Assessing Treatment Effect Using Propensity Score Matching within the U.K. Population of Crohn's Disease Patients

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Outline

- **Medical/Population Health Motivation**
- Study Design Issues
- Purpose of Propensity Score Matching (PSM)
- Implementation of PSM & Balance Diagnostics
- Application to Treatment in Crohn's Disease Using CPRD Data
- Next Steps/Other Areas of Application

Population Health Application: Crohn's disease

- > 70% of Crohn's disease (CD) patients have complications within 10 years of diagnosis (Cosnes et al. 2002)
  - ≥ 50% require surgical resection within this time
  - 70-80% require it within lifetime (Loftus 2006)

- Medical treatment needed to reduce surgeries

- Thiopurines (TP)
  - Used in maintenance of remission of CD (Prefontaine et al. 2009)

- Increases in TP use concurrent with falls in surgical resections (Ramadas et al. 2010)

Research Questions/ Medical Practice Evaluation

- ***Evaluate temporal trends in TP prescribing & 1st intestinal resection***
- ***Compare 1st intestinal resection rates in patients treated with and without TP***
- ***When should therapy be initiated?***
- ***For how long should therapy be administered to achieve optimal results in long-term reduction in surgery risk?***

Causal Effect of Thiopurine Treatment on 1st Intestinal Resection in CD

- **Non-randomized study** (longitudinal cohort study)
- U.K. Clinical Practice Research Datalink (CPRD)
  - Over 13 million registered patients with primary care physicians
  - Clinical & prescribing data
  - Practices are regularly audited to ensure data accuracy & completeness
  - Validation studies report high level of inflammatory bowel disease (IBD) recording against medical records (Lewis et al. 2002; 2004)
- CD incident cases diagnosed through 2005 (n=6,159)
  - Patients followed from diagnosis up to 5 years (1989-2010) (registered for ≥ 1 year)
- Excluded patients with:
  - Co-morbid conditions (n=165)
  - Diagnosis with CD at 1st surgery (n=354)
- 5,640 resulting patients

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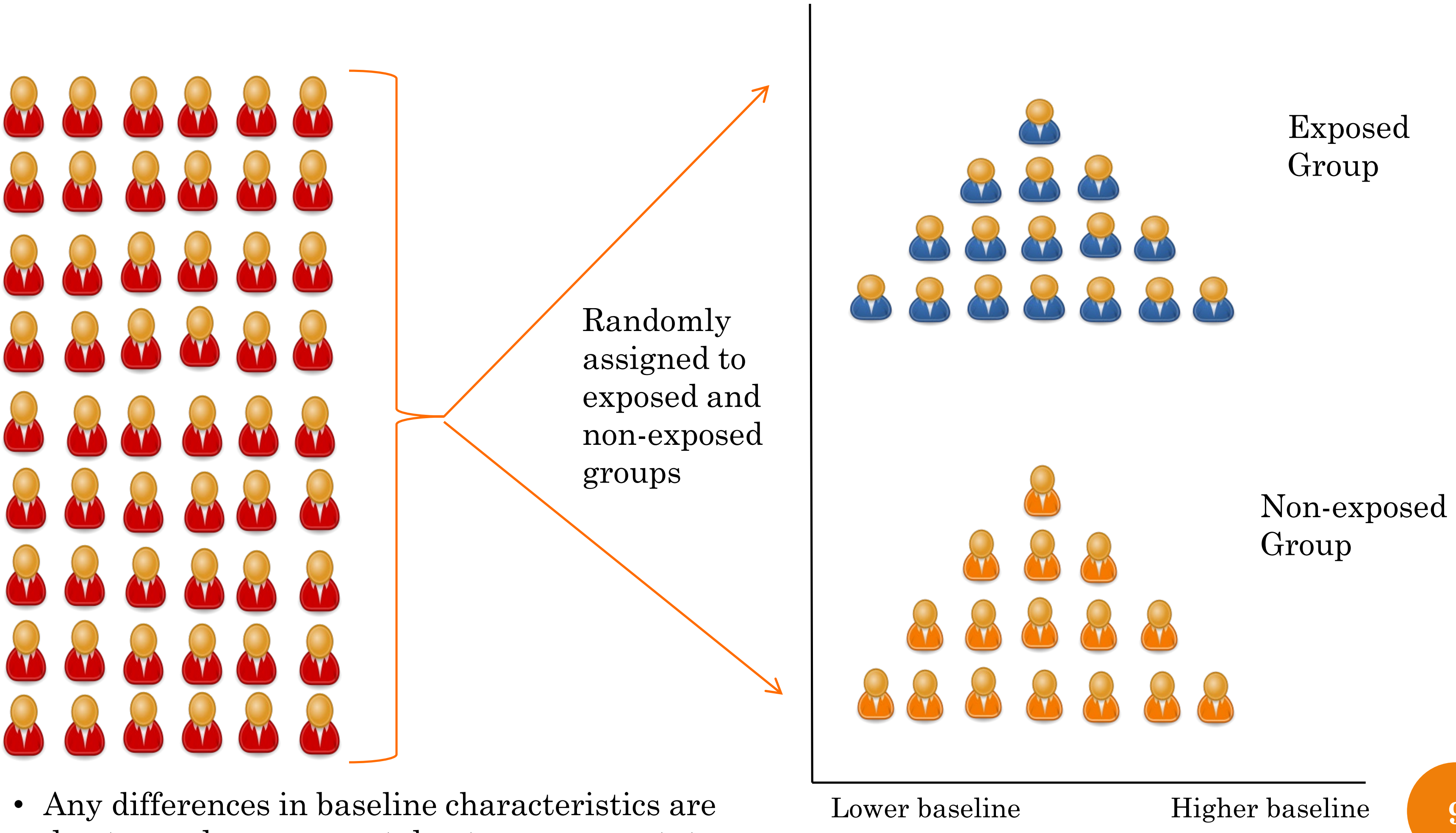
Randomised Controlled Trials (RCTs)

