Comparative Effectiveness Based on Observational Data: An Overview

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BASS 2012

Outline

I. Introduction

II. Standard Comparative Effectiveness Analyses Based on Propensity Scoring

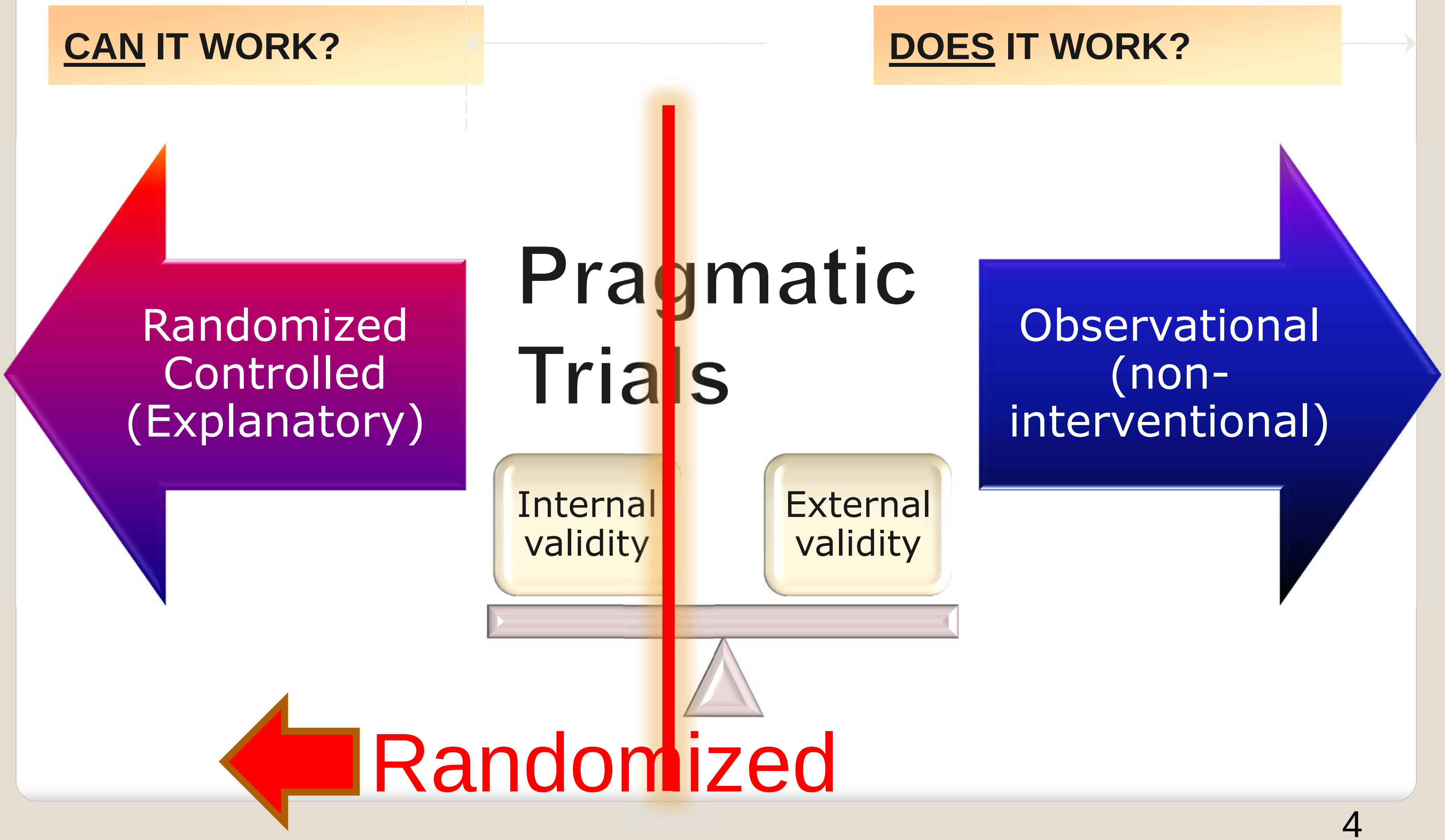
III. Improvements in Bias Adjustment

IV. Improvements in Sensitivity Analyses (unmeasured confounding)

Part I. Introduction

- Need for Observational Research
- Problems with Bias
- Guidances
- Motivating Example

Design Continuum



CAN IT WORK?

DOES IT WORK?

Randomized Controlled (Explanatory)

Pragmatic Trials

Observational (non-interventional)

Internal validity

External validity

Randomized

Growing Use of Observational Data

- Data Sources
  - Prospective: Trials / Registries / Surveys
  - Retrospective: Insurance Claims, EMRs

- Practicalities
  - Large N, Low Cost, Immediate availability, impracticality of RCTs

- Usual Care Data are of Interest:
  - Better data for: Adherence/Persistence, cost, resource utilization, concom. meds, switching, PROs, treatment patterns, epidemiology, characteristics of populations ….
  - Generalizability

The Observational Research Problem

Selection Bias

- Physicians/patients did not select treatment ‘at random’ but based on a variety of factors – so Groups A and B differ in some aspects other than treatment

Confounders

- A variable is a Confounder if it is associated with both treatment selection and outcome

The Observational Research Challenge

Selection Bias

- Physicians/patients did not select treatment ‘at random’ but based on a variety of factors – so Groups A and B differ in some aspects other than treatment

Confounders

- A variable is a Confounder if it is associated with both treatment selection and outcome

Measured: Information is collected within the study and statistical adjustment is possible

Unmeasured: Information on the confounder is not available from the study

RCTs vs Observational Studies

- With randomization – standard methods produce estimation of causal treatment effects

- Without randomization (observational) – due to selection bias - standard methods produce only ‘associations’ and not ‘causal effects’ ……… unless selection bias is appropriately controlled

Lower Hiearchy of Evidence for Observational Research

Basic Assumptions for Causal Inference

Propensity Score (or other) adjustments can provide for estimates of the causal group differences under the following assumptions:

- No Unmeasured Counfounders
  - All variables related to both outcome and treatment assignment are included
- Positivity

  $0 < P(Z=1|X) < 1$ for all X

  {"sufficient overlap" or "no perfect confounding"}
- Correct Statistical Models

Controversies with use of Observational Data for Comparative Effectiveness

- Lack of Replication
  - 80% Fail to Replicate or produce substantial less effect (Ionnidis 2005)
  - “Any claim coming from an observational study is most likely to be wrong.” – Observational effects were re-examined in RCTs (-5 for 12)
- Examples:
  - Matthews (2008) – “you are what your mother eats”
  - Szydo (2010) – Zodiac sign and Transplants
- Clash of Paradigms: Data mining with no multiplicity adjustment (Young 2009)

Controversies … (ctd)

- Biased Analyses
- Low on Hierarchy of Evidence
- Lack of Clear Standards
- Literature Survey (Pocock 2004) -- inadequacies in the analysis and reporting of epidemiological publications

Biggest Problem: Don’t know operating characteristics of such studies so how do we interpret and make decisions on such data?

Recent Guidance Documents

- PCORI
  - Draft Methodology Report
- STROBE
  - Von Elm et al 2007: 22 item checklist
- ISPOR Retrospective Research: Good Research Practices (2009)
  - Design and Reporting (Berger et al)
  - Mitigating Bias (Cox et al)
  - Analytic Methods (Johnson et al)
- GRACE
  - Dreyer et al (2010) (Good Research Practices in Comparative Effectiveness)

DIA Comparative Effectiveness Scientific Working Group

A non-competitive collaboration among staff from regulatory agencies, pharmaceutical and biotech companies, and academia to share ideas and advance the science of CER.

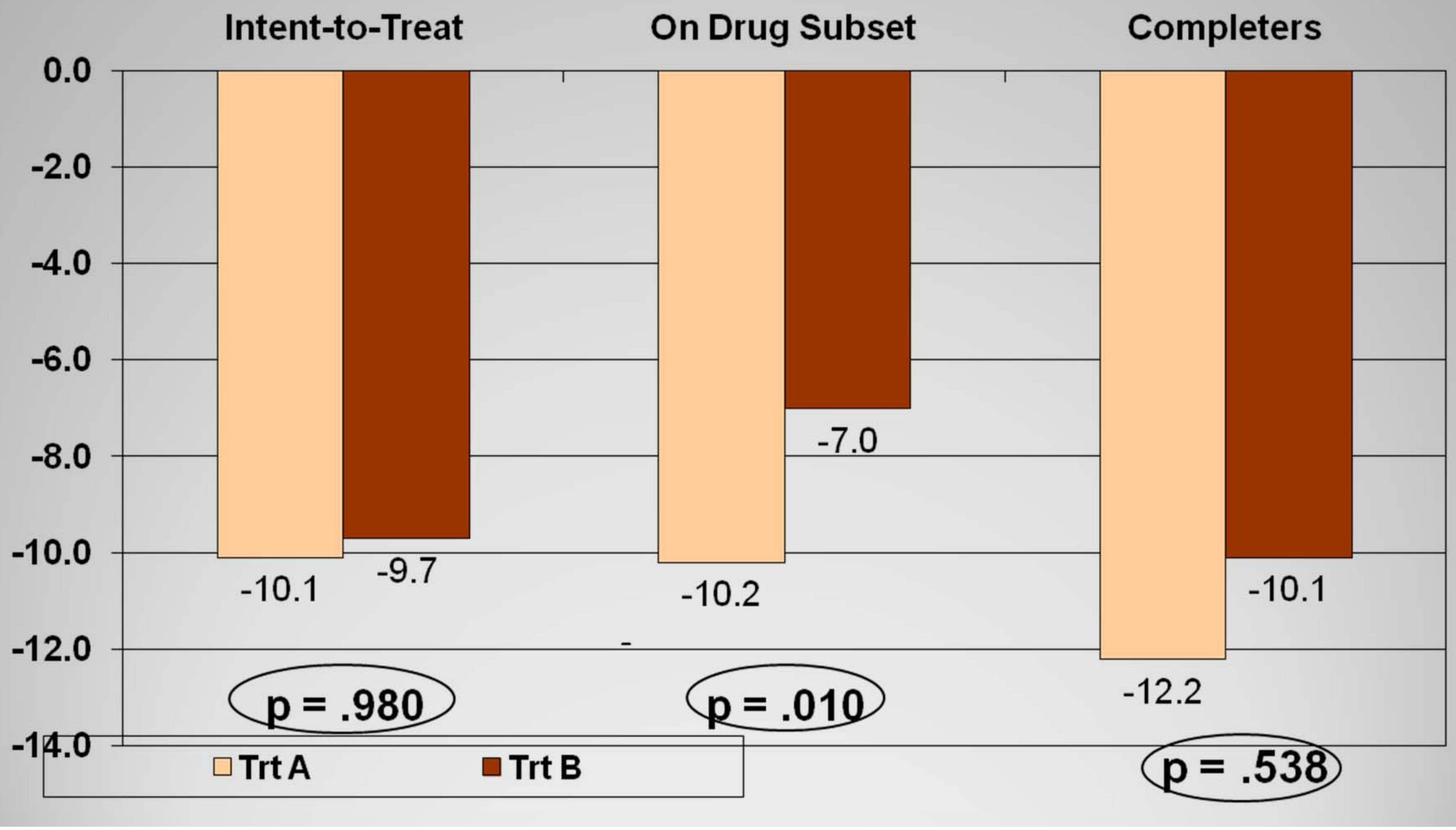
- Co-Chairs Matt Rotelli (Lilly) & Alan Menius (GSK)
- Goal: Improve the reliability and validity of CER used for making health care decisions.
- Subgroup (Lead: Cindy Girman): What Good Looks Like-- Emphasize Core Statistical Principles Under-represented in Current Guidance

Quality Implementation – Rubin's Key Points (2007)

- "Approximate RCTs"
  - Pre-specify the analysis plan / control multiplicity …
- Design with No outcome data in sight!
  - Key idea: conduct the design before ever seeing any outcome data; do it in such that future model-based adjustments will give similar point estimates
    - E.g. Propensity Stratification established with baseline data, then various regression models within strata on well balanced patients will give similar results

? What about Retrospective Observational Analyses?

