Lecture 12
Meta-analyses

Outline

- Definition of meta-analysis
- Basic outline of method
- What model to use?
  - Simple regression
  - Fixed effects
  - Random effects
- Examples
  - Evaluation of community based mental health program
  - World-wide incidence rates for Alzheimer's disease

Meta-analysis

- Wikipedia definition:

- In statistics, a **meta-analysis** combines the results of several studies that address a set of related research hypotheses. In its simplest form, this is normally by identification of a common measure of effect size, for which a weighted average might be the output of a meta-analyses. Here the weighting might be related to sample sizes within the individual studies.
- Meta-analyses are often, but not always, important components of a *systematic review* procedure. Here it is convenient to follow the terminology used by the Cochrane Collaboration[1], and use "meta-analysis" to refer to statistical methods of combining evidence, leaving other aspects of 'research synthesis' or 'evidence synthesis', such as combining information from qualitative studies, for the more general context of systematic reviews.

General roadmap:

- Formulation of the problem
  - Outcome selection, e.g. comparison of drug A vs. placebo for treatment of disease X
    - Identification of appropriate statistic
      - Difference in two proportions
      - Log relative risk
      - Log Odds ratio
      - Difference in two means
      - Effect size: difference in two means / pooled variance
  - Study selection criteria, e.g. randomized trials, prospective cohorts, etc.
    - Will unpublished studies be included to avoid publication bias?
- Search of literature
  - Typically includes calendar date restrictions, specification of searched databases, etc.
- Model selection for pooling of results

Model Selection: Fixed Effects Meta-regression

- Without study predictors:

$$y_i = \theta + \varepsilon_i$$

y_i *is statistic from study* i

θ *is true effect*

ε_i *is a measure of within* $-$ *study uncertainty*, $\varepsilon_i \sim N(0, {\sigma_i}^2)$

NOTE: no between study variation!

- With study predictors:

$$y_i = \theta + \beta_1 x_{i1} + \cdots + \beta_p x_{ip} + \varepsilon_i$$

where x_{i1} ... x_{ip} *are study level characteristics*

Model Selection: Random Effects Meta-regression

- Without study predictors:

$$y_i = \theta + b_i + \varepsilon_i = \theta_i + \varepsilon_i$$

$y_i\ is\ statistic\ from\ study\ i$

$\theta\ is\ average\ effect\ across\ the\ population\ of\ all\ studies$

$\theta_i\ is\ the\ true\ effect\ for\ study\ i, \theta_i \sim N(\theta, \tau^2) or\ b_i \sim N(0, \tau^2)$

$\varepsilon_i\ is\ a\ measure\ of\ within-study\ uncertainty, \varepsilon_i \sim N(0, {\sigma_i}^2)$

- With study predictors:

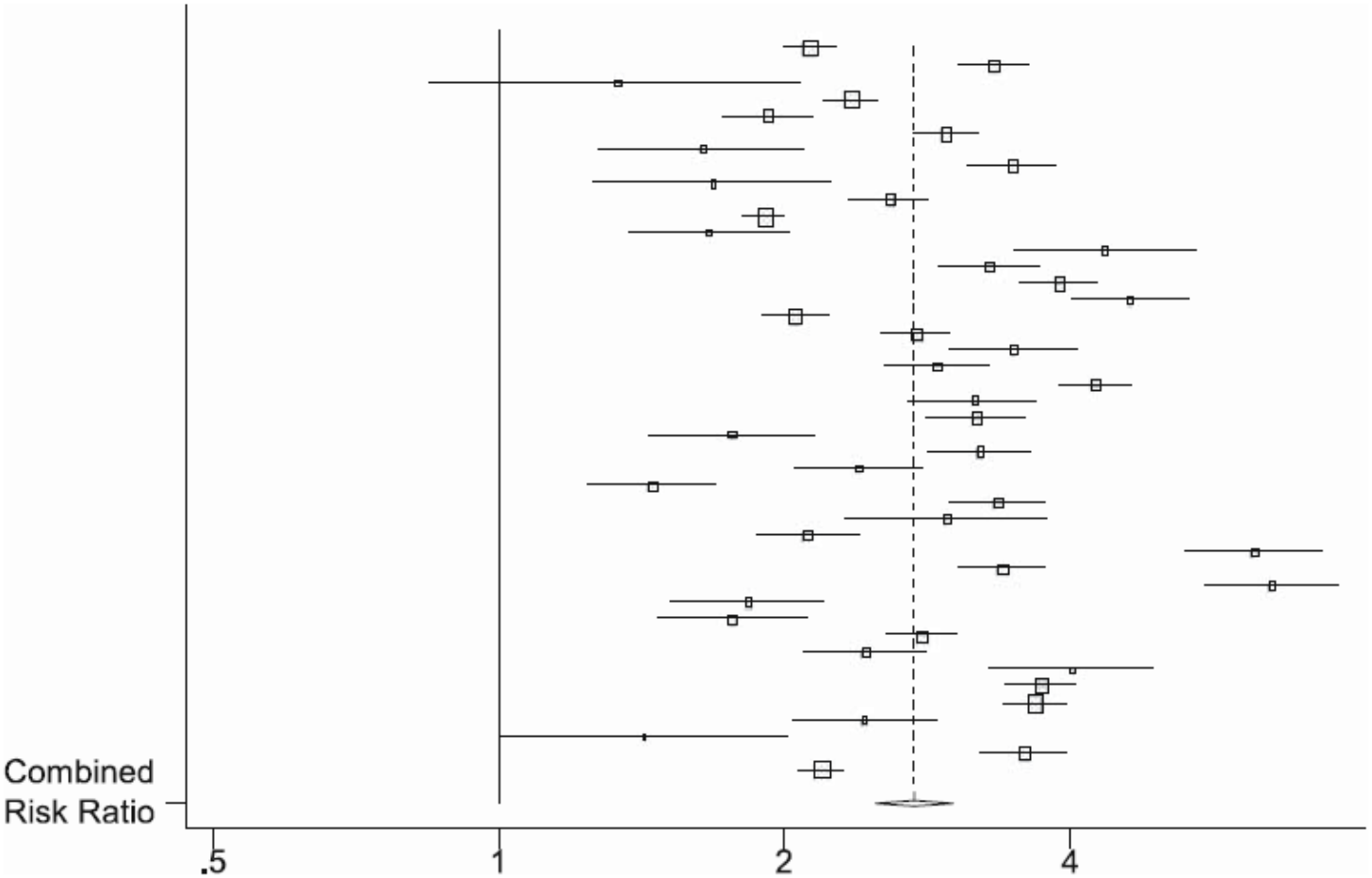
$$y_i = \theta + b_i + \beta_1 x_{i1} + \cdots + \beta_p x_{ip} + \varepsilon_i$$

$$y_i = \theta_i + \beta_1 x_{i1} + \cdots + \beta_p x_{ip} + \varepsilon_i$$

Common presentation: Forest Plot

Figure 1

Forest plot of risk ratios comparing percentage poor in program to percentage poor in target catchment area