- Gold standard for estimating treatment effects on health outcomes
- Direct comparison of outcomes between intervention & control groups to estimate treatment effect
  - Random allocation of subjects prevents confounding between intervention status & measured baseline characteristics
  - On average, distribution of baseline covariates is similar between intervention & control groups
  - Yields **unbiased** estimate of average treatment effect
    - Continuous data → (Standardized) Difference in Means
    - Binary data → Odds Ratios, Relative Risks, Difference in Proportions
    - Time to Event data → Hazard Ratios

Non-Randomized Studies

- Aim: Estimate a causal effect within an observational study (e.g., not feasible to conduct RCT)
- ***Patient characteristics influence treatment selection***
- Leads to systematic differences in baseline characteristics between exposure & control subjects
  - Produces **biased** estimates of treatment effects
- **Propensity score matching *reduces confounding effects* in observational studies**
  - Creates a pseudo-RCT framework for analysis of exposure effects on outcomes

RCT: Similar Baseline (Distribution) Characteristics by Construction



Randomly assigned to exposed and non-exposed groups

Exposed Group

Non-exposed Group

Lower baseline

Higher baseline

- Any differences in baseline characteristics are due to randomness - not due to exposure status.
- Individuals & their baseline characteristics do not influence exposure status.

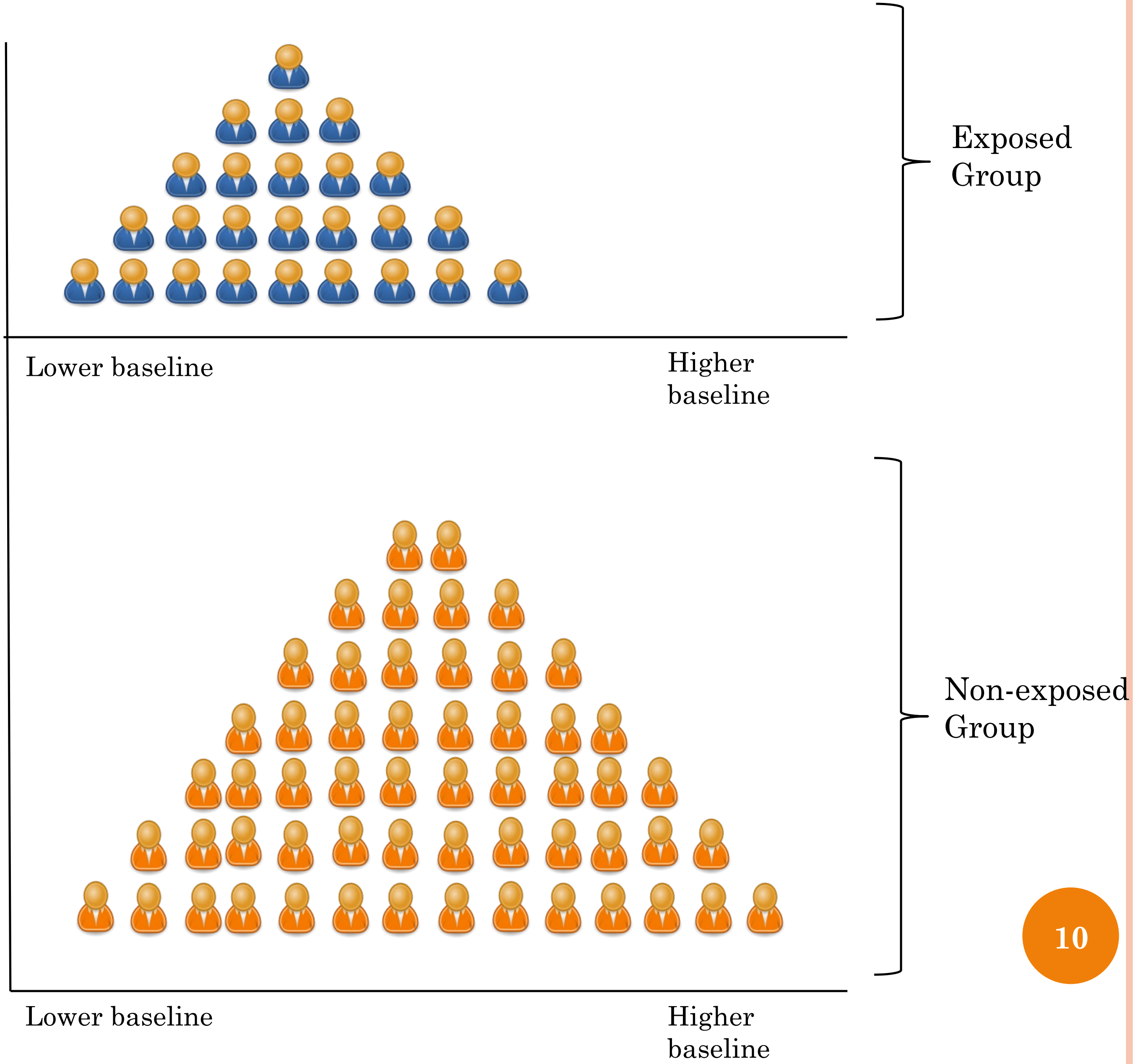
Non-Randomized Studies

- Distribution of baseline characteristics may be different for exposed & non-exposed

- Difference may not occur at random, but determined by exposure/treatment status

- **Crohn's disease patients were not randomized before being exposed/not exposed to TP**

- ***Therefore, exposure status to TP (treatment status) could be affected by baseline characteristics.***