Methods Matter! BPRS Changes



Faries et al. 2007

Part II – Standard Methods

- Propensity Scoring Approaches
- Implementation Steps
  - Defining Propensity Model
  - Confirming Balance
  - Analysis of cohort differences
  - Sensitivity Analyses
- Quality Implementation

Examples for Today

1. Simulated Observational Depression Study
   - Faries 2010: Analysis of Observational Health Care Data Using SAS
   - 5 covariates, N=100 per arm, Outcome: Remission
   - Goal: Compare Remission Rates between cohorts

2. Type 2 Diabetes Claims Database Analysis
   - Pawaskar et al J Med Econ. 2011
   - Goal: Compare 1-year Total Costs for those initiating various Type II Diabetes Medications
   - Data Source: Insurance Claims Database

Bias Adjustment Tools

- Regression Models
- Propensity Scoring
- Instrumental Variables
- Newer Techniques:
  - Entropy Balancing
  - Exact / Optimal Matching
  - Prognostic Scoring
  - Local Control
- Longitudinal Methods (MSMs)

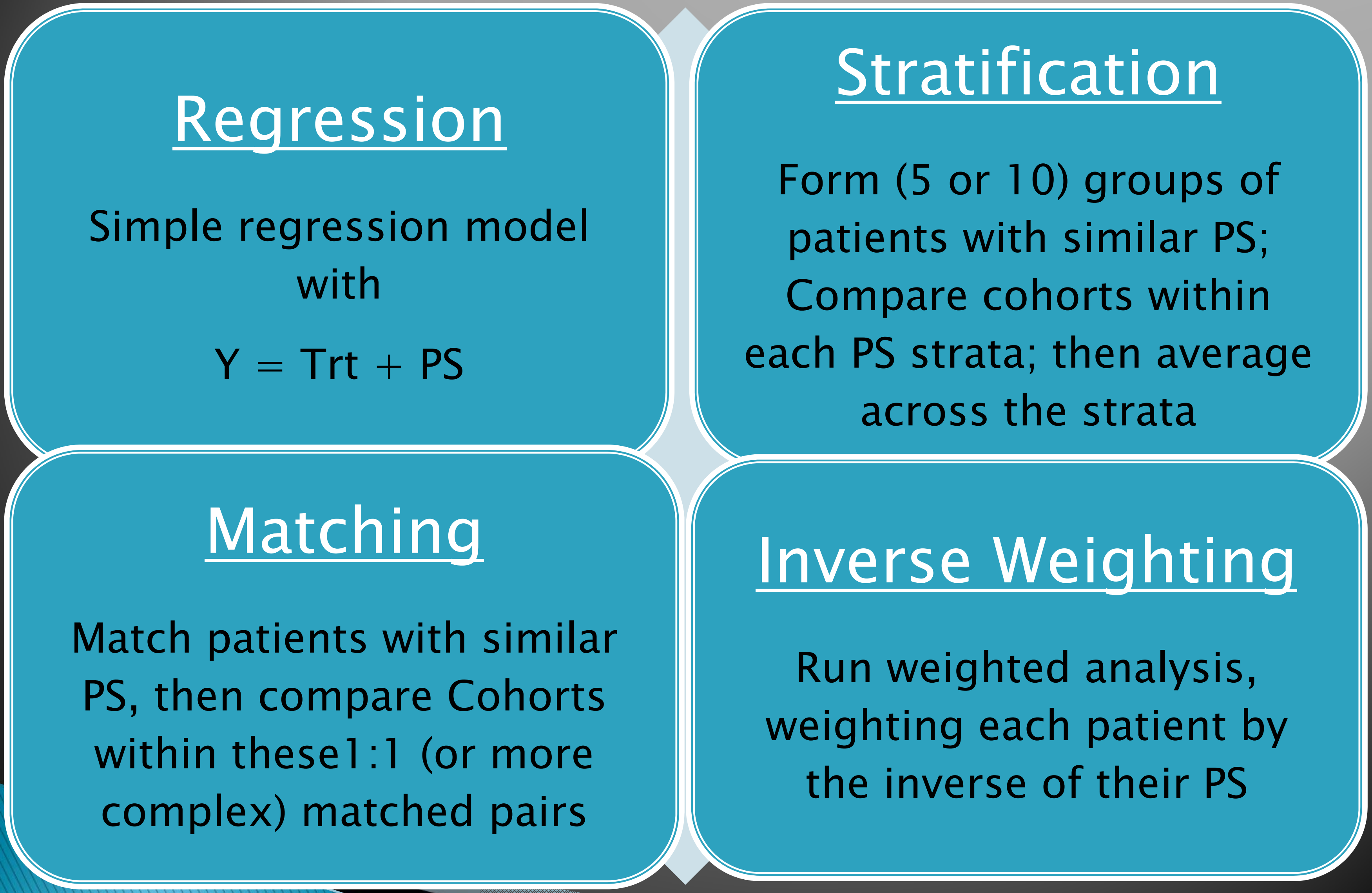
The Propensity Score (PS)

- PS – the conditional probability that a patient received treatment 1 given their set of observed baseline covariates X

- Usually computed via logistic regression

- Idea: compare treatments between patients with similar propensity scores to allow “apples to apples” comparisons (like ‘stratification’)
  - Practical even when there are a large number of covariates to adjust for unlike direct stratification

Basic Methods for Implementing PS



Regression

Simple regression model with

Y = Trt + PS

Stratification

Form (5 or 10) groups of patients with similar PS; Compare cohorts within each PS strata; then average across the strata

Matching

Match patients with similar PS, then compare Cohorts within these1:1 (or more complex) matched pairs

Inverse Weighting

Run weighted analysis, weighting each patient by the inverse of their PS

Which Method is Best??

No Gold Standard Recommendation

- Matching plus sensitivity analyses
  - best for bias control (Austin 2006)
  - Use sensitivity analysis from a method incorporating a larger proportion of the patients
- Stratification + Regression (Lunceford 2004, D'Agostino 2007)
  - PS Stratification is the main approach
  - Regression is used WITHIN each propensity score strata to account for residual imbalance within each strata ("Doubly Robust" method)

Why not just use Regression?

- Regression may be biased when there are large baseline differences between cohorts (as there typically are in observational research)

- Propensity Scoring

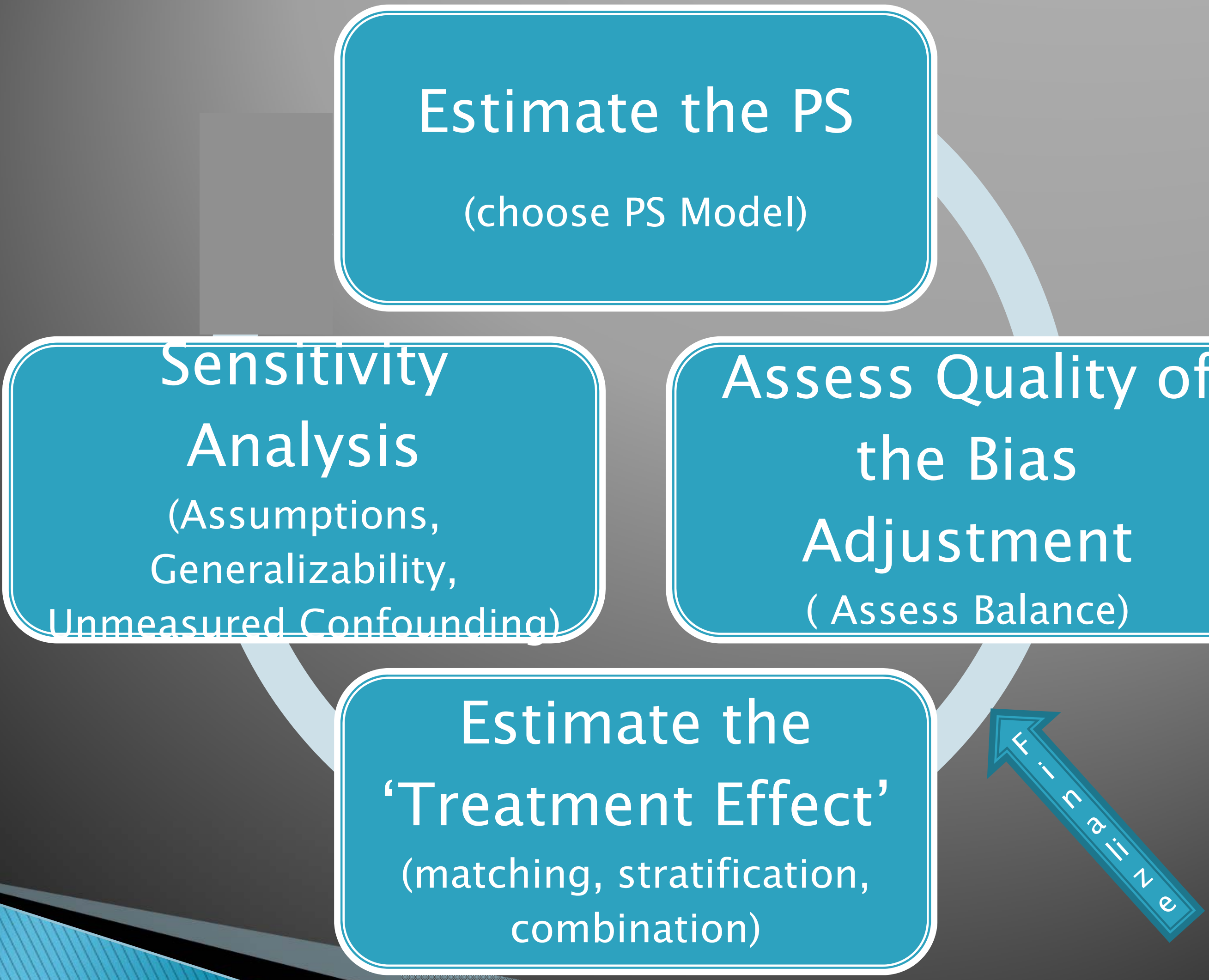
  - A more Robust analysis: makes less assumptions

  - Has a built in quality check: "regression analysis may not alert investigators to situations where the confounders do not adequately overlap …" (Shah 2005)

  - Allows more flexibility in modeling

  - Allows modeling to be done in a blinded fashion

Steps to a Quality Propensity Score Analyses



Estimate the PS

(choose PS Model)

Assess Quality of the Bias Adjustment

(Assess Balance)

Estimate the 'Treatment Effect'

(matching, stratification, combination)

Sensitivity Analysis

(Assumptions, Generalizability, Unmeasured Confounding)

10 Commandments of Choosing a Propensity Model

- I. Thou shalt examine covariates for collinearity
- II. Thou shalt value parsimony
- III. Thou shalt test predictors for statistical significance
- IV. Thou shalt have 10 times as many subjects as predictors
- V. Thou shalt carefully examine regression coefficients

Acknowledge:
Thomas Love

10 Commandments of Choosing a Propensity Model

- VI. Thou shalt perform bootstrap analyses to assess shrinkage
- VII. Thou shalt perform regression diagnostics and evaluate residuals
- VIII. Thou shalt hold out a sample for model validation
- IX. Thou shalt employ external validation on a new sample of data