Miech, et al The Journal of Behavioral Health Services & Research 35:3 July 2008

Meta-analysis

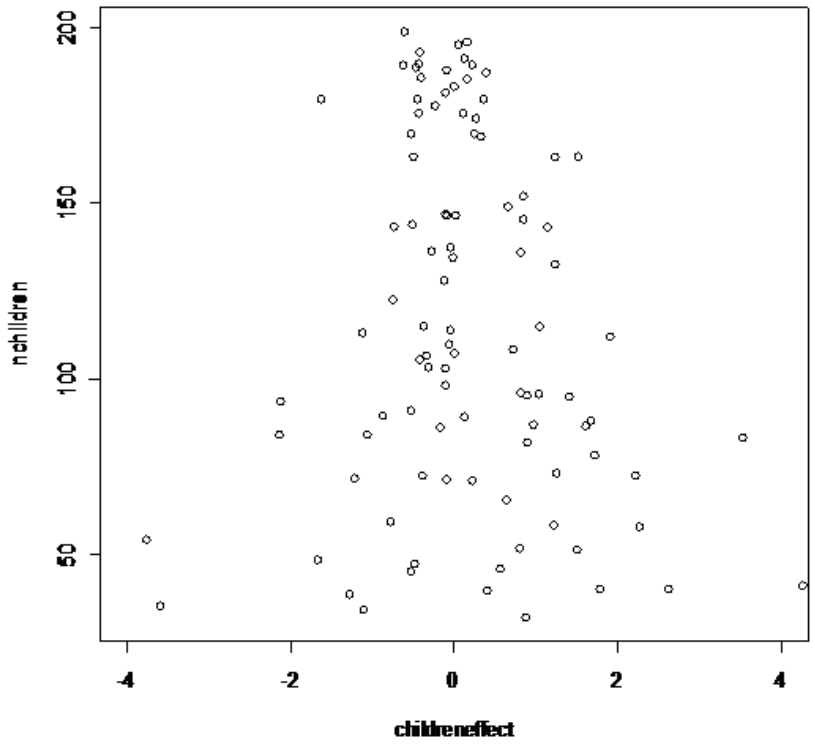
Advantages of meta-analysis (eg. over classical literature reviews, simple overall means of effect sizes etc.) include:

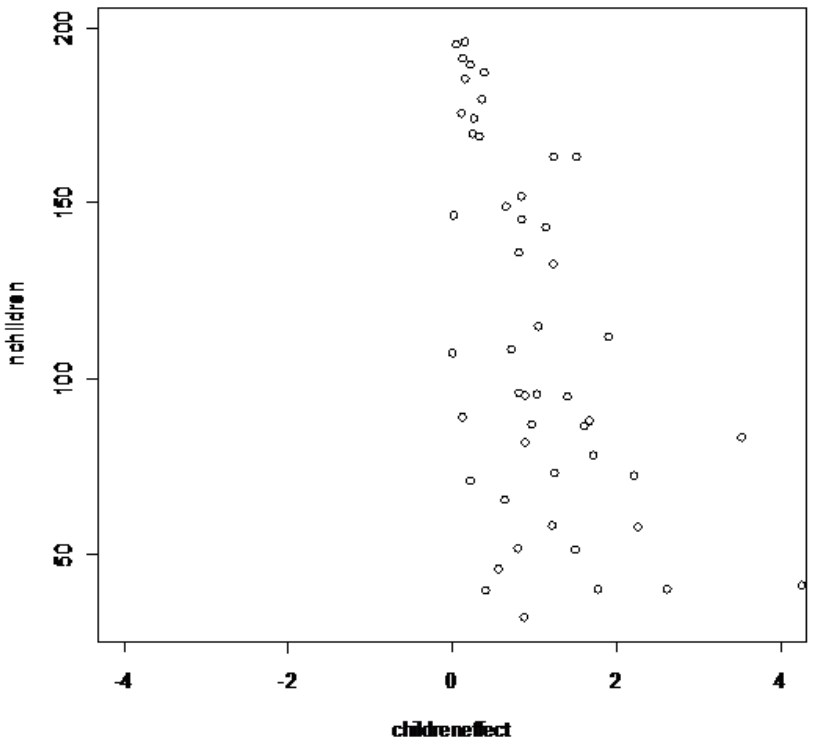
- Estimates two sources of variation: within study effects due to diversity of participants, measurement error,… and among study effects due to variation if treatment efficacy among studies.
- Derivation and statistical testing of overall effect size parameters from related studies
- Generalization to the population of studies
- Ability to control for between-study variation
- Including moderators to explain variation in effect sizes
- Higher statistical power to detect an effect than in ‘n=1 sized study sample’
- Deal with information overload: the high number of articles published each year.
- It combines several studies and will therefore be less influenced by local findings than single studies will be.
- Makes it possible to show if a publication bias exists.

Weaknesses of Meta-analysis

- Not an original data generation, rather a statistical evaluation of available scientific studies
- Sources of biases may not be controlled
  - i.e. meta-analysis of biased studies gives unbiased estimate of biased effect!
- Publication bias
  - Published effect sizes represent a biased sample of all studies
    - It is much harder to get “negative” studies published and impossible to know exactly how many total studies have been done.
  - This can be visualized with a funnel plot which is a scatter plot of sample size and effect sizes.
  - Some statistical tests available for testing for bias

Publication Bias





Examples

- Miech et al (2008)
  - Interesting meta-analysis demonstrating that a community based mental health program disproportionately reaches under-represented youth
  - This program is then positioned to provide useful targeted interventions within this group
- Ziegler-Graham et al (2008)
  - Meta-analysis of incidence rates for Alzheimer's disease
  - Primary focus was to understand variation by gender and geographic location
  - Nested within larger project to forecast global prevalence of Alzheimer's disease

Regular Article

The Potential to Reduce Mental Health Disparities Through the Comprehensive Community Mental Health Services for Children and Their Families Program

Richard Miech, PhD, MPH
Melissa Azur, PhD
Tracy Dusablon, MHS
Keri Jowers, M.Ed.
Amy B. Goldstein, PhD
Elizabeth A. Stuart, AM, PhD
Christine Walrath, PhD, MHS
Philip J. Leaf, PhD

The Journal of Behavioral Health Services & Research *35:3* *July 2008*

Introduction

Disparities in children's mental health are present across socioeconomic strata and race–ethnicity. Specifically, children and adolescents who are poorer are more likely to have serious emotional difficulties,[1–4] as are Black and Hispanic children in comparisons to Whites.[1] Both the National Institute of Mental Health and, more broadly, the National Institutes of Health prioritize the reduction of disparities in health, including mental health;[5] in fact, the National Institutes of Health ranks disparity reduction as one of its top three goals.[6] However, despite intentions to reduce known disparities in child and adolescent mental health, national programs explicitly designed to reduce them are lacking.

