Real World Evidence

In the pharmaceutical industry

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Stefan Franzén PhD RWE S&P Expert

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Outline

- What is Real World Evidence (RWE)?
- How can RWE be used in the industry?
- Challenges with RWE

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Real world evidence (RWE) uses observational data, taking information outside of controlled trials to create insights on diseases, products, and patient populations.

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Data sources

- Healthcare data registries
- Insurance claims data e.g. HealthCore
- Disease specific registries
- Prospective registries

?:

- How patients enter the data base?
- How patients leave the data base?
- What selection occur in the data base?
- What is recorded / not recorded?

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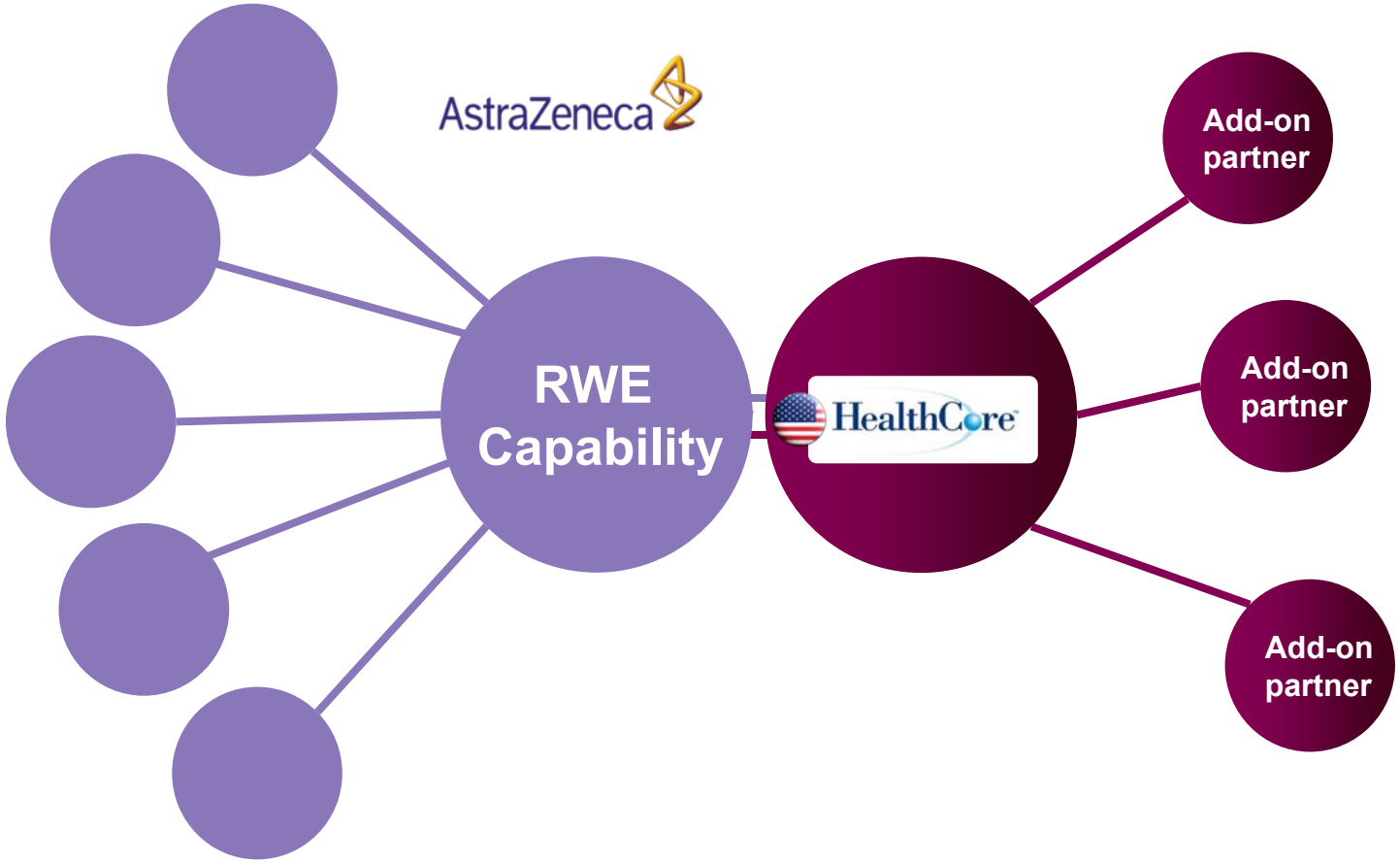
Strategic data partnerships are a key component of the RWE vision, and HealthCore is the first hub partner