10 Commandments of Choosing a Propensity Model

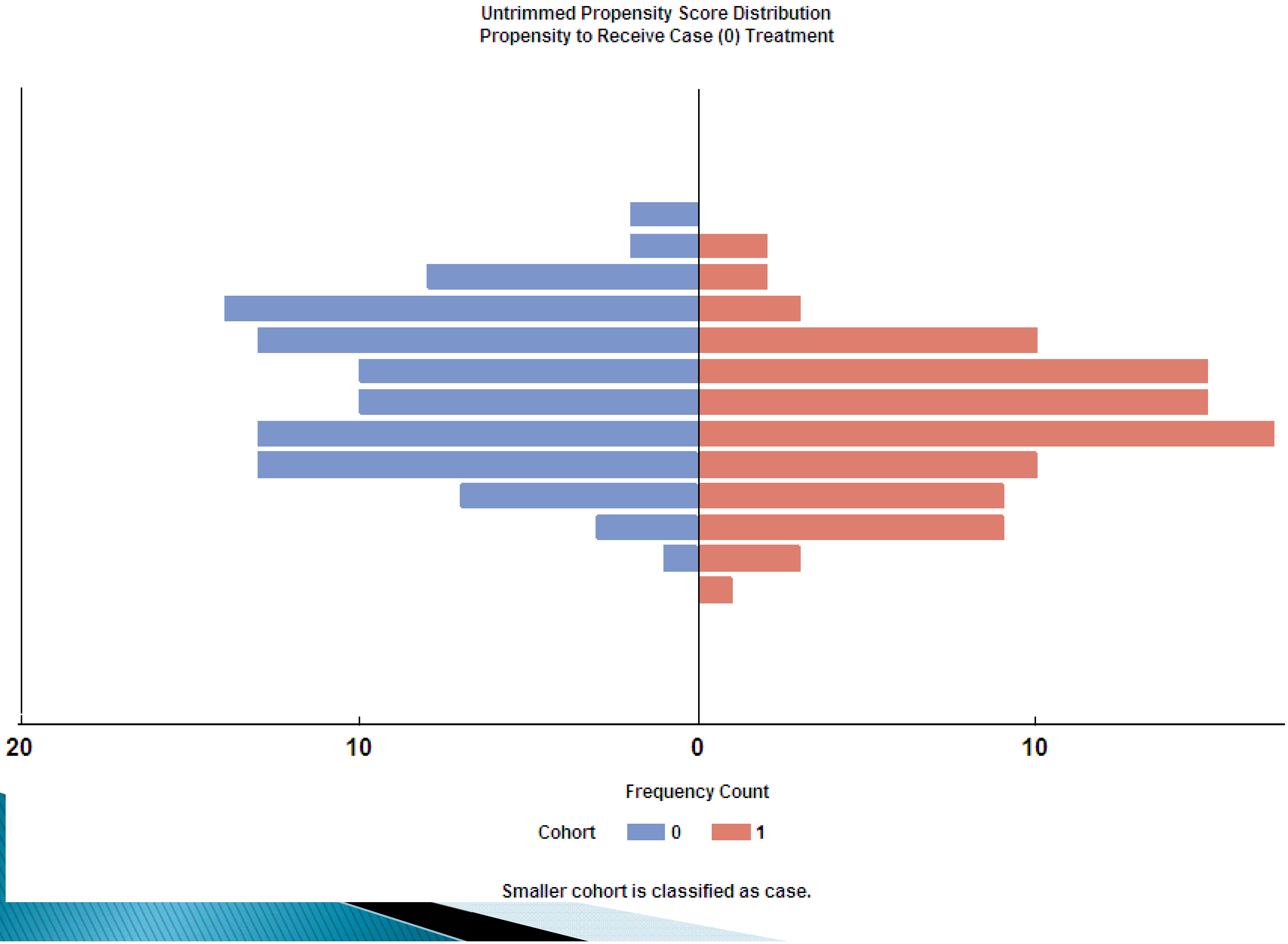
- **10th Commandment:**

Ignore the previous 9

Instead – simply ensure that the model adequately balances the covariates

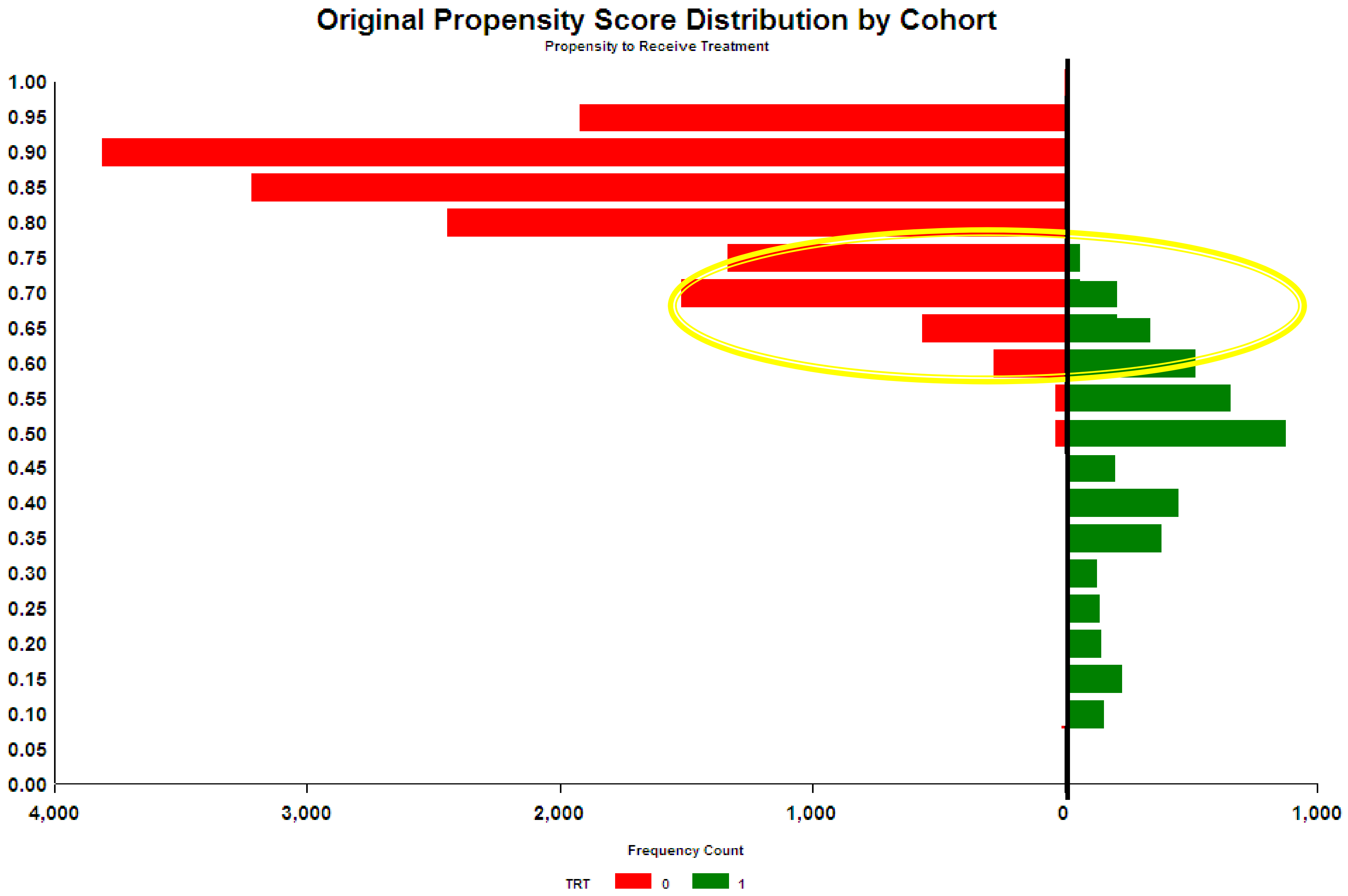
- *"the success of the propensity score modeling is judged by whether balance on pretreatment characteristics is achieved between the treatment and control groups …" (D'Agostino 2007)*

Depression Example: Distribution of Propensity Scores



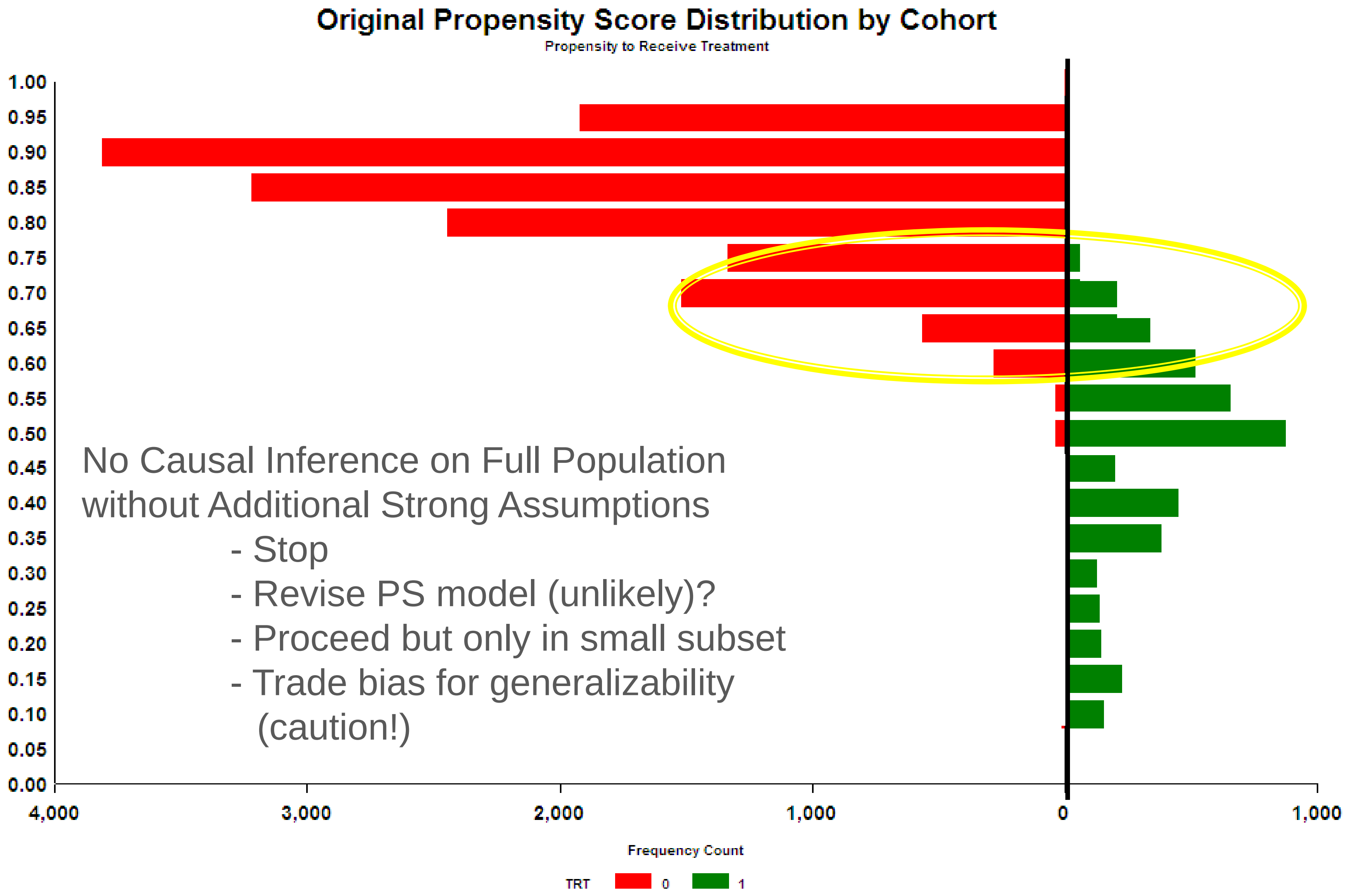
Example

What if Little Overlap?



Example

What if Little Overlap?