This paper examines the potential of the federally funded Comprehensive Community Health Services for Children and Their Families Program (hereafter referred to as the Children's Mental Health Initiative (CMHI)) to work to meet this goal, though not designed expressly for this purpose. The analysis examines whether the funded CMHI communities successfully reach disadvantaged youth by comparing the demographics of CHMI enrollees to the demographics of their respective catchment areas. If the CMHI communities disproportionately serve children who are poorer and in minority groups, then it may actually be acting as one of the largest and most influential programs to reduce health disparities, to the extent that it successfully treats serious emotional disorders among its clients.

Data and Methods

- National evaluation of the program
  - Roughly 45 sites
  - Each site provided data on demographics including race, income, gender among enrolled individuals
- US census 2000
  - Corresponding to each site a catchment service area was identified
  - Extracted distribution of race, income and gender from population within the catchment service area

- Meta-analysis to compare the distribution of characteristics among the enrolled individuals and the general population

Statistical target

- Parameter of interest
  - Risk ratio: p_1/p_2
  - p_1: proportion of children in the program with characteristic X
  - p_2: proportion of people in the catchment area with characteristic X
  - Values greater than 1 indicate children with characteristic X are more represented in the program than in the population

Statistical uncertainty

The standard error of each risk ratio—which is necessary to compute a 95% confidence interval—is calculated using the equation:

$$\sqrt{\frac{1-p1}{p1 \times n1} + \frac{1-p2}{p2 \times (n2/6)}}$$

where $p1$ is equal to the percentage of youth at the program level, $n1$ is the sample size of the program, $p2$ is the percentage of youth at the catchment area level (from Census data), and $n2$ is the population size of the catchment area (from Census data). The value of $n2$ is divided by 6 because the weighted, population estimates from the Census used in this analysis come from a one-in-six sample, and therefore the sample size used to generate the weighted estimates is six times smaller the population size reported by the Census.

Fixed or Random Effects Meta-Regression

Meta-analysis requires a decision whether to use a fixed or random effects model. A fixed effect model would work on the assumption of a single, "true" risk ratio that is the same across all programs, with any variation attributable to measurement error. A random effect model allows the true, underlying risk ratios to vary across programs. Our assumption is that different CHMI programs have different abilities to recruit disadvantaged populations, and consequently we chose to run and report results from a random effects model.

Results

Figure 1

Forest plot of risk ratios comparing percentage poor in program to percentage poor in target catchment area

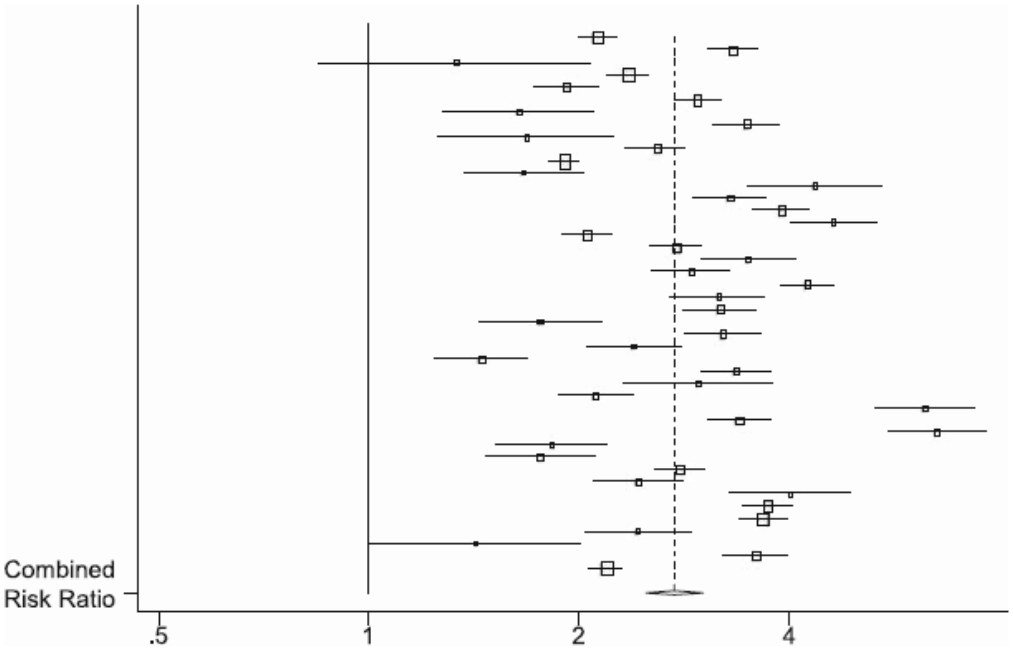
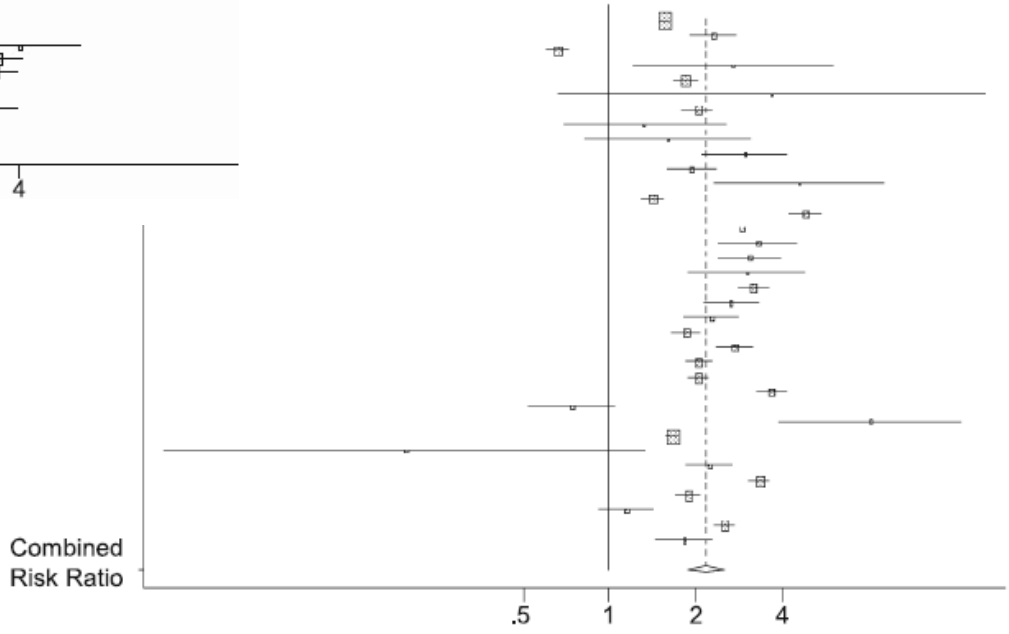