RWE will support R&D and Commercial customers across the product lifecycle

Target selection – Phase IIa	Phase IIb – Phase III / Launch	Commercialization
▪ Understand **unmet medical needs** based on RWE	▪ Support the preparation of **reimbursement** and **regulatory** dossiers	▪ Provide RWE insights that support **reimbursement** and **market access**
	▪ Provide RWE insight to guide **trial design** and support **interpretation of trial results**	▪ Provide RWE **comparative effectiveness** evidence relative to competitors
	▪ Provide RWE insight into product **go/no go decisions**	▪ Provide **long-term safety** and **effectiveness evidence**

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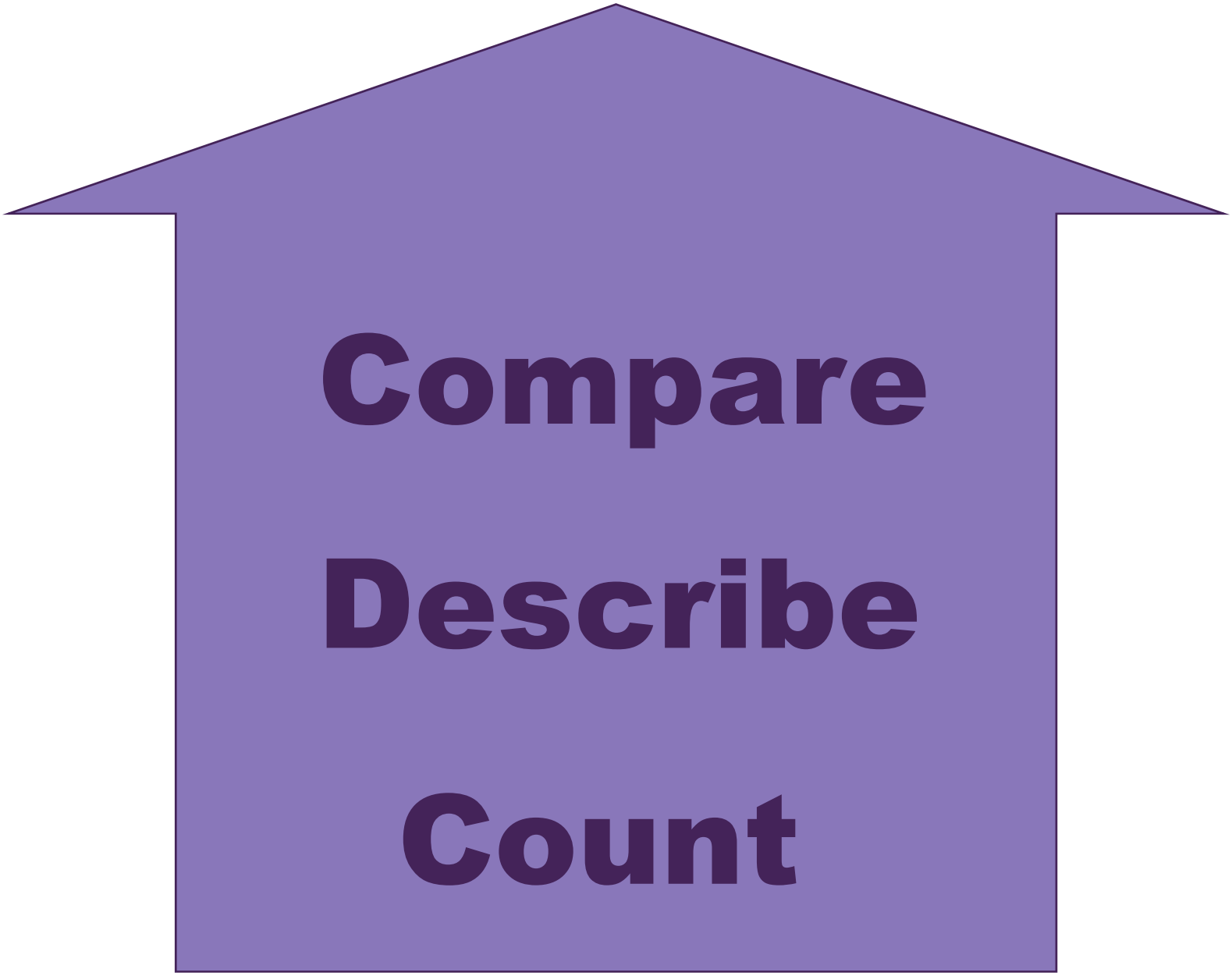