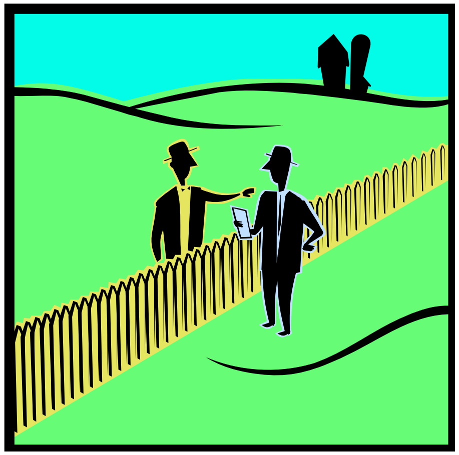
No Causal Inference on Full Population without Additional Strong Assumptions

- Stop
- Revise PS model (unlikely)?
- Proceed but only in small subset
- Trade bias for generalizability (caution!)

Matching Decisions

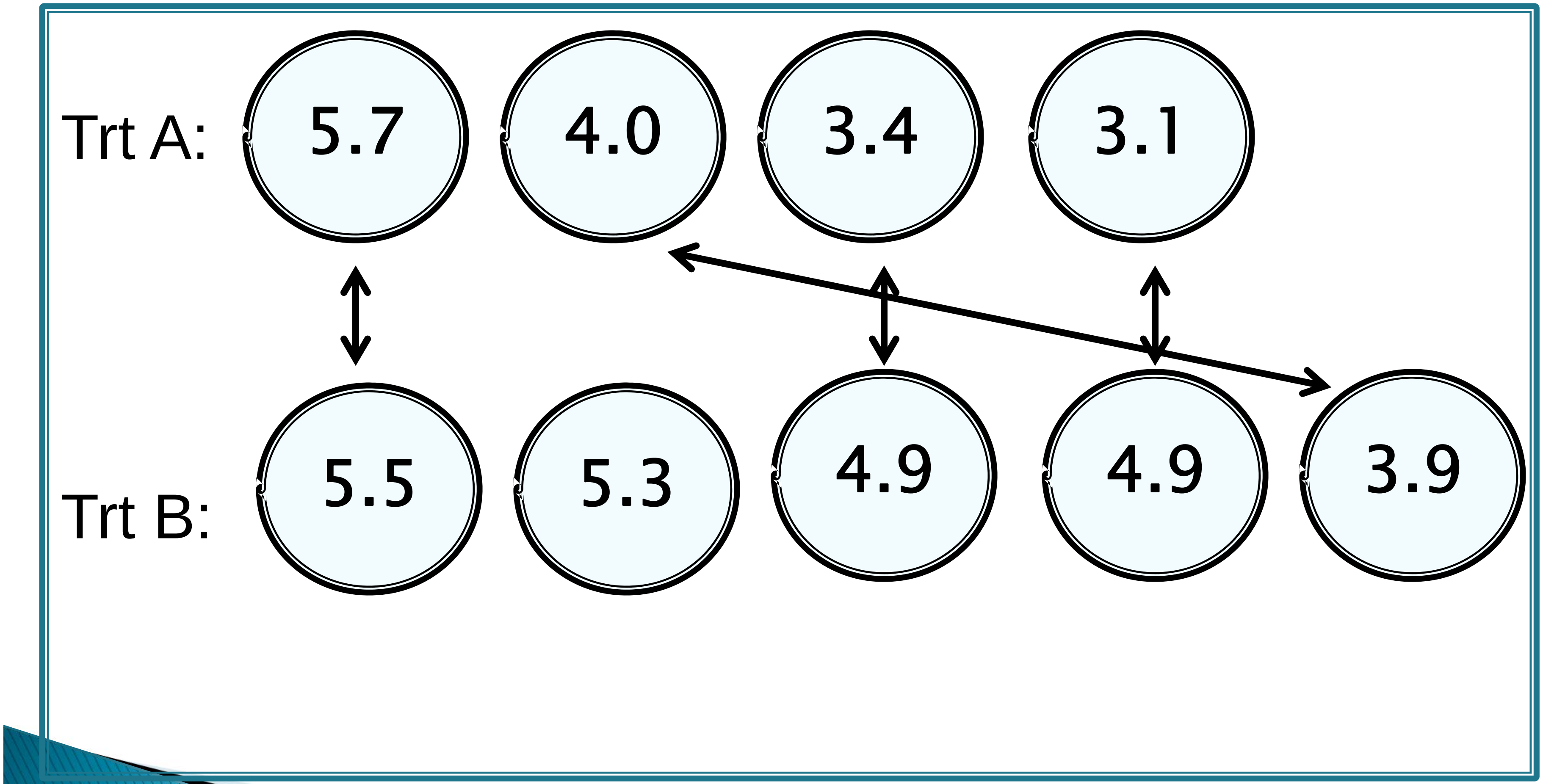
1. Distance Measure
   - Absolute Diff in PS; Mahalanobis; ….
   - Caliper used to limit poor matches
   - Rosenbaum (2010)
     - Rank Based Mahalanobis with 0.2 SD of PS as caliper
2. Ratio
   - 1:1 (best balance); 1:n; 1:variable; var:1 & 1:var
3. Algorithm
   - Greedy or Optimal / Full or Matching with Replacement or ….

Methods: Nearest Neighbour (Greedy)

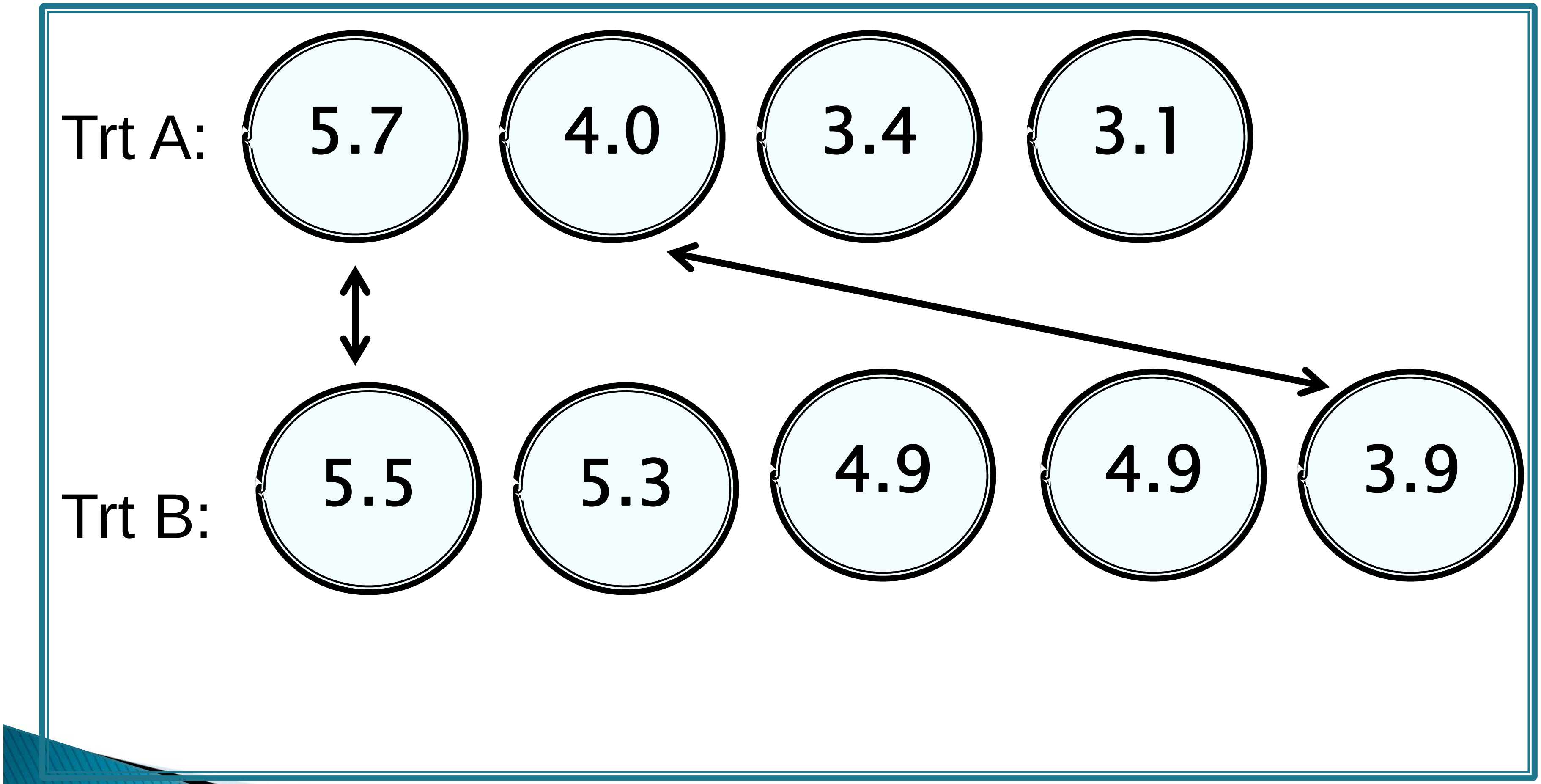


- Most frequently used matching algorithm
- 1st Treated patient is matched to closest Control patient (this match is then fixed), 2nd Treated patient is matched …..
- Does not optimize any overall measure of balance
- Different match each time you sort the data set

Greedy Algorithm Example



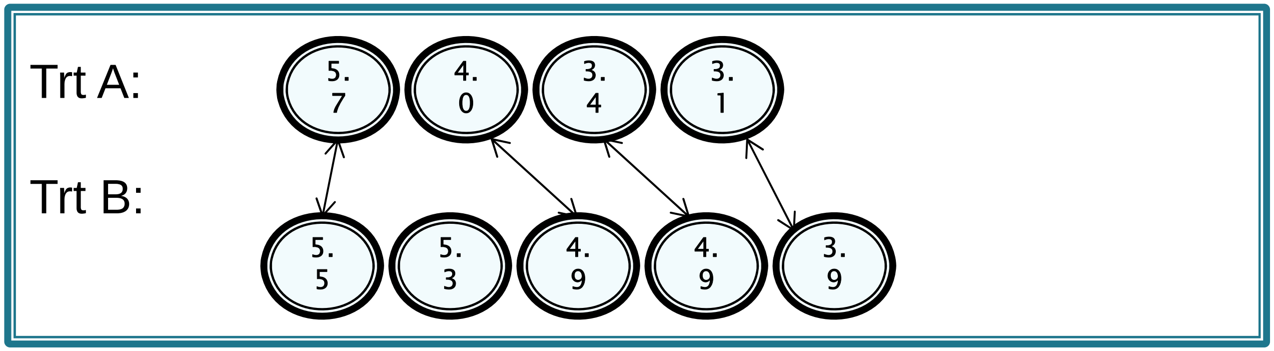
Greedy Algorithm Example -- With a Caliper of 1.0



(Full) Optimal Matching

Optimal Matching

- Minimize sum of absolute differences in distance measure
- Does not depend on order of the dataset



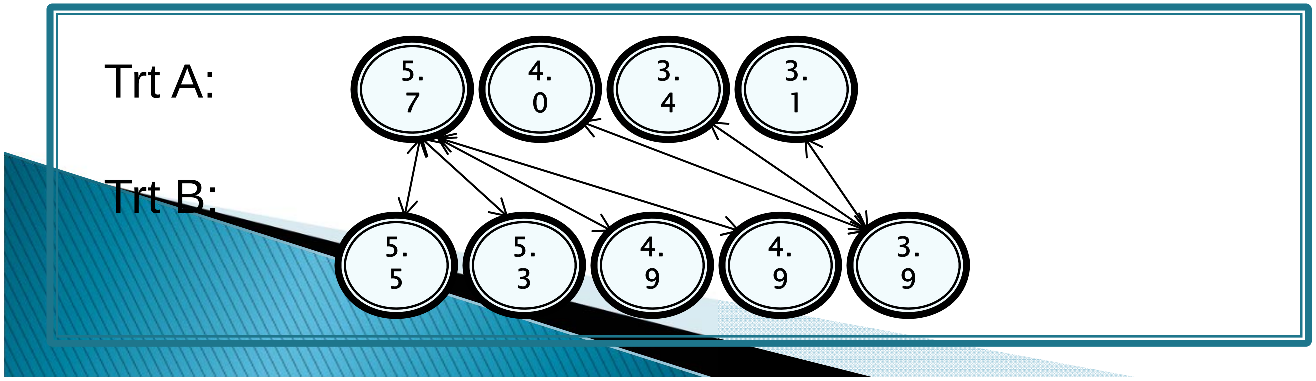
Trt A:

Trt B:

Avg imbalance 0.85

Optimal Full Matching (Hansen 2004)

- Also allows 1:many and many:1 matches



Trt A:

Trt B:

Avg imbalance 0.51

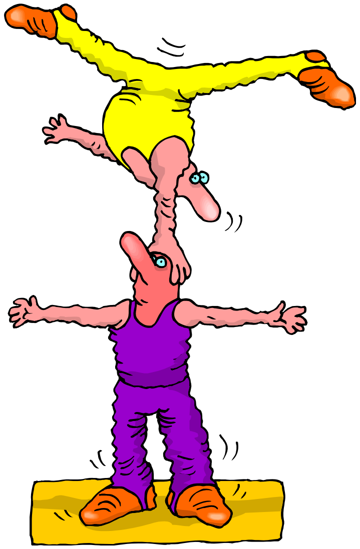
Depression Example: Matching Analyses

- Used (1:1) PS Matching as the primary analysis – Greedy Algorithm

- Matched 74 pairs (of 96 possible)
  - Need to summarize generalizability

- Next Assess the Balance
  - D'Agostino: quality of the PS adjustment is judged by the balance acheived

Assessing the Balance

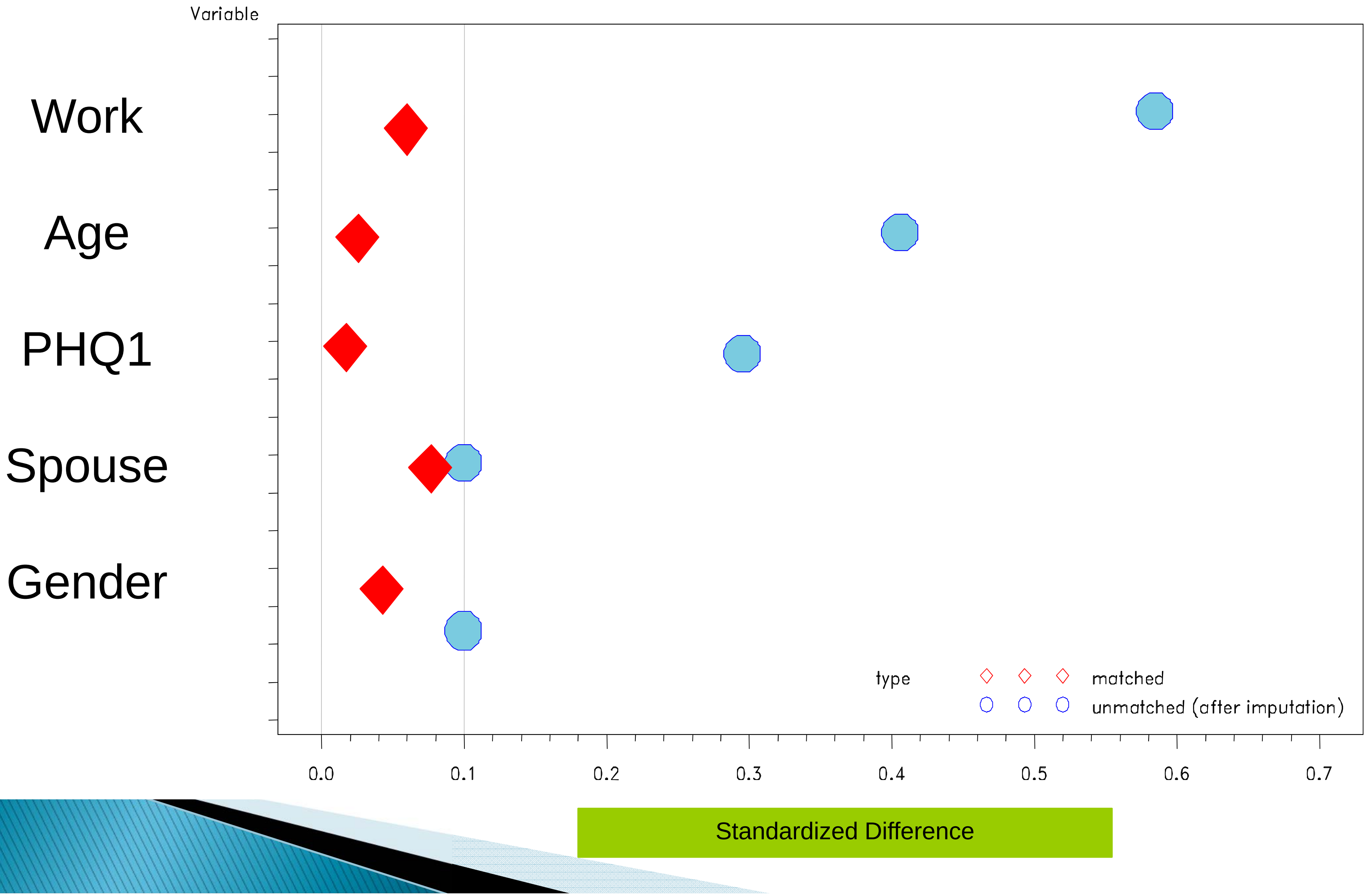


- Hypothesis Testing
  - Common – but sample size dependent
- <u>Standardized Differences</u>
  - Recommended (Austin, Imbens)
  - “difference in means / pooled SD” (not sample size dependent)
  - Rule of Thumb: < 0.1 is OK

Balance: Hypothesis Testing

	Pre-Matching				Post-Matching			
	Trt A N=96	Trt B N=96	P-val		Trt A N=74	Trt B N=74	P-val	
Age	42.8	47.2	.031		44.0	43.7	.889	
Male	17.7	21.9	.469		18.8	20.3	.824	
PHQ	13.7	16.0	.004		14.9	14.7	.880	
Married	62.5	66.7	.546		67.2	64.1	.710	
Work	59.4	31.3	<.01		46.9	43.8	.723	
…								

Balance: Standardized Differences



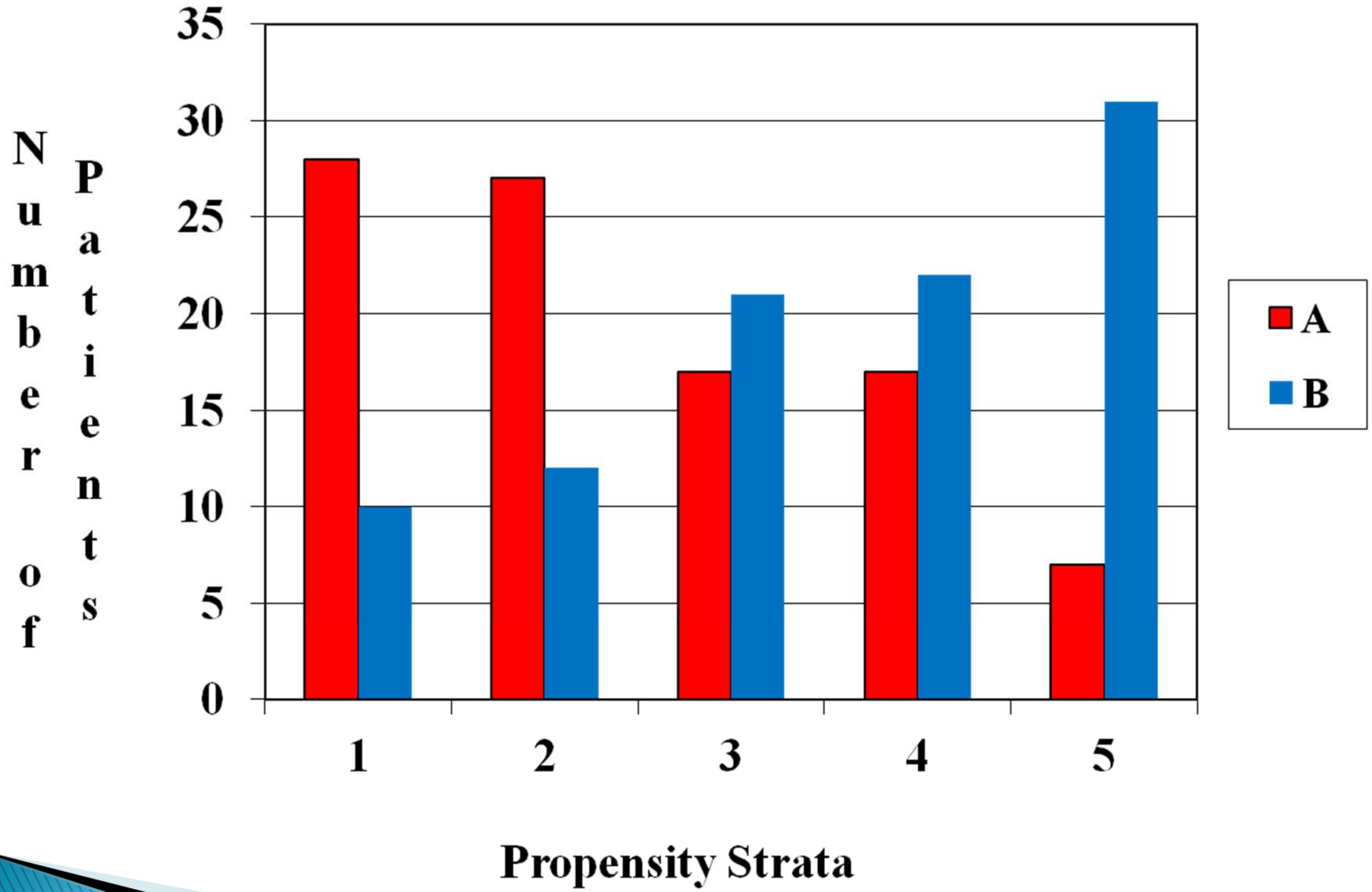
Propensity Score Stratification

- Compute PS
- Group PS into homogeneous Strata
  - How Many?
    - Grouping on Quintiles 5 most common (Cochran 1968), 10 if larger N …..
    - Imbens (2010): Data Driven algorithm – split if not sufficiently homogeneous
- Assess Balance (within strata)
- Trim non-overlapping PS if necessary