Non-Randomized Studies

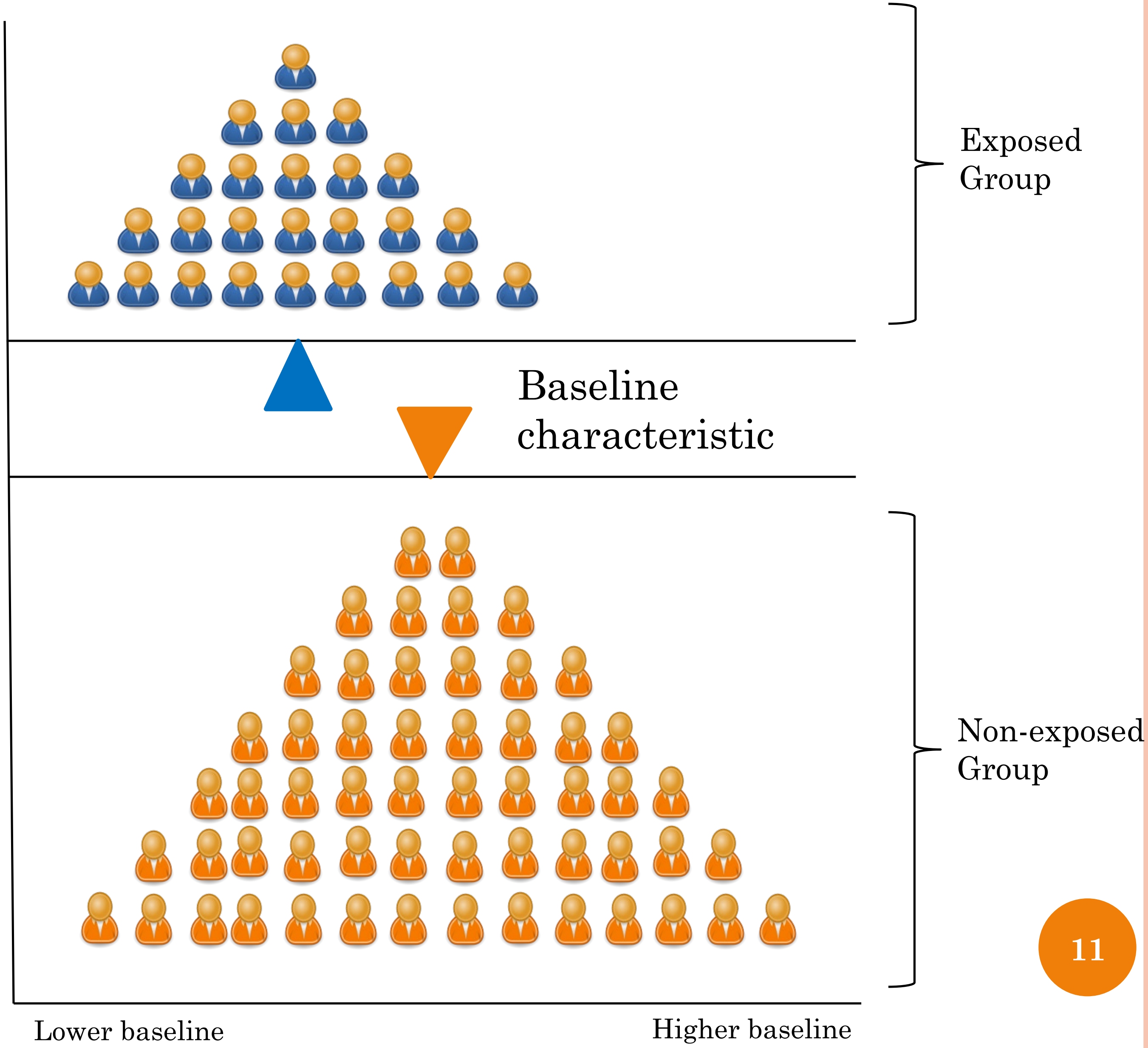
- Different mean levels of a baseline characteristic for the exposed & unexposed groups

- **Baseline characteristic differences can impact differences in average treatment effect**

- For example, the impact of a treatment may be different by age of the treated:

Cannot compare effect of treatment on younger group versus non-treatment on older group.