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Compare

Describe

Count

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Compare

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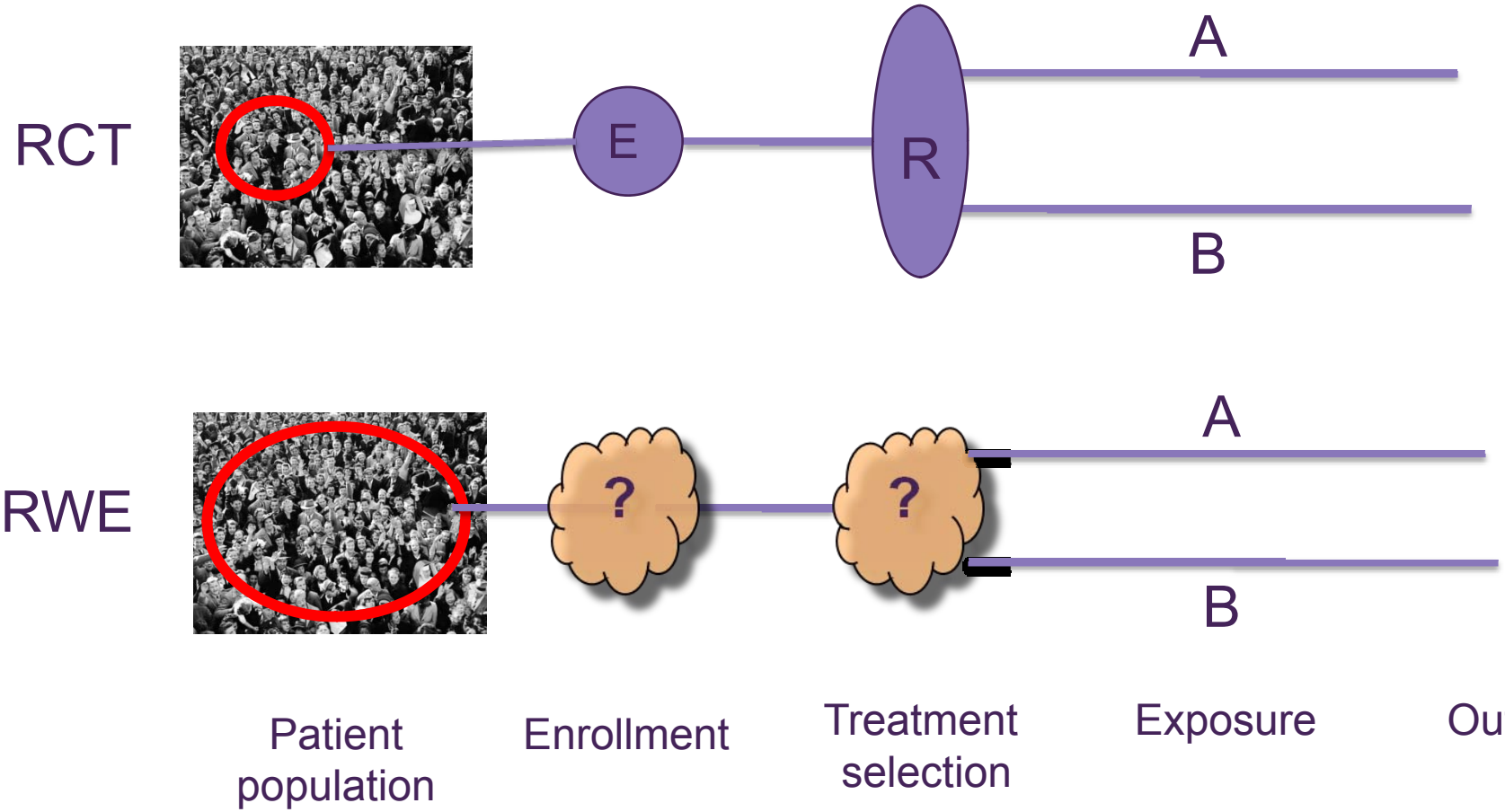
RWE vs RCT