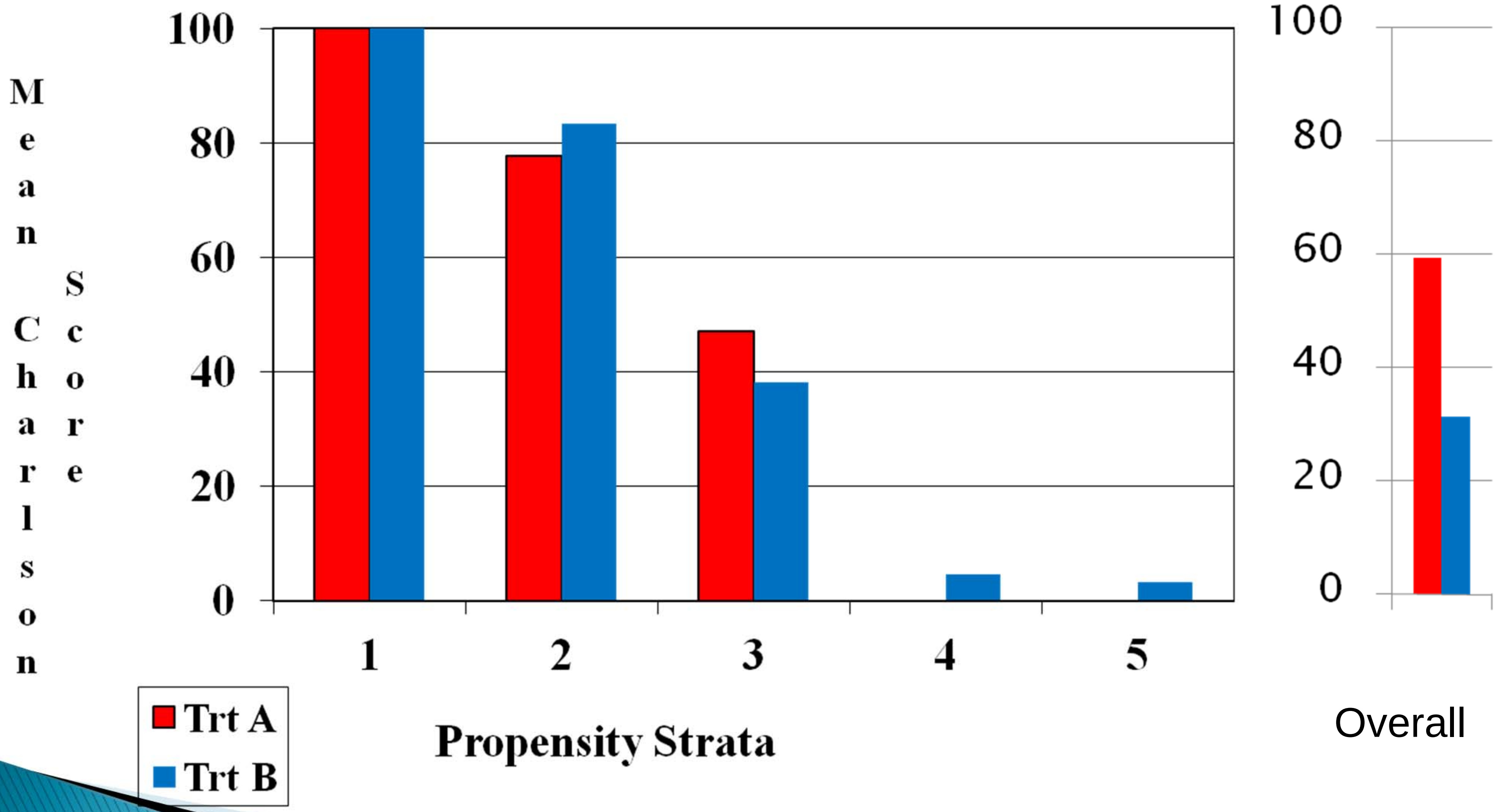
Propensity Score Stratification (ctd)

- Analysis
  - Compare Treatments Within Strata, then Average Across Strata
    - Difference in Means Within Strata
    - Regression Within Each Strata to account for residual imbalance
    - Stratified bootstrapping if non-normal outcomes

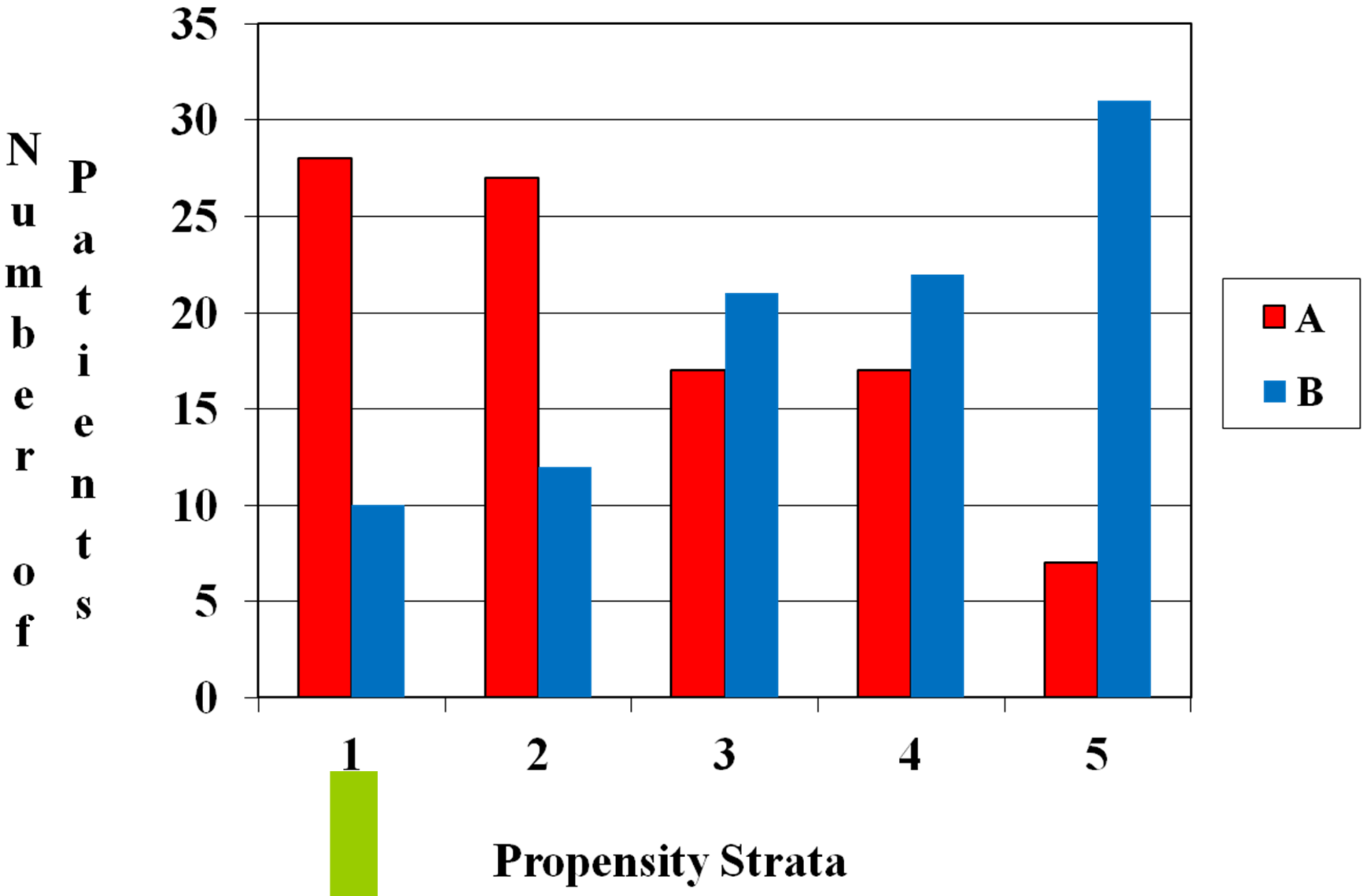
Depression Example: Propensity Score Strata



Balance Produced by Propensity Scores: Variable: Work



Propensity Score Bins



Strata 1: Compare Cohorts using Regression (to adjust for residual confounding) in Stratum 1. Then repeat for Strata 2-5, then average across the Strata

Part III – Improvements in Bias Adjustment

What is New?

Entropy Balancing Example

NEW AND IMPROVED BIAS ADJUSTMENT?

- Exact Matching (plus)
- Prognostic Scores
- Optimal Matching
- Entropy Balancing
- Local Control ……

ENTROPY BALANCING
(HAINMUELLER 2012)

Maximum entropy reweighting scheme that calibrates unit weights so that the reweighted treatment and control group satisfy a potentially large set of pre-specified balance conditions

- Finds the ‘weights’ for each patient that ….
  - Produces balanced means and variances
  - Between any number of cohorts
  - Keeps weights as close to ‘1’ as possible while achieving balance
- Compare Cohorts using Weighted analysis

ENTROPY BALANCING

Advantages

-No need for iterative assessment of balance
-Handles > 2 Treatments
-Can balance on more than just the mean (any specified moments or interactions …..)
-Does not require access to outcome data
-Can specify target population of interest

Limitations

Unable to find solution / Large Weights

EXAMPLE: ENTROPY BALANCING

Depression Data

- Balance means and variances
- …. on 5 covariates
- …. between 3 treatment groups
- Target Population: Full Population (ATE)

Code:
http://www.mit.edu/~jhainm/Paper/ebalance.pdf

Balance: Original Analysis

	Pre-Matching				Post-Matching			
	Trt A N=96	Trt B N=96	P-val		Trt A N=74	Trt B N=74	P-val	
Age	42.8	47.2	.031		44.0	43.7	.889	
Male	17.7	21.9	.469		18.8	20.3	.824	
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Married	62.5	66.7	.546		67.2	64.1	.710	
Work	59.4	31.3	<.001		46.9	43.8	.723	
…								

Balance: Produced by Entropy

	Trt A N=96	Trt B N=96	Trt C N=94	P-val	
Age	45.3	45.3	45.3	1.00	
Male	24.5	24.5	24.5	1.00	
PHQ	14.8	14.8	14.8	1.00	
Married	59.8	59.8	59.8	1.00	
Work	44.1	44.1	44.1	1.00	
…					

Balanced on Means and Variances; Balanced across all 3 groups; Better balance

SUMMARY OF ENTROPY WEIGHTS

tx	N Obs	N	Mean	Std Dev	Min	Max
0	96	96	1.00	0.65	0.08	3.70
1	96	96	1.00	0.54	0.28	2.94
2	94	94	1.00	1.36	0.08	10.02

DEPRESSION RESULTS: ALL METHODS

	Trt A	Trt B	P-val
Original Data	62.5%	46.9%	.030
Propensity Match	60.9%	53.1%	.372
Propensity Strata	58.6%	50.1%	.218
Entropy	54.8%	50.4%	.524

Part IV – Sensitivity

- Focus Here: Unmeasured Confounding
  - Full Sensitivity should include
    - Assessment of Generalizability, Models, Statistical Assumptions, Missing Data ….
- Unmeasured Confounding Methods
  - Rule Out
  - External Adjustment
  - Internal Adjustment
    - Propensity Calibration / Bayesian Modeling / Multiple Imputation / Inverse Weighting
  - Prior Event Rate Adjustment

Example: Type 2 Diabetes Comparison
(Pawaskar J Med Econ 2011)

- Utilized Propensity Score Matching to compare costs between patients initiating Byetta vs Insulin Glargine

- Insurance Claims Database Analysis
  - N1 = 7255, N2 = 2819
  - Adjusted for patient demographics, comorbidities, complications, resource use and costs of care in 6 month pre-initation period.
  - Unable to adjust for: BMI, duration of diabetes, glycemic control

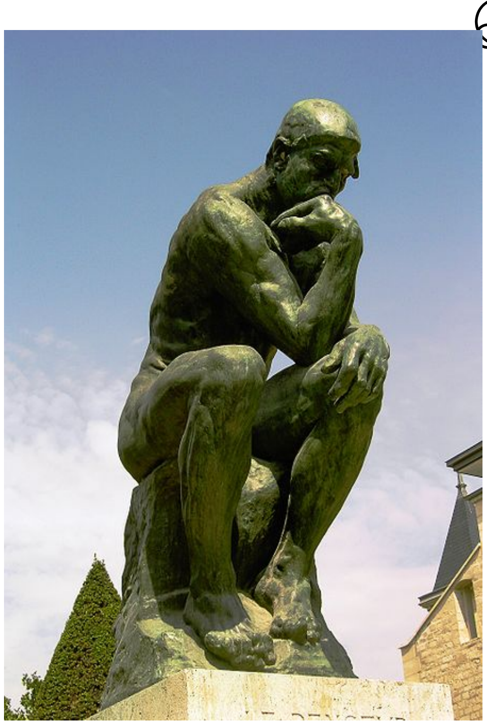
Diabetes Example: Original Results

Estimated mean cost difference

$2597 (690, 4542)
p < .05

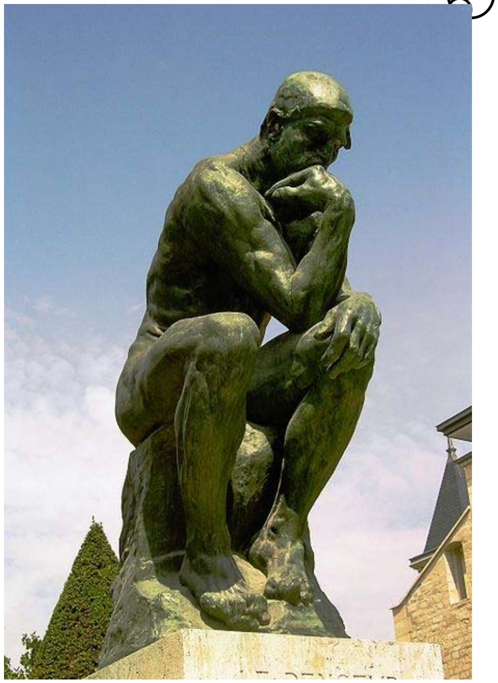
Interpretation Depends on Assumption of No Unmeasured Confounding

What should I do about unmeasured confounding?