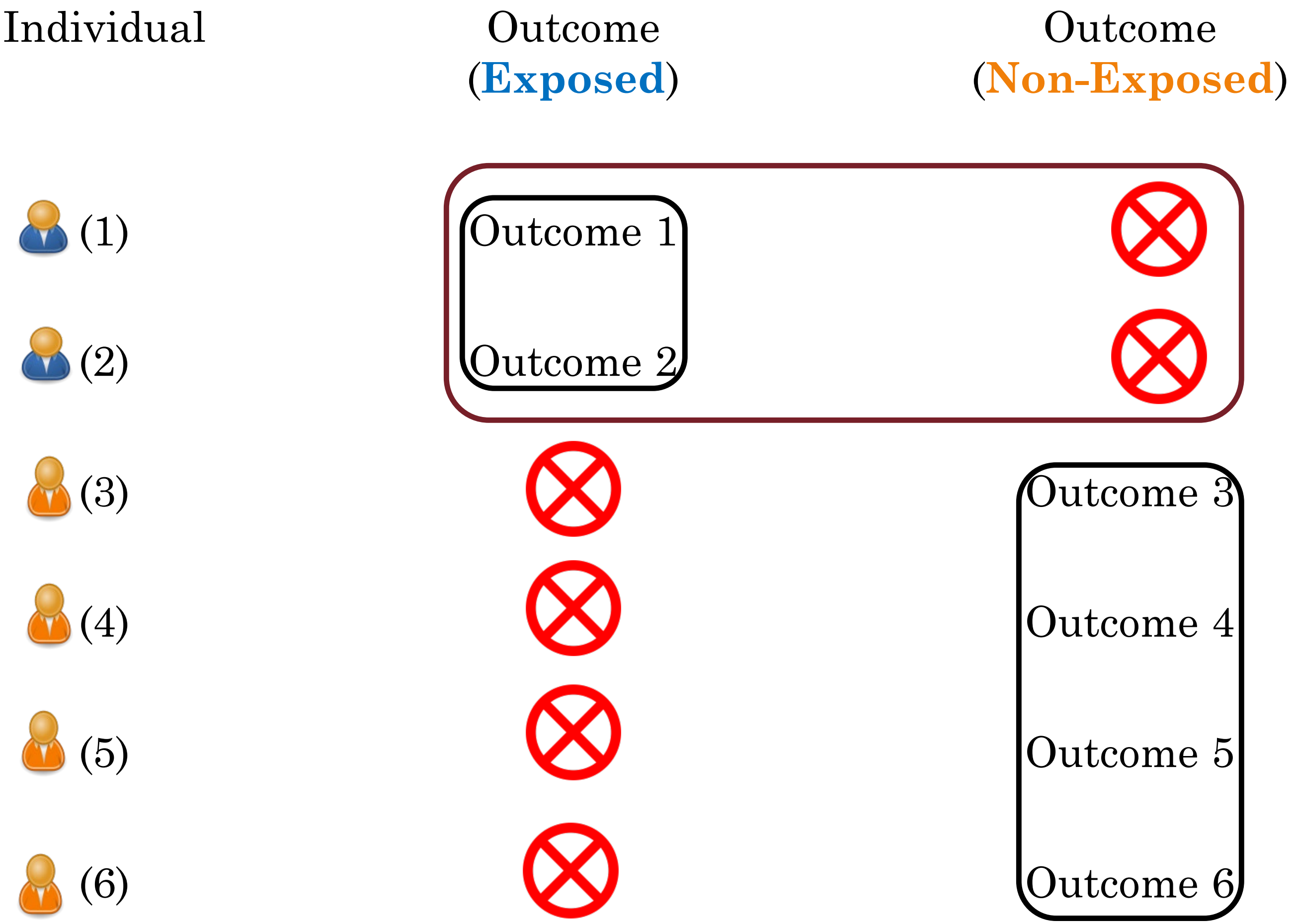
Differences can be due both to age and treatment.



Non-Randomized Studies

- Observational data: what can we estimate?
  - ✓ Average outcome for exposed group
  - ✓ Average outcome for non-exposed group
  - ✗ Differences in outcome *only* due to exposure (i.e., average treatment effect)
- Need non-exposed group to be *similar* to exposed group to assess treatment effect
  - **Propensity score matching methods**
    - **Find a subset of non-exposed individuals who are *similar* to exposed subjects**
    - Estimate the effect of non-exposure only on those individuals
    - Treatment effect: Difference in outcome for exposed vs. matching subset of non-exposed