Figure 2

omparing percentage Black youth in program to percentage Black youth



Forecasting the Global Burden of AD

- Ron Brookmeyer, Sarah Gray, and Claudia Kawas. "Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset." *American Journal of Public Health* 88.9 (1998): 1337-1342.
- 2006: Brookmeyer approached by Elan and Wyeth Pharma (then)
- Goals:
  - Project global prevalence of AD
  - Allow for assessment of potential impact of preventative or therapeutic interventions

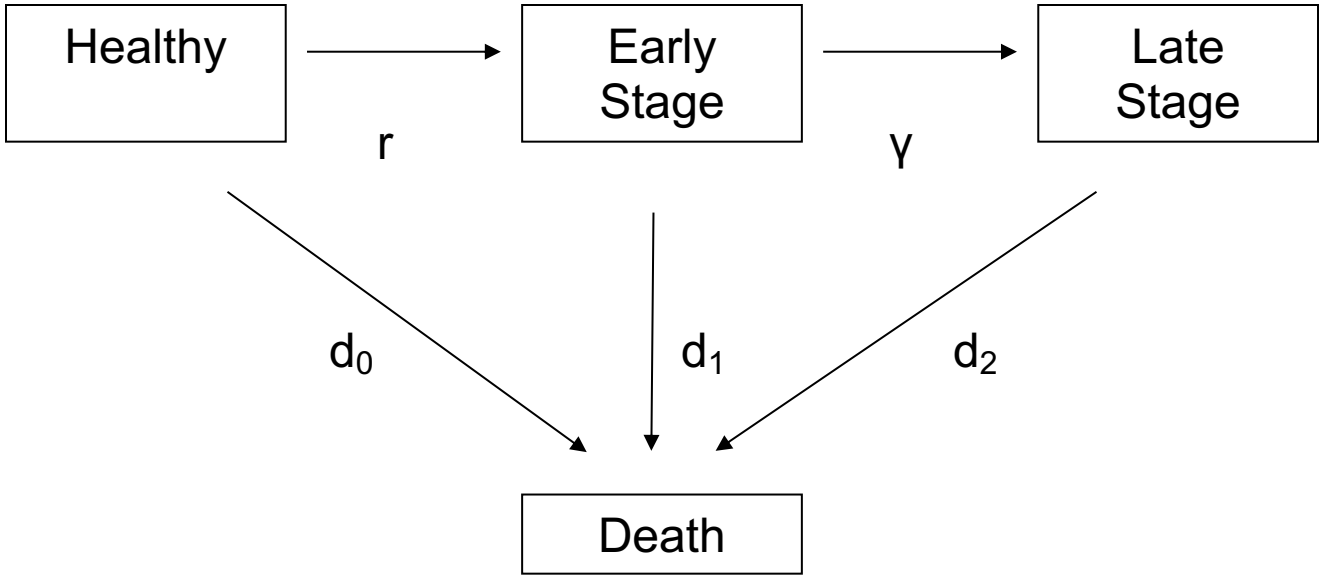
Strategy

- Incidence to Prevalence approach
  - Obtain prevalence rate for each age, gender, region and calendar year
  - Apply these rates to population projections

- Population projections were obtained from:
  - UN population projections (http://esa.un.org/unpp/index.asp?panel=2)
  - US Census Bureau

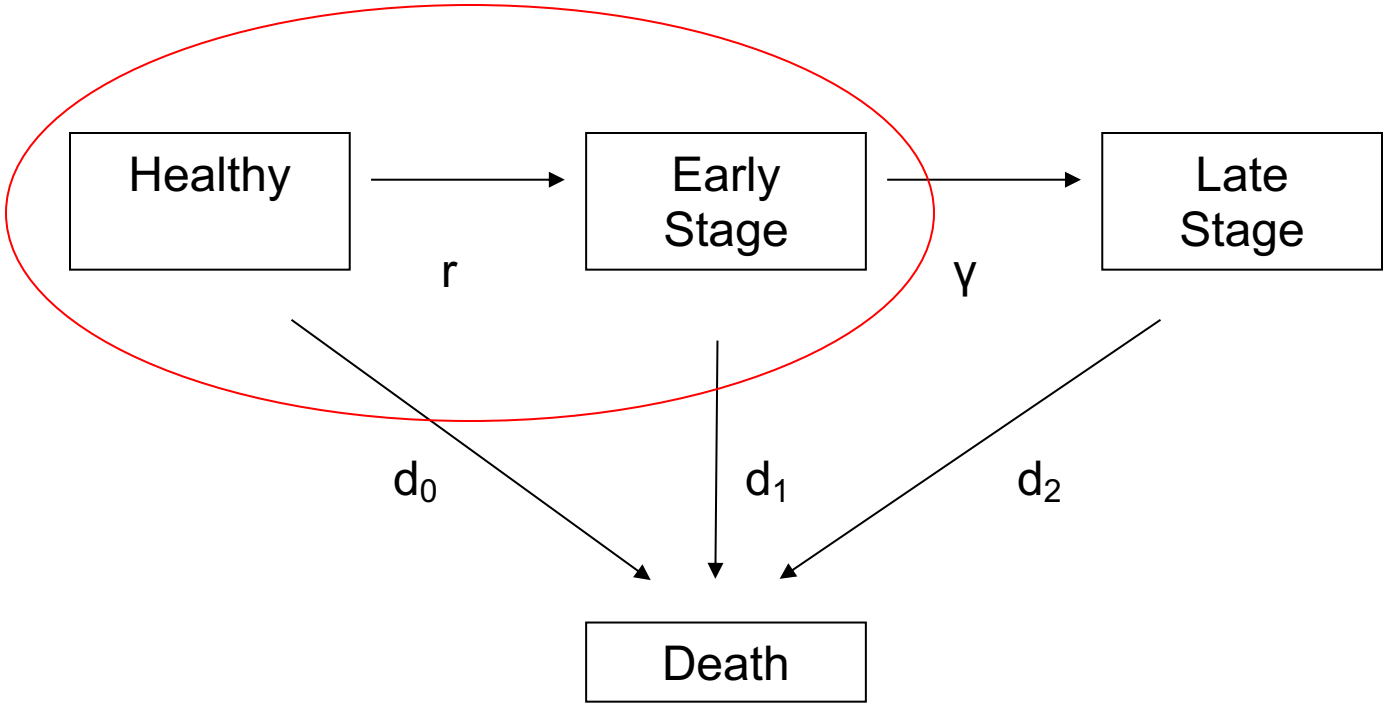
  (http://www.census.gov/population/www/projections/natdet-D1A.html)

