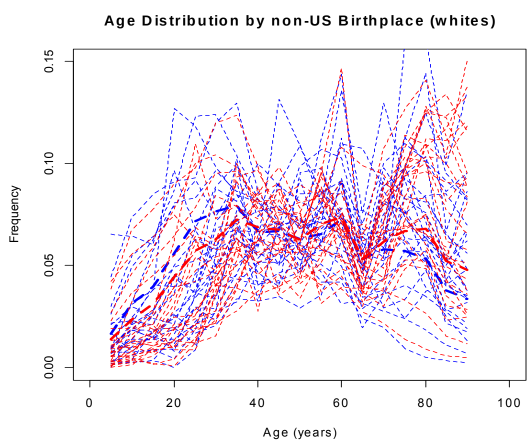
Associations with POI



66

Associations with POI



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Example

- We need to worry about
  - How we summarize over age
  - Confounding by age across country of birth

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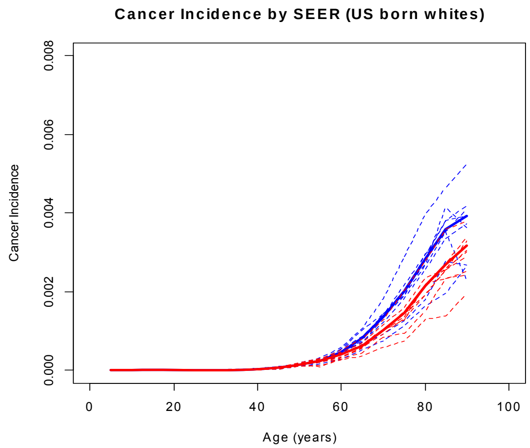
Associations with POI



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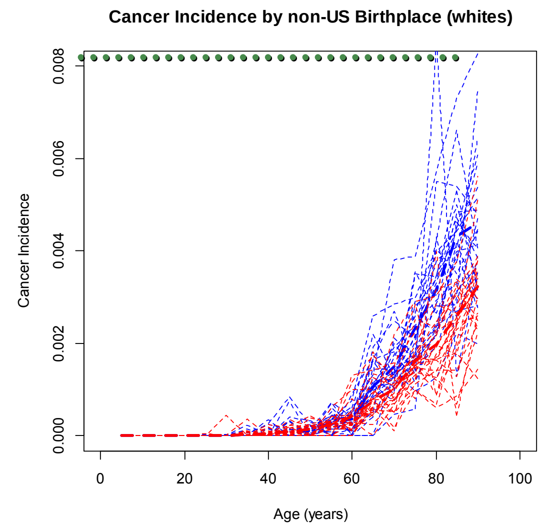

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Example

- We need to worry about missing data
- Missing completely at random
- Missing at random
- Missing not at random

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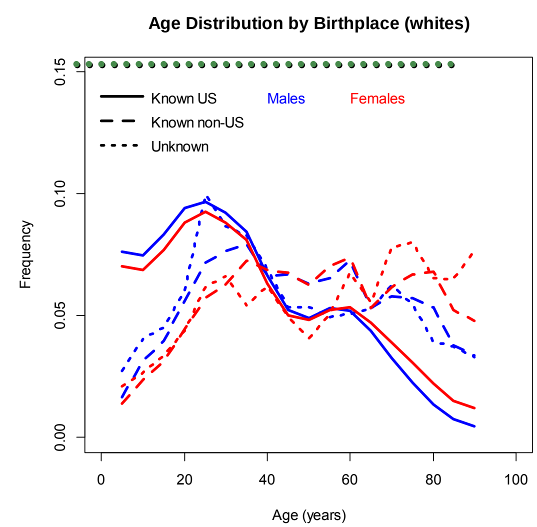

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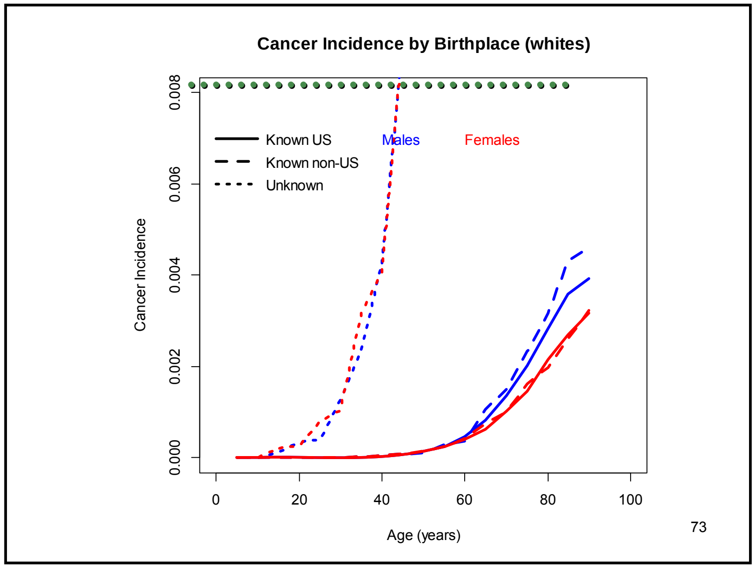
Cancer Incidence by Birthplace (whites)
Known US
Known non-US
Unknown
Males
Females
Cancer Incidence
0.000
0.002
0.004
0.006
0.008
0
20
40
60
80
100
Age (years)
73