Non-Randomized Studies

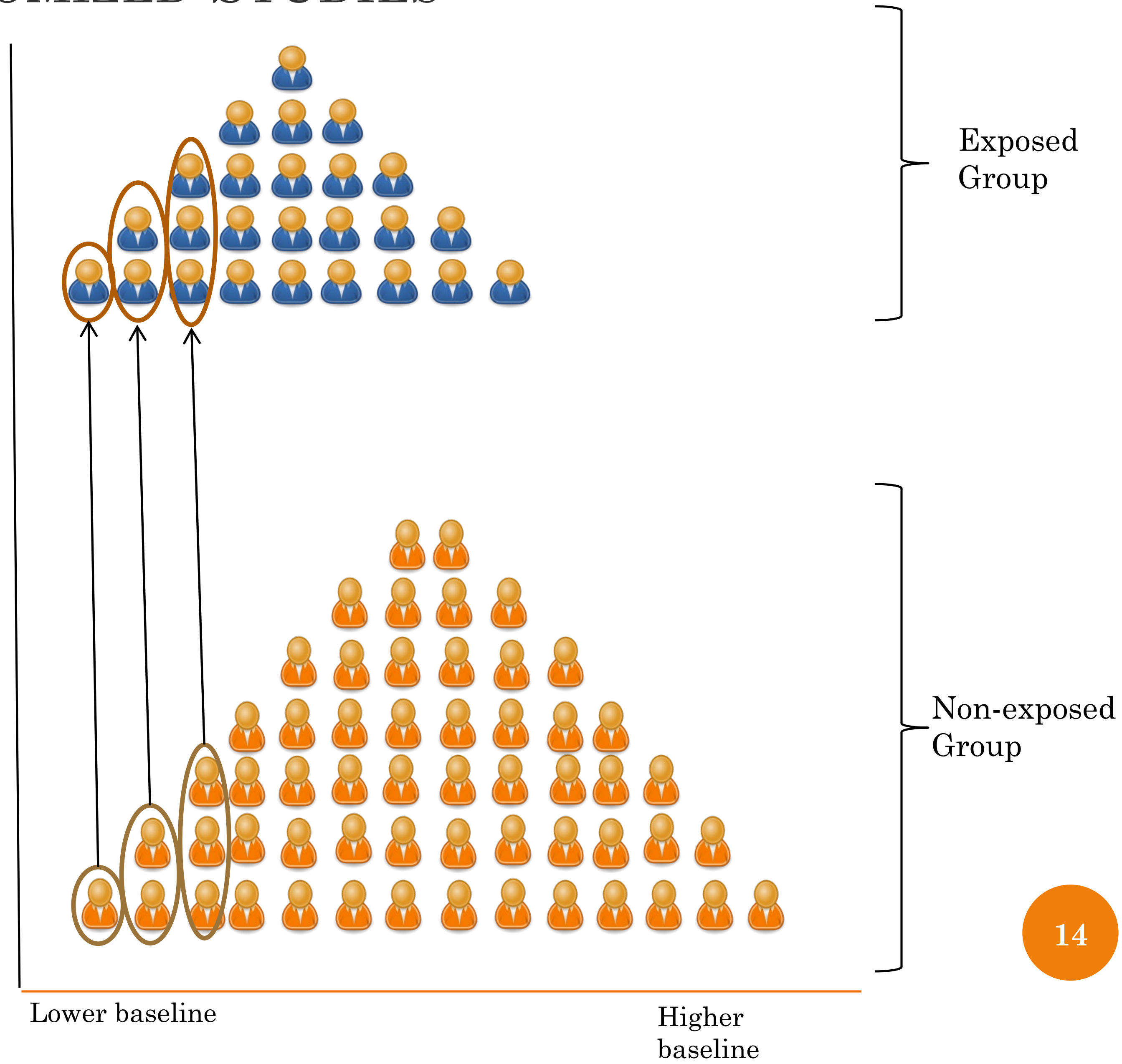


Individual	Outcome (**Exposed**)	Outcome (**Non-Exposed**)
(1)	Outcome 1	⊗
(2)	Outcome 2	⊗
(3)	⊗	Outcome 3
(4)	⊗	Outcome 4
(5)	⊗	Outcome 5
(6)	⊗	Outcome 6

Non-Randomized Studies

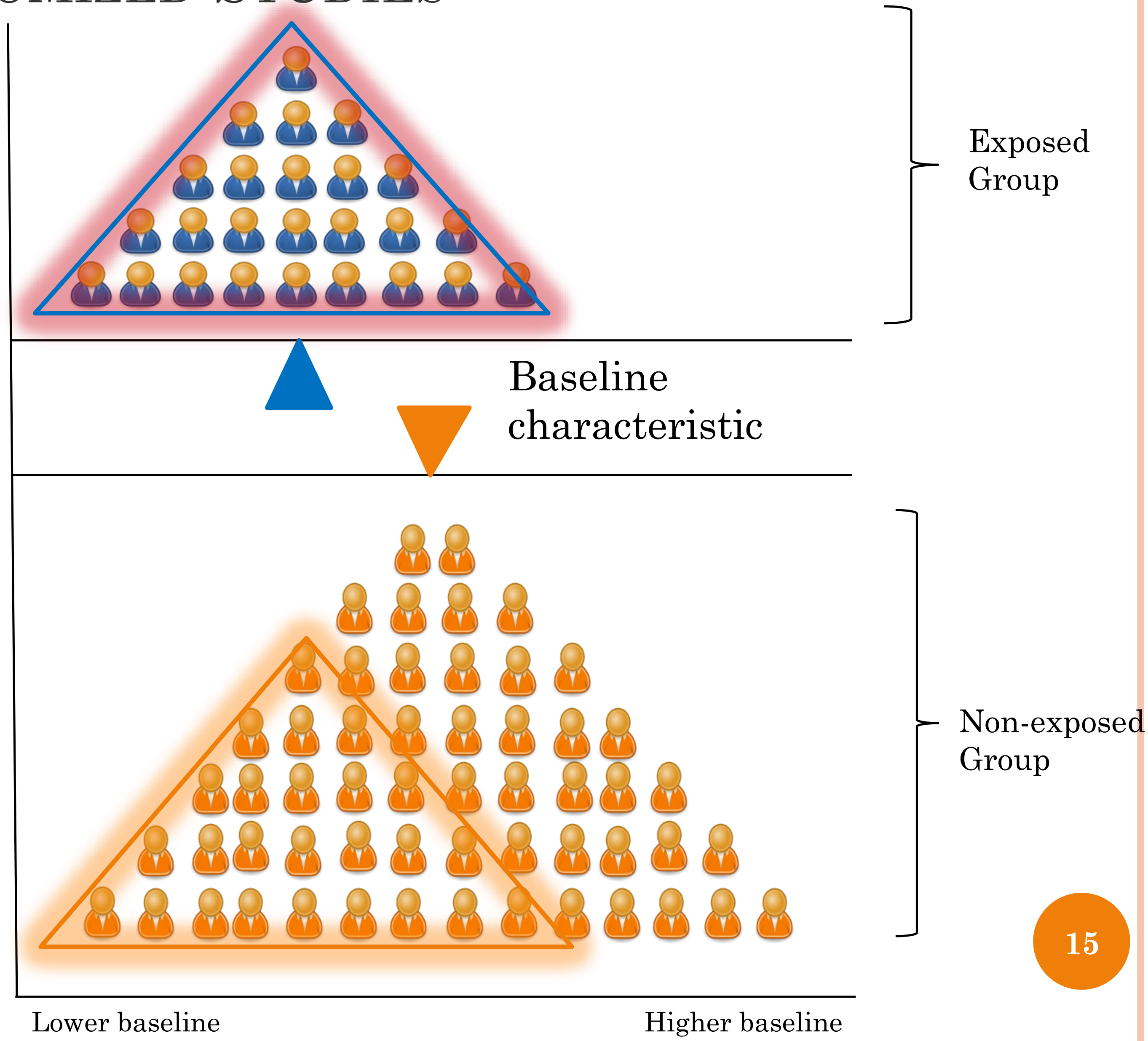
Step 1: Match (i.e., identify) individuals with a similar baseline characteristic.

We find the untreated individuals who best resemble the treated ones by level of the baseline characteristic.