Multi-state Disease Model



- The intensities or transition probabilities may depend on age, gender and calendar year
- This will be defined in review of each intensity

Multi-state Disease Model



- Systematic review of worlds literature on cohort studies of AD
- Must have provided age-specific incidence rates for at least two age ranges
- Update of meta-analysis performed by Jorm and Jolley (1998)

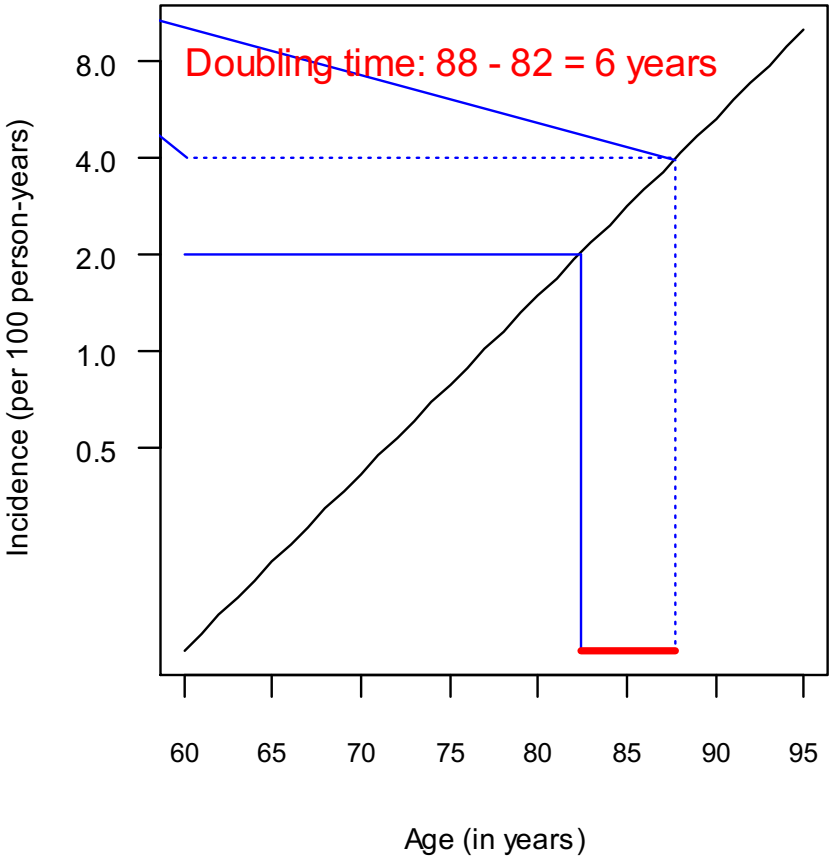
Incidence Rates

- 27 studies identified
    - 26 provided overall incidence rates
    - 18 provided incidence rates by gender
    - Geographic regions
        - 11 North American
        - 10 European
        - 6 from other locations:
            2 Japan
            1 Nigeria, Taiwan, India and Brazil

- Assessment of
    - Evidence of differences by geographic region
    - Evidence of differences by gender

Doubling Time

- Doubling time: age in years for the age-specific incidence rate to double



Statistical Methods

- Simple regression approach:
  - Data:
    - $\log(incidence\ rate_{ij})$: log incidence rate for study i in age range j
    - $midage_{ij}$: mid-point of age range for study i in age range j
  - Fit a study-specific linear regression model of:

$$\log(incidence\ rate_{ij}) = \beta_{0i} + \beta_{1i}(midage_{ij} - 60) + \varepsilon_{ij}$$

    for each study *i*
  - Calculate the average intercept and slope across all studies, use this as our pooled estimates

Statistical Methods

- Random effects approach:
  - Data:
    - y_{ij}: number of incident cases of AD for study i during age range j
    - PY_{ij}: number of person years of observation for subjects from study i during age range j
  - Fit a Poisson mixed model

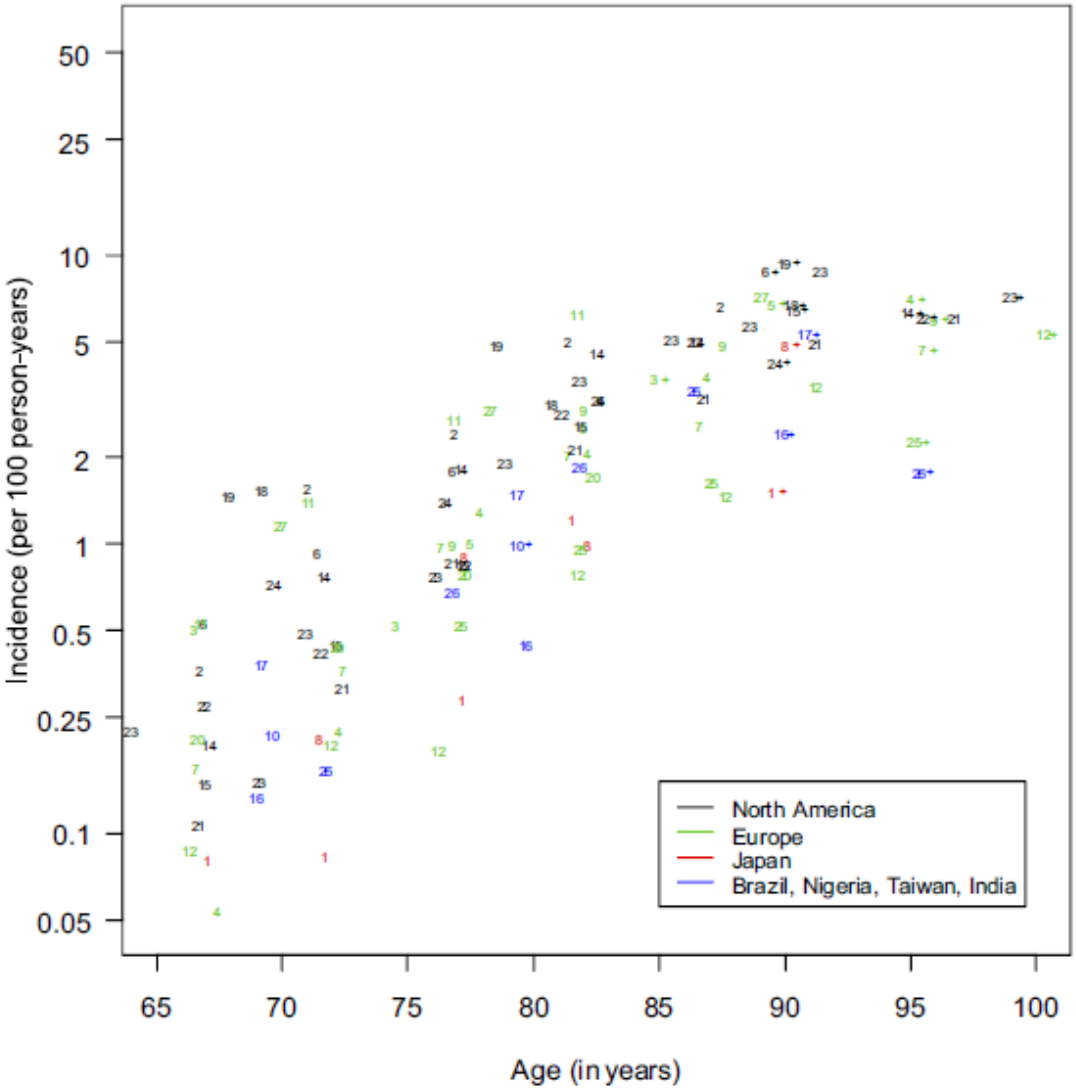
$$y_{ij} \sim Poisson(\lambda_{ij} PY_{ij})$$