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RWE vs RCT

	RWE	RCT
Patient population	Big, limited selection	Small highly selected
Treatment selection	Uncontrolled	Controlled by randomization
Treatment	As in clinical practice	Restricted by the protocol
Exposure	Prescription fill	Pills returned
Outcome	Often observed indirectly	Directly observed
External validity	High	Limited
Data quality	Low	High
Cost of treatment	Observable	Unknown
Direct comparisons	Invalid due to confounding	Valid due to randomization

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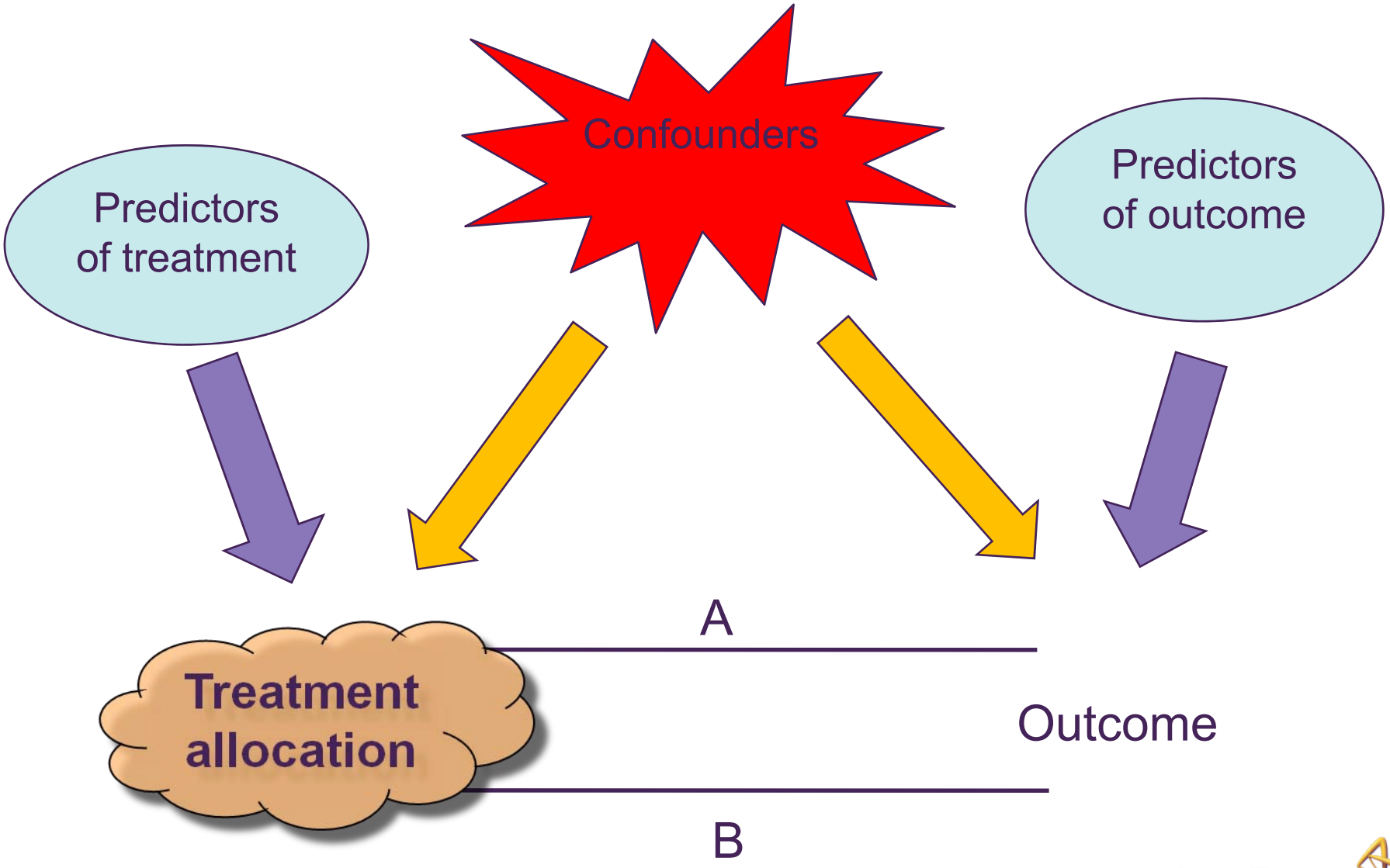
Confounding