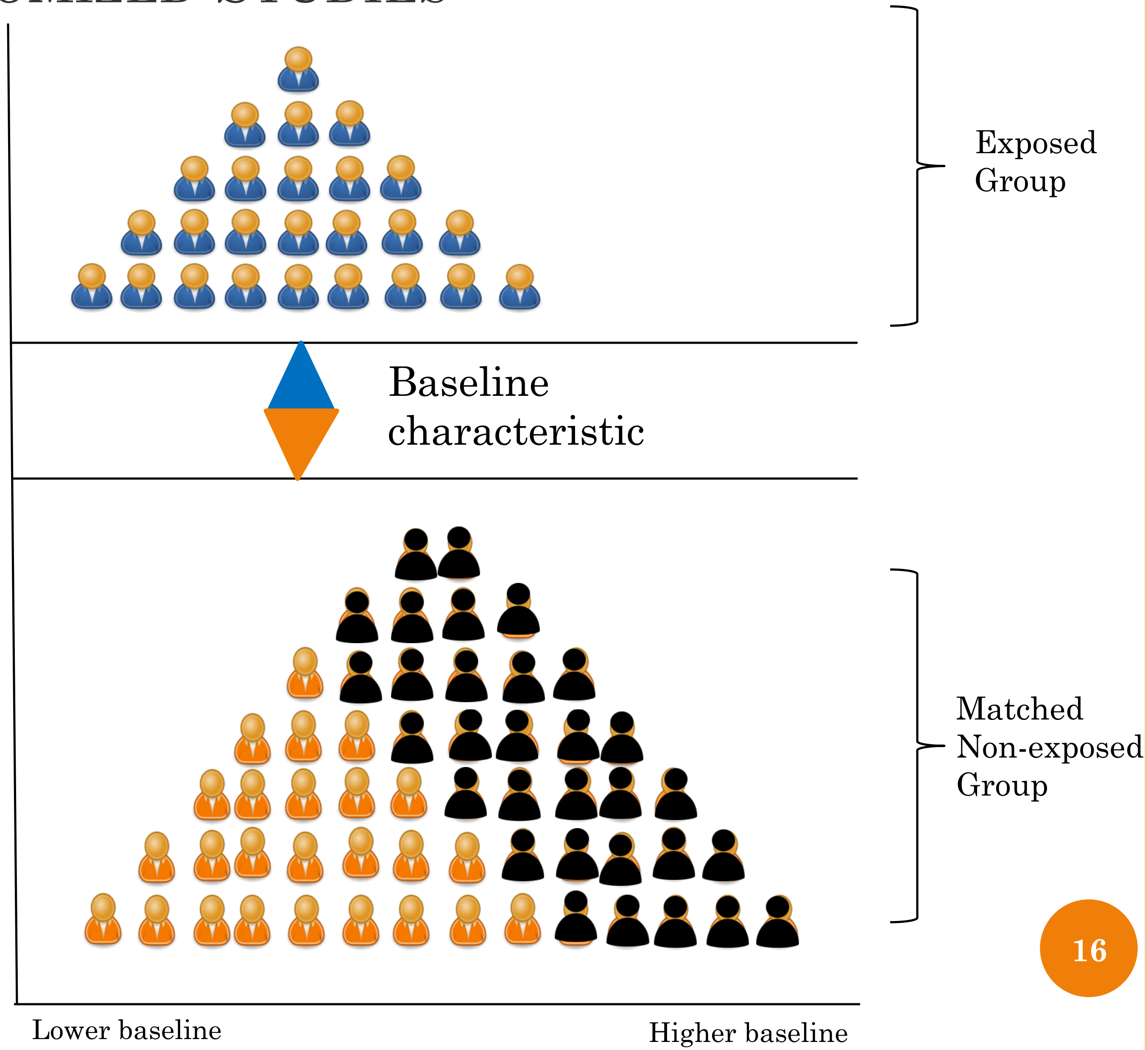
Non-Randomized Studies

Individuals selected from the unexposed group will be the best available matches (by baseline characteristic) for those in the exposed group.



Non-Randomized Studies

Step 2:
Remove individuals who are not a good match, so that the baseline characteristic has no impact on exposure/treatment status.