$$\log\left({}^{y_{ij}}/_{PY_{ij}}\right) = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})(midage_{ij} - 60)$$

$$\begin{pmatrix} b_{0i} \\ b_{1i} \end{pmatrix} \sim MVN\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{bmatrix} {\sigma^2}_0 & \sigma_{01} \\ \sigma_{01} & {\sigma^2}_1 \end{bmatrix}\right)$$

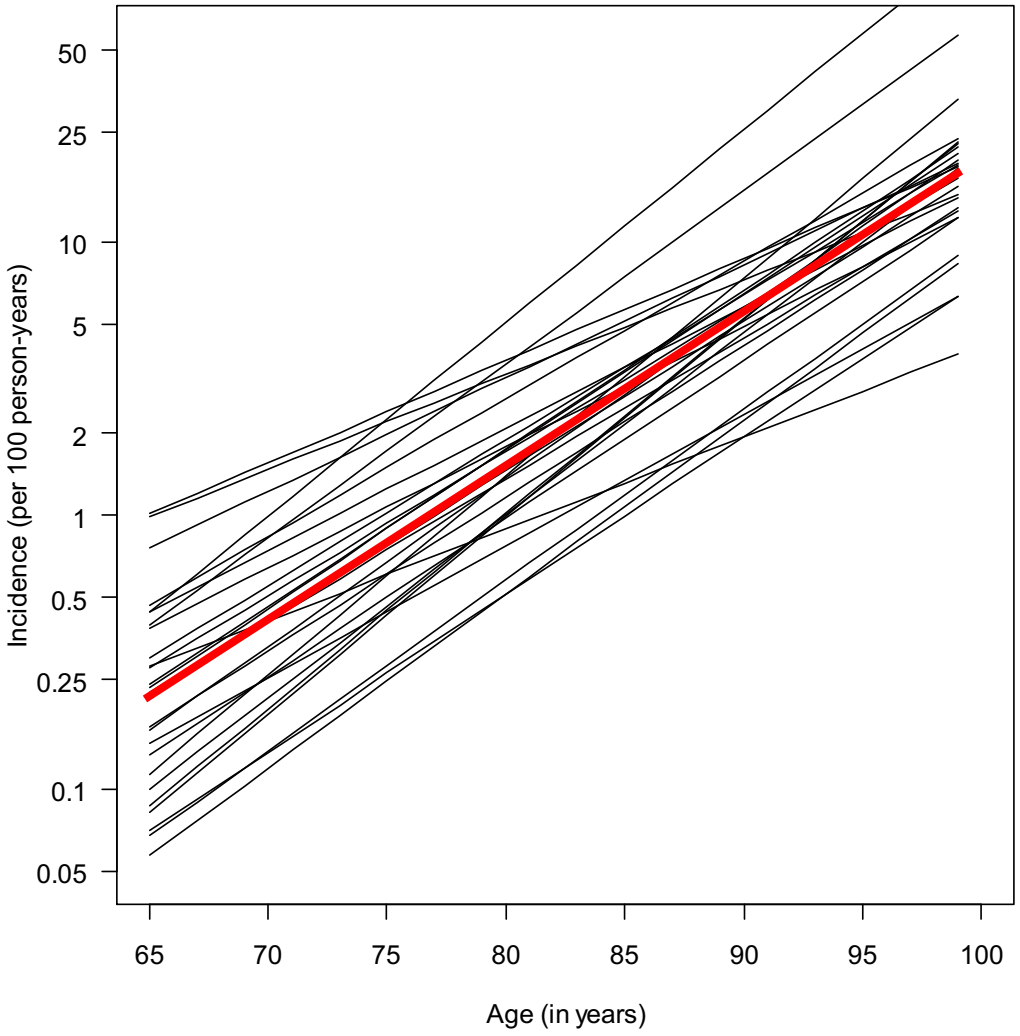
Results

Incidence of Alzheimer's disease (per 100 person-years) vs. age



Results: Simple Regression Approach

For each study, the estimated linear function of log(incidence) vs. age



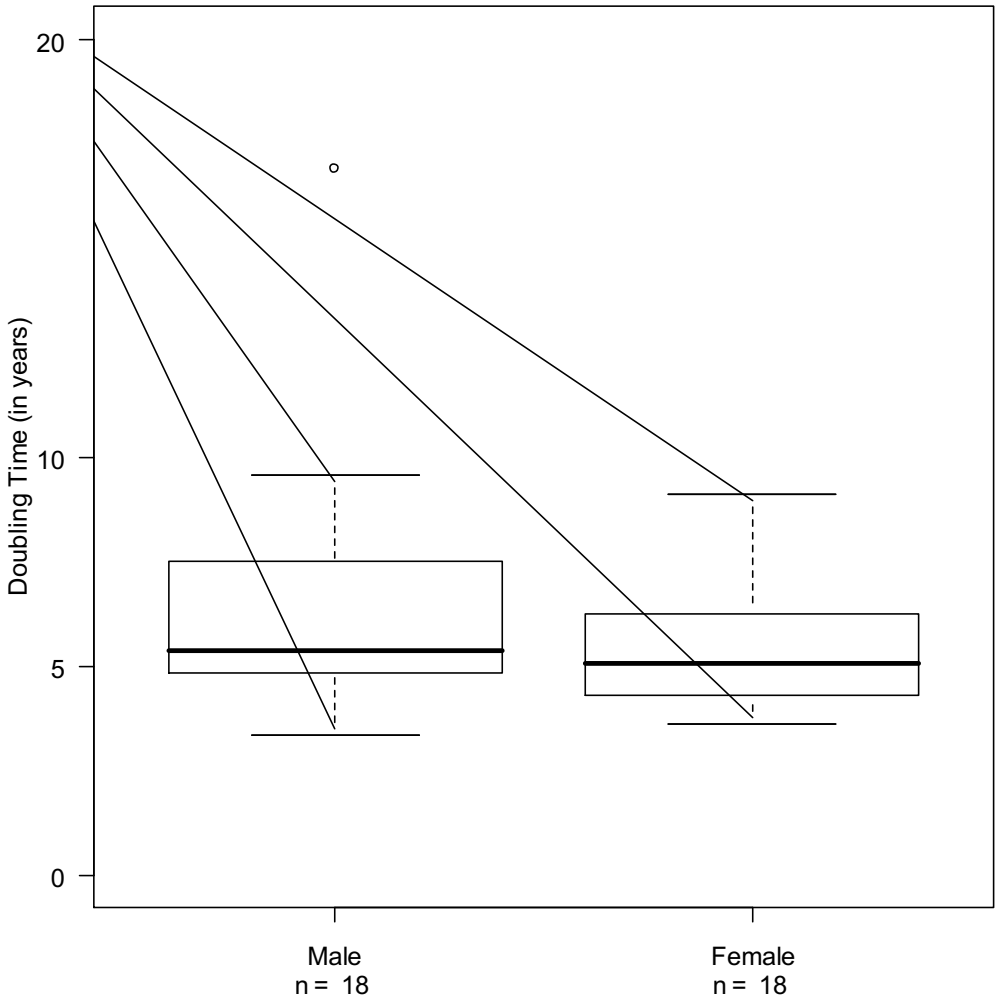
log(incidence) =
2.146 + 0.1271(age-60)

Average doubling time of AD is 5.5 years.

The average incidence of AD among 80-year-olds is 1.48% per year.

Results

Comparison of doubling times by gender using paired t-tests (p = 0.31)



Results: Random Effects Approach

- 18 studies provided
  - Number of cases and person-years
  - Incidence rate and standard error

```
gllamm alln allagem_c if allagem>=65, i(studyno) nrf(2) eqs(int slope) family(poisson)
link(log) offset(logpy) ip(m) adapt


log likelihood = -285.31719
------------------------------------------------------------------------------
        alln |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   allagem_c |   .1264482   .0066139    19.12   0.000      .1134852    .1394112
       _cons |  -6.691924   .2093382   -31.97   0.000    -7.102219   -6.281628