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Example

Smoking Cigarettes is not so bad but watch out for Cigars or Pipes (at least in Canada)

Variable	Non smokers	Cigarette smokers	Cigar or pipe smokers
Mortality rate*	20.2	20.5	35.5

*) per 1000 person-years %

Cochran, Biometrics 1968

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Example

Smoking Cigarettes is not so bad but watch out for Cigars or Pipes (at least in Canada)

Variable	Non smokers	Cigarette smokers	Cigar or pipe smokers
Mortality rate*	20.2	20.5	35.5
Average age	54.9	50.5	65.9

*) per 1000 person-years %

Cochran, Biometrics 1968

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Example

Smoking Cigarettes is not so bad but watch out for Cigars or Pipes (at least in Canada)

Variable	Non smokers	Cigarette smokers	Cigar or pipe smokers
Mortality rate*	20.2	20.5	35.5
Average age	54.9	50.5	65.9
Adjusted mortality rate*	20.2	26.4	24.0

*) per 1000 person-years %

Cochran, Biometrics 1968

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Adjustments for Covariates

- Three common methods of adjusting for confounding covariates:
  - Matching
  - Stratification
  - Regression (Covariate) adjustment

Problematic if the number of covariates is large

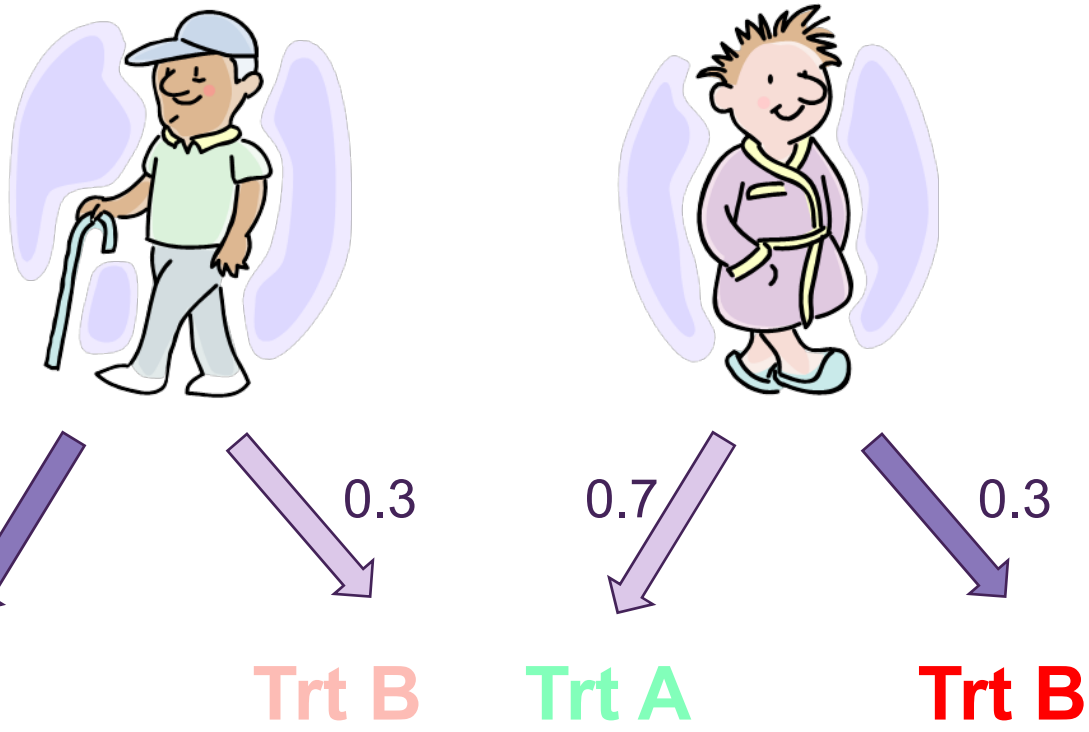
Propensity Score*

- Replace the collection of confounding covariates with one scalar function of these covariates: the propensity score.