OUTLINE

- Medical/Population Health Motivation
- Study Design Issues
- **Purpose of Propensity Score Matching (PSM)**
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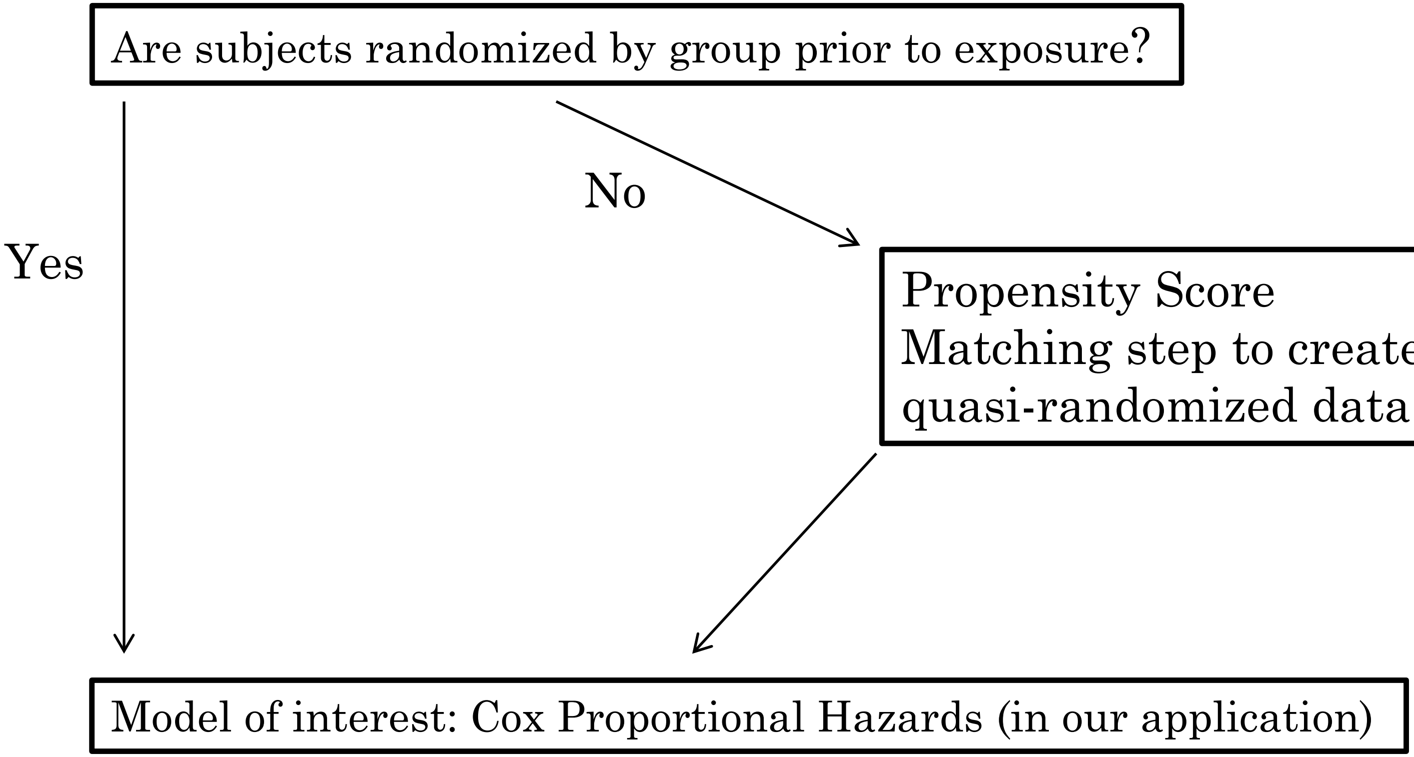
Roadmap to Data Analysis: Causal Effects from Observational Data



Are subjects randomized by group prior to exposure?

Yes

No

Propensity Score Matching step to create quasi-randomized data

Model of interest: Cox Proportional Hazards (in our application)

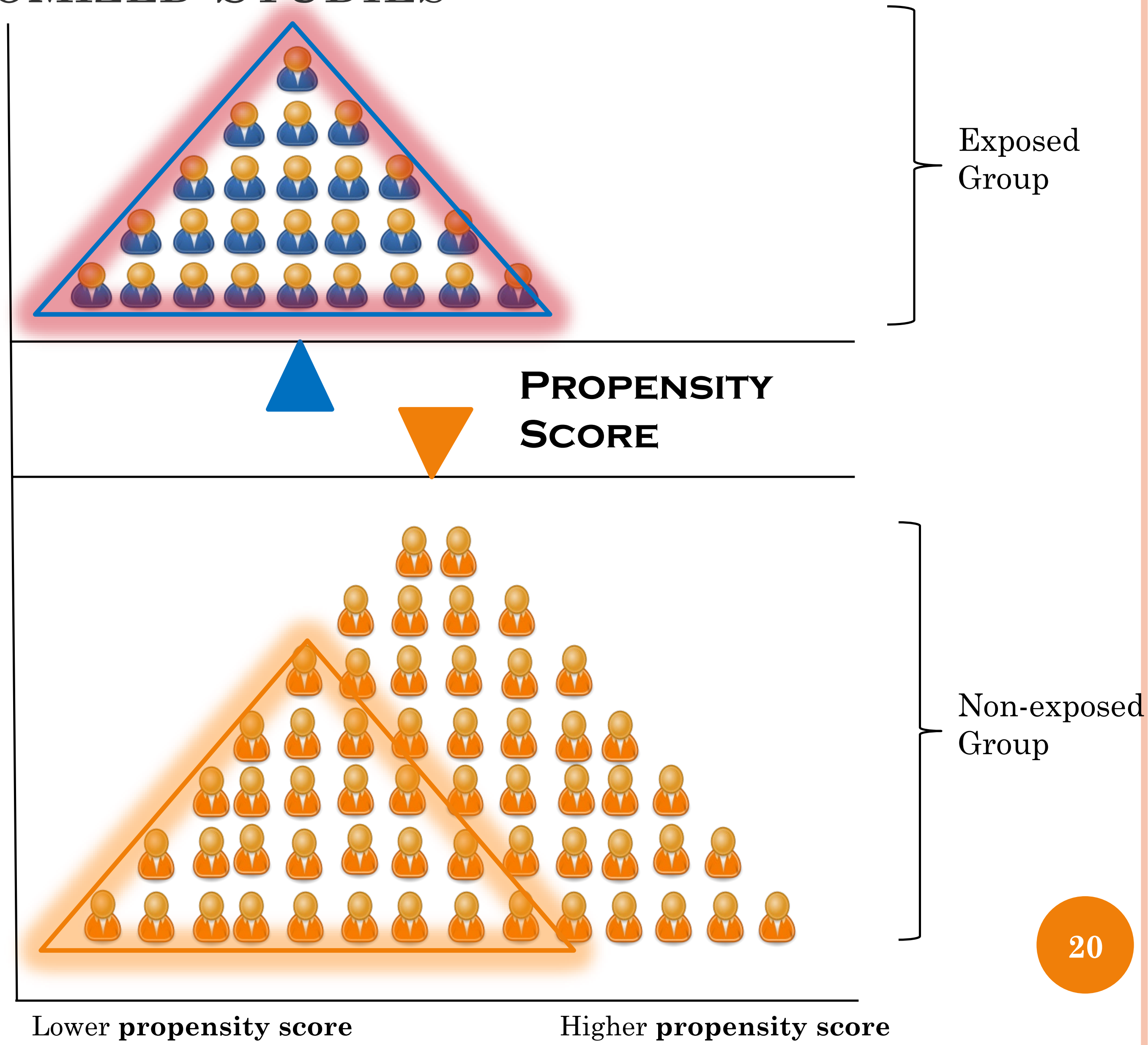
The Need for Propensity Score Matching

- ***Multiple*** baseline characteristics
  - Propensity scores reduce all these characteristics to a *single measure per individual*
    - **This single measure is the probability of exposure given the baseline characteristics**
  - Individuals are matched by propensity score, rather than by each individual baseline characteristic
    - Each individual in the exposure group is matched with an individual having a **similar propensity score** in the non-exposure group
    - For each individual, we can observe the outcome after exposure or outcome after non-exposure, but we cannot observe both
    - The 'matched' non-exposed individuals will assist in estimating the effect of non-exposure for the 'paired' exposed subjects