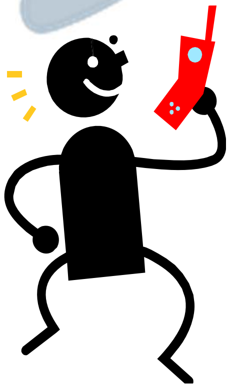


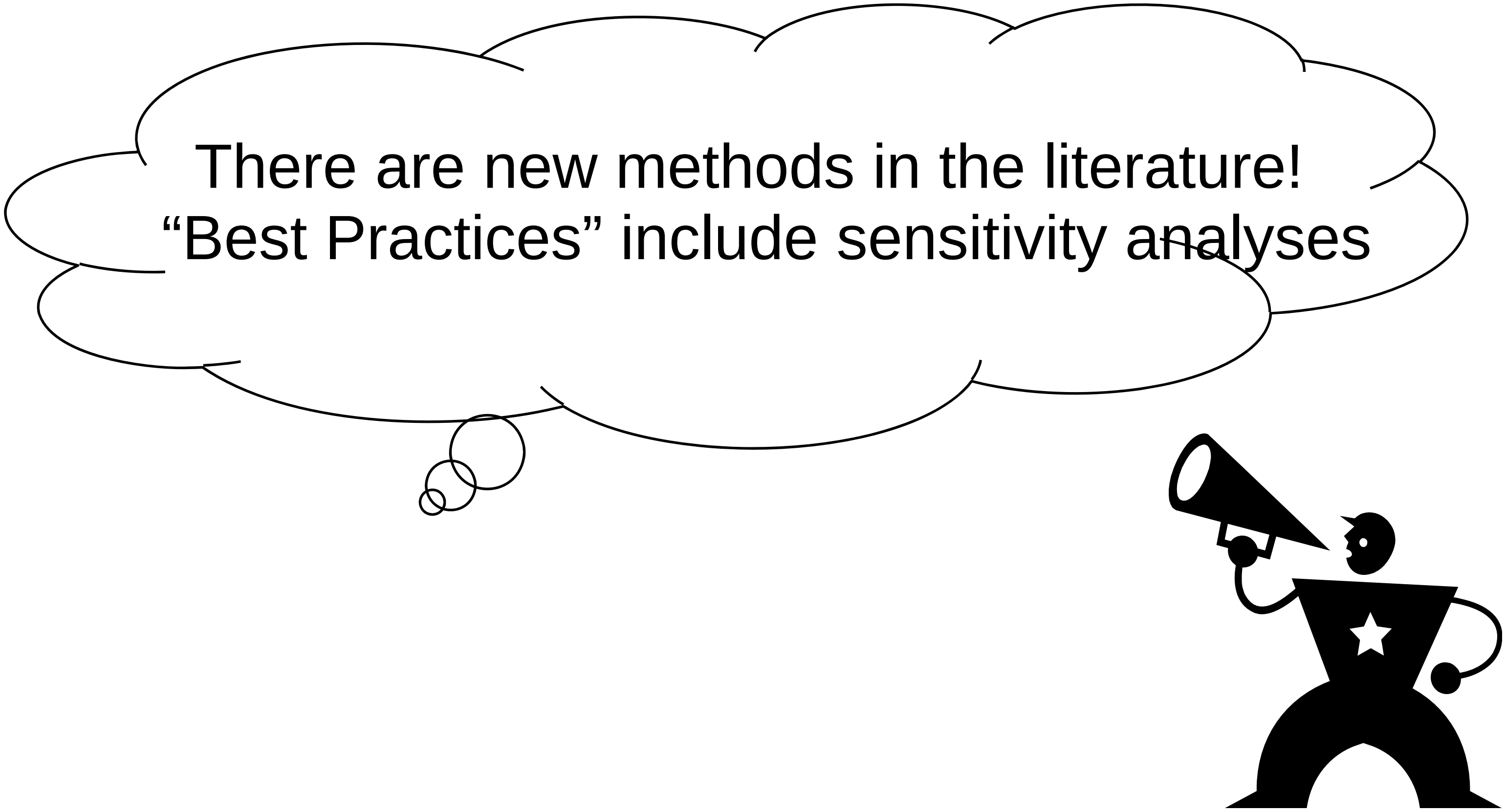
Current State of the Union Regarding Unmeasured Confounding

What should I do about unmeasured confounding?



Just mention it as a limitation in the Discussion Section and move on!

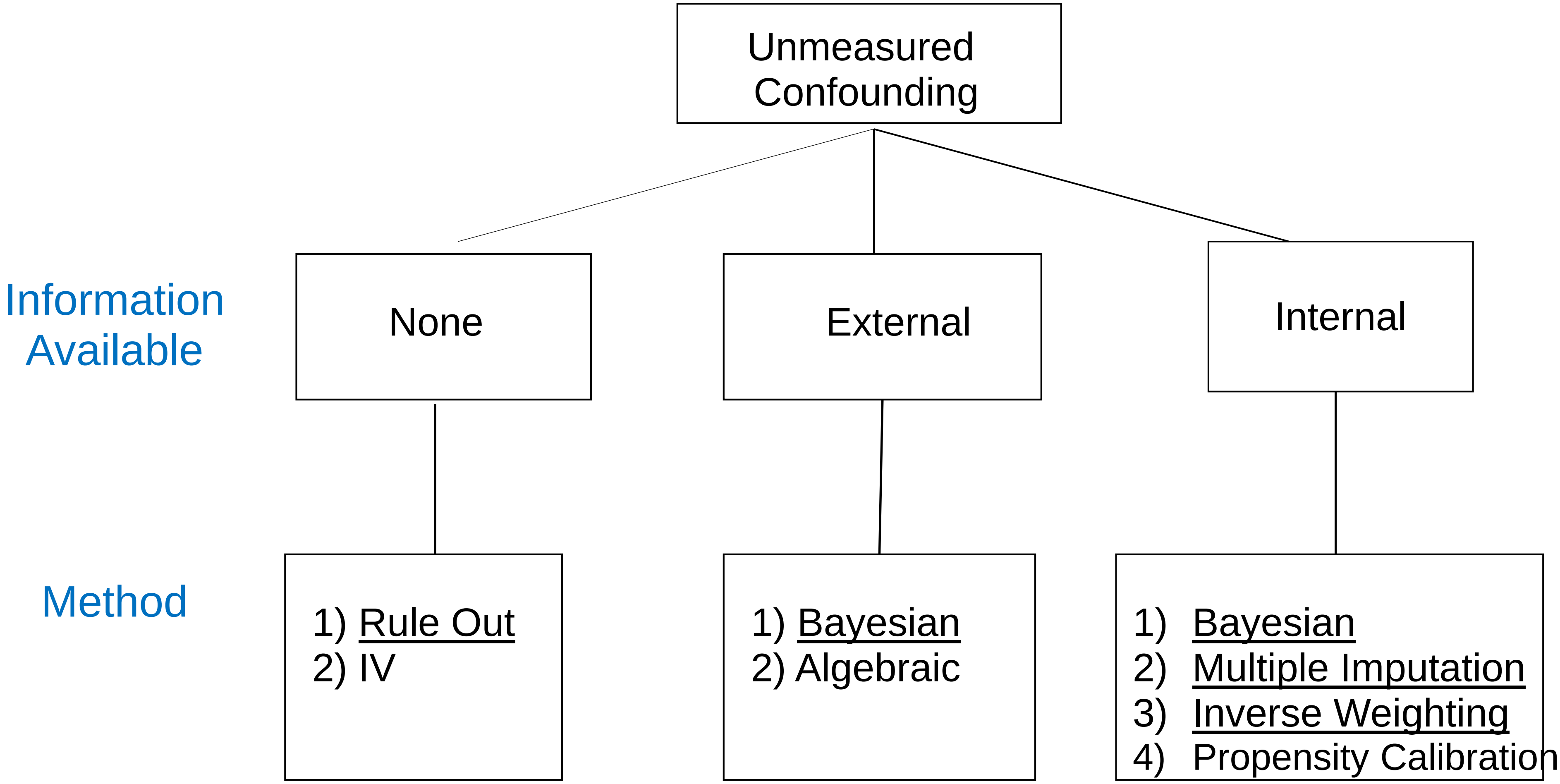




There are new methods in the literature!
“Best Practices” include sensitivity analyses

EXPERT

Unmeasured Confounding Options



Unmeasured Confounding

Information Available

None

External

Internal

Method

1) Rule Out
2) IV

1) Bayesian
2) Algebraic

1) Bayesian
2) Multiple Imputation
3) Inverse Weighting
4) Propensity Calibration

Rule-out Method (no data)

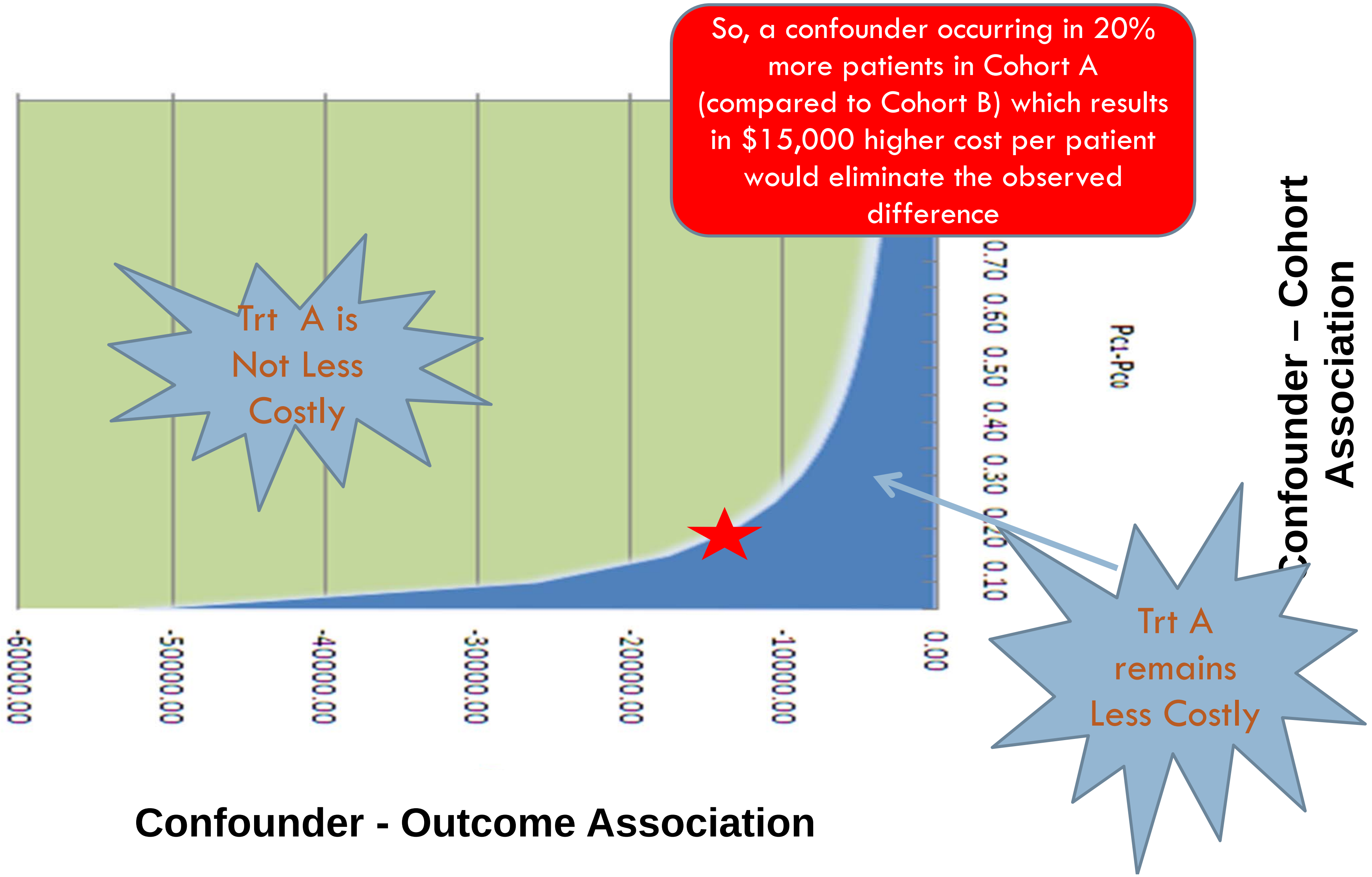
Concept: Quantify how strong and imbalanced a confounder would need to be in order to explain ("rule out") the observed result.