- **The conditional prob. of receiving Trt A rather than Trt B, given a collection of observed covariates.**

*) Rosenbaum&Rubin 1983

Propensity Score=0.7



When the propensity scores are balanced across two treatment groups, the distribution of all the covariates are balanced in expectation across the two groups.

Stratifying on the propensity score

- 5 strata takes care of most of the bias*
- Use a stratified analysis

*) Rosenbaum&Rubin 1983

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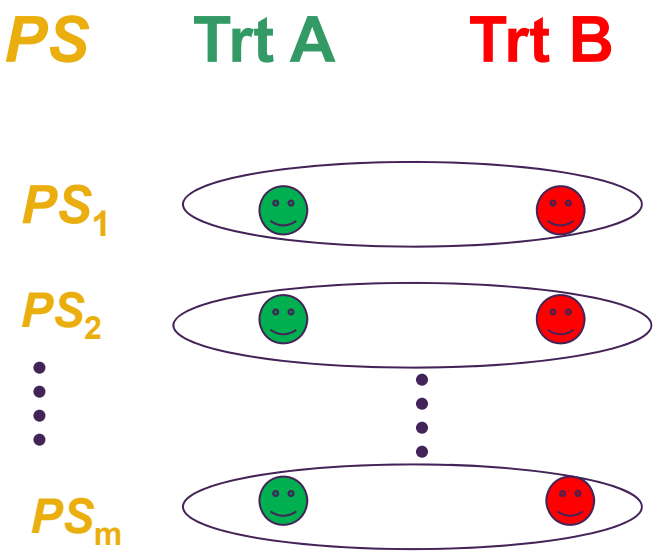
Matching on the propensity score



- Greedy matching
- Optimal matching
- Mahalanobis distance

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Practical Issues

- Issues in propensity score estimation
  - **How to handle missing baseline covariate values**
  - **Which covariates should be included**
  - **Evaluation of treatment group comparability**
- Issues in treatment comparison:
  - **Which method: matching, stratification, regression**
  - **How to account for the matching?**

Reading

Rosenbaum & Rubin ”The central role of the propensity score in observational studies for causal effects. Biometrika 1983

d’Agostino ”Tutorial in biostatistics: propensity score methods…” Stat in Med 1998

Austin ”A critical appraisal of propensity score matching in the medical literature between 1996 and 2003” Stat in Med 2008

Gou & Fraser ”Propensity score analysis” 2010

Rothman & Greenland ”Modern Epidemiology” 1998