       logpy |   (offset)
------------------------------------------------------------------------------

Variances and covariances of random effects
------------------------------------------------------------------------------
 ***level 2 (studyno)

    var(1): .67127602 (.27860665)  -> SD: 0.82
    cov(2,1): -.01371856 (.00755401) cor(2,1): -.773674

    var(2): .00046838 (.00024696)  -> SD: 0.02
------------------------------------------------------------------------------
```

Interpretation

- Intercept: log incidence rate per person year among persons aged 60
  - exp(-6.69) = 0.0012
- Based on the random intercept variance:
  - We expect that 95% of the studies will have incidence rates (per person year) among 60 year olds that range between
    - exp(-6.69-2x0.82) = 0.00024
    - exp(-6.69+2x0.82) = 0.0064
- So we expect that 95% of the studies will have incidence rate (per 100 person years) among 60 year olds that range between 0.024 and 0.64

Interpretation

- Slope for age: log relative incidence of AD per additional year of age
  - exp(0.126) = 1.13
- Based on the estimated variation in the log relative incidence, we would expect that 95% of the studies will have relative risks of AD that fall between:
  - exp(0.126-2*0.02) = 1.09
  - exp(0.126+2*0.02) = 1.18
  - NOTE: not much variation in slopes
- What about the correlation between random intercept and slope? -0.77?