This approach attempts to find all combinations of

1) the confounder-outcome relationship and
2) the confounder-treatment relationship,-

necessary to move the observed point estimate to zero.

Rule-out Method – Diabetes Example



So, a confounder occurring in 20% more patients in Cohort A (compared to Cohort B) which results in $15,000 higher cost per patient would eliminate the observed difference

Trt A is Not Less Costly

Trt A remains Less Costly

Diabetes Example

Results:
Estimated mean cost difference

$2597 (690, 4542) $p < .05$

Internal Data Sensitivity Opportunity!!

- No measure of glycemic control was available in the original claims database. However, after linking with a laboratory file, A1C values were obtained in a subset (about 25%) of the sample;

Information Available: Internal

Concept: Use information from the patients in the study (e.g. subsample of chart review data for a retrospective claims database study) to estimate parameters regarding unmeasured confounding

With Internal data can avoid transportability assumption and can account for correlation between unmeasured confounder and measured confounders

Information Available: Internal

Methods

Propensity Score Calibration

Sturmer et al (Am J Epi 2005)

Bayesian Modeling

McCandless (Stat Med 2007)

Multiple Imputation

Toh et al (Pharmacoepi Drug Saf 2012)

Bayesian Twin Regression Models

Concept: Bayesian models naturally incorporate additional sources of information – such as internal subset data or external information from other studies - through prior distributions

$$\text{Outcome} = \beta_0 + \beta_1 * \text{Treatment} + \beta_2 * \text{UnmConf} + \beta_3 * \text{MeasConf}$$

$$\text{Logit } P(\text{UnmConf} = 1) = \gamma_0 + \gamma_1 * Treatment + \gamma_2 * \text{MeasConf}$$

Internal data serves in essence as informative prior information for parameters relating to unmeasured confounder

Implementation: WinBUGS (SAS 9.3 code upcoming)

R1

Bayesian Twin Regression Models

$$\text{Outcome} = \beta_0 + \beta_1 * \text{Treatment} + \lambda * \text{UnmConf} + \eta * \text{MeasConf} + \varepsilon$$

$$\text{logit } P(\text{UnmConf} = 1) = \gamma_0 + \gamma_1 * TRT + \gamma_2 * \text{MeasConf}$$

Priors:

Uninformative: β_0, β_1, η

Informative: $\lambda, \gamma_0, \gamma_1, \gamma_2$

Slide 66

R1 may want to further comment on flexibility here in sense that this is continuous outcome and binary covariate. need not be the case ... ie , can be other combinations in terms of binary outcome/binary confounder, etc, so here we highlight a framework

RM36604, 3/15/2011

Keys to Bayesian Approach

- Incorporates available info via Informative Priors
  - Best available data – whether internal or External
  - Informative Priors – not just adding uncertainty (McCandless 2007)

- Yields a posterior distribution for the treatment effect adjusted for the unmeasured confounder *U*.
  - Fixed Modeling failed to incorporate variability (Schneeweiss 2006)
- Flexible data driven model
  - No restrictions on relationships on associations between variables as in PS Calibration (Sturmer 2007).

Missing Data Multiple Imputation (for internal data)

Concept: This is a missing data problem – use a well accepted method -- Multiple Imputation!

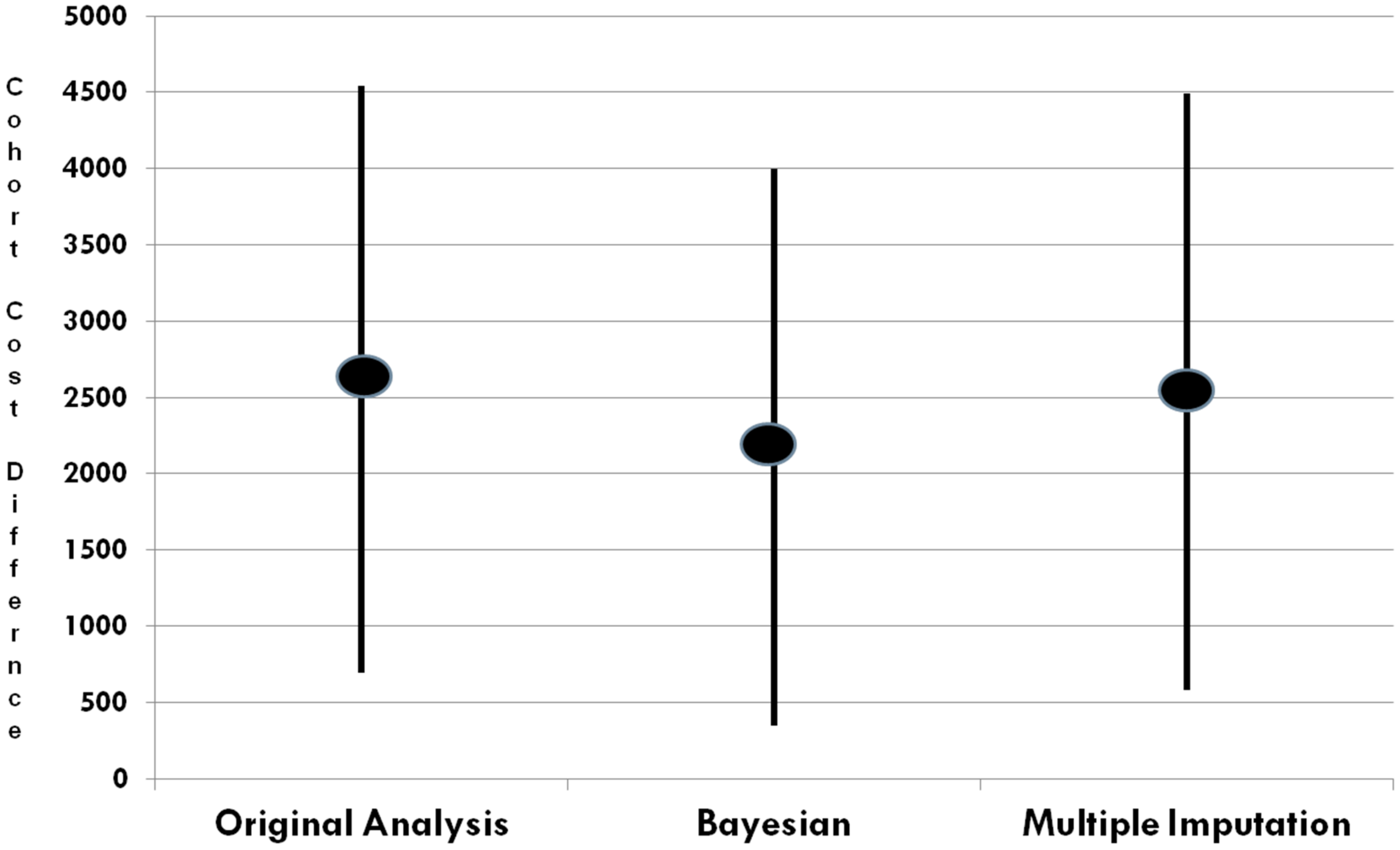
Imputation Model:

Treatment, Measured Covariates, and Outcome

Used > 5 replications due to amount of missing data

Implementation: PROC MI in SAS

Diabetes Example: Summary of Sensitivity Analyses



Faries et al VIH accepted

Unmeasured Confounding Conclusions

Comparative effectiveness research should include ‘Unmeasured Confounding’ sensitivity to help consumers of the data understand the robustness of the findings.

Bayesian and MI methods are promising approaches

- naturally incorporate additional info (internal or external)

- can use internal data to avoid development of prior.

Lots of Remaining Questions ???

- When is one method preferred to another?
- How much ‘internal data’ is needed for each method?
- When is it cost effective to obtain the internal information as opposed to more easily available external data?

Overall Summary

- Causal Inference from Observational Data requires making un-testable assumptions
  - We DON'T KNOW the operating characteristics of current practices
  - Publications are not sufficiently transparent for appropriate interpretation of the value/quality
- Quality Analyses includes:
  - Pre-specification, appropriate bias adjustment, replication, and sensitivity analyses …. CORE STATISTICAL PRINCIPLES
- Newer Methods are very promising for:
  - Better bias adjustment (for <u>measured</u> confounders)
  - Better Sensitivity Analyses (for <u>unmeasured</u> confounders)

Backup Slides

Schizophrenia Pragmatic Trial Example (Tunis 2006)

- Randomized, Open Label, 1-Year, Cost Effectiveness Study
- 3 treatment regimens (total N = 664)
  - Olanzapine / Risperidone / Conventionals
- Naturalistic: patients may switch, stop, augment, change doses … and remain in study
- Primary Analysis: Cost Effectiveness
- Effectiveness Outcome: BPRS Total Score

Propensity Score Calibration

Concept: Utilize additional data - variables not in full sample but available for a subset of patients - to modify the propensity score adjustment

- Two propensity scores (PS) are calculated:
- - "Error Prone" PS: utilizes only covariates available in the full sample
- - "Gold Standard" PS: utilizes additional confounding covariates (in subset with all covariates)

- Regression calibration (measurement error modeling) is then applied to adjust the regression coefficients and thus compensate for the unmeasured confounding.

Propensity Score Calibration

- Validity relies on surrogacy of the error prone propensity for the gold standard propensity.
  - "error prone PS" must be independent of the outcome given "gold standard PS" and treatment.

For our example – surrogacy assumption not clearly satisfied

- Correlations of A1C & Outcome was negative
- Correlations of Other Covariates & Outcome was positive

Propensity Score Calibration (ctd)

Error Prone Propensity Score Model (PS_{EP})

$$PS_{EP} = \Pr(X = 1 | z_1, z_2, \ldots, z_n)$$

Gold Standard Propensity Score Model (PS_{GS})

$$PS_{GS} = \Pr(X = 1 | z_1, z_2, \ldots, z_n, \mu)$$

Calibration Model:

$$E[PS_{GS}] = \delta_0 + \delta_1 X + \delta_2 PS_{EP}$$

Why not just use Regression?

D’Agostino 2007

- “regression” can produce biased estimates of treatment effects if there is extreme imbalance of the background characteristics and/or the treatment effect is not constant across values of the background characteristics”

Rule of Thumb (Imbens)

- If all normalized differences are less than 0.1 the choice of adjustment method is unimportant, whereas for differences exceeding 0.25 simple adjustment methods such as linear covariance adjustment are unlikely to be adequate