Results: Random Effects Approach

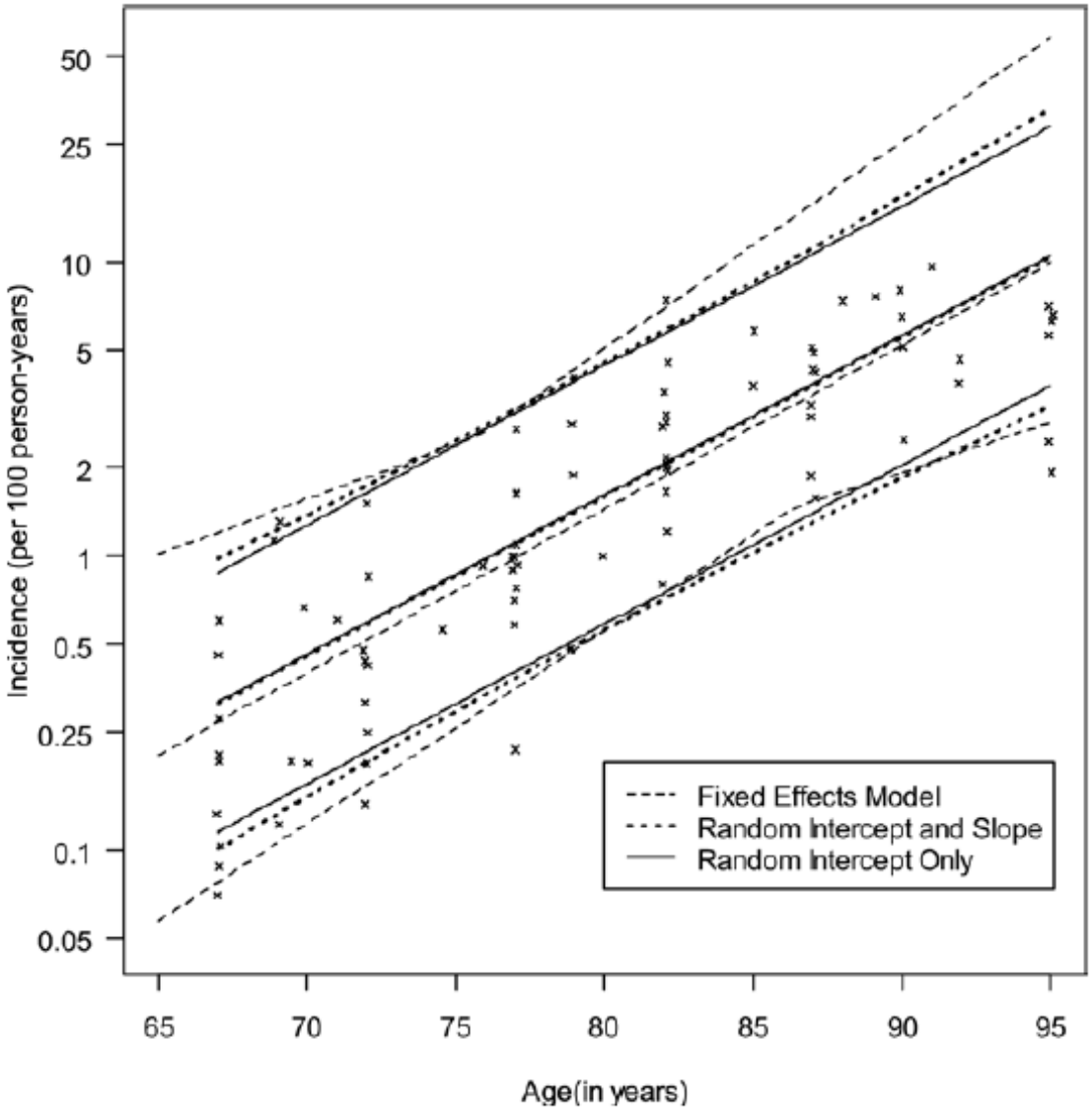
```
gllamm alln allagem_c if allagem>=65, i(studyno) family(poisson) link(log)
offset(logpy) ip(m) adapt


log likelihood = -295.93725
------------------------------------------------------------------------------
        alln |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   allagem_c |    .123553   .0032726    37.75   0.000     .1171389    .1299671
       _cons |  -6.629993   .1487614   -44.57   0.000     -6.92156   -6.338426
       logpy |   (offset)
------------------------------------------------------------------------------

 Variances and covariances of random effects
------------------------------------------------------------------------------
***level 2 (studyno)

    var(1): .29033086 (.10529323)  -> SD:  0.54
------------------------------------------------------------------------------
```

Results: Random Effects Approach



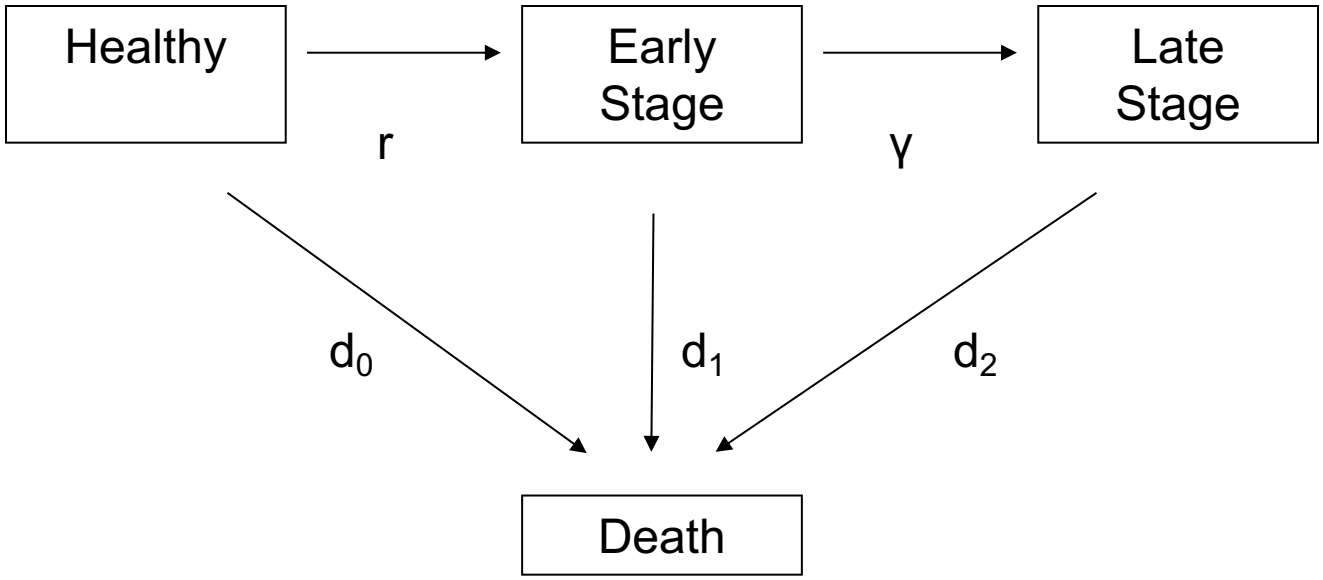
Incidence Rates: Conclusions

- Doubling times of Alzheimer's disease incidence rates are remarkably similar by region and gender -> same thing as thinking about slopes!

- There is heterogeneity in incidence rates across studies but no strong evidence to suggest region (maybe Asia) or gender differences.

- We used the “average” fitted line that does not depend on gender or region.

Multi-state Disease Model



Worldwide Variation in the Doubling Time of Alzheimer's Disease Incidence Rates. **Ziegler-Graham, Johnson, Arrighi and Brookmeyer. *Alzheimer's and Dementia* (2008)**

Forecasting the Global Burden of Alzheimer's Disease. **Brookmeyer, Johnson, Ziegler-Graham and Arrighi, *Alzheimer's and Dementia* (2007)**

Modeling the Effect of Alzheimer's Disease on Mortality. **Johnson, Ziegler-Graham, and Brookmeyer, *International Journal of Biostatistics* (2007)**

http://www.biostat.jhsph.edu/project/globalAD/index.htm

Lecture 14 Summary

- Meta-analysis
  - Tool used to summarize a body of scientific knowledge relating to an association of interest
    - Be aware of “trash-in trash-out”
    - Study quality super important!
    - Publication bias is a major issue
  - Analysis strategy
    - Natural place to apply mixed models
    - Allows us to incorporate the within study and between study variation
- Considered a couple of non-standard examples to demonstrate the use of mixed models in more general settings.