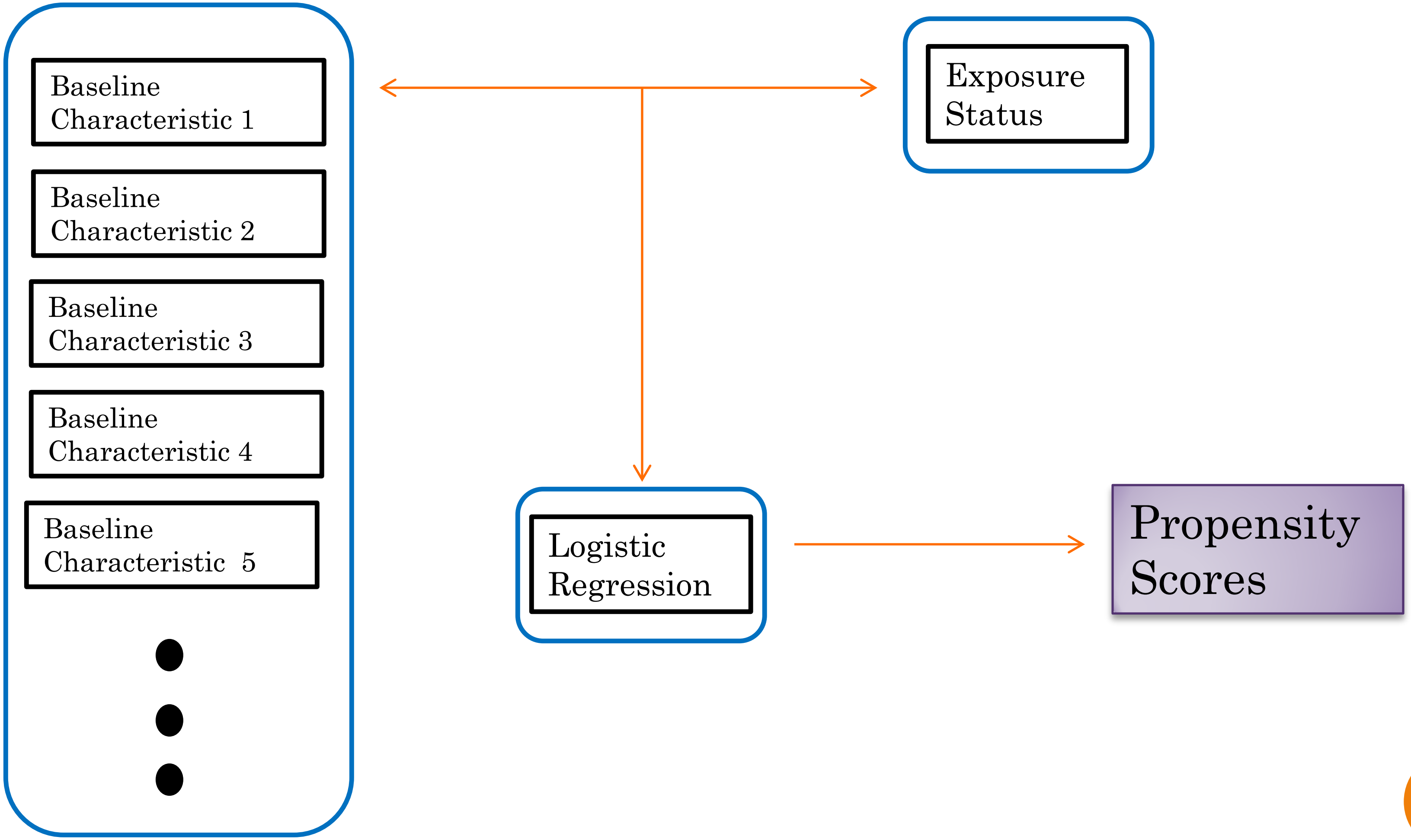
Non-Randomized Studies

When multiple baseline characteristics are present, we match by propensity scores.

Well-known that matching by propensity scores reduces biases (Rosenbaum & Rubin 1985)



Propensity Scores Building Blocks


Baseline Characteristic 1

Baseline Characteristic 2

Baseline Characteristic 3

Baseline Characteristic 4

Baseline Characteristic 5

Exposure Status

Logistic Regression

Propensity Scores

Propensity Score Properties

- Propensity Score (PS) → ***predicted probability of exposure/intervention/treatment given observed baseline characteristics***
- PS is a ***balancing score***
  - Conditional on the PS, the distribution of observed baseline factors is similar between exposed & unexposed individuals
- PS is (usually) estimated with logistic regression
  - Exposure status regressed on observed baseline covariates
  - Other methods also used (see Austin 2011)
- PS ***reduces*** average treatment effect estimation ***biases* in observational studies**

Propensity Score Matching Summary

- **PSM**: process of forming a matched set of exposed & unexposed subjects with a similar PS to estimate the average treatment effect

- Using a matched sample, direct comparisons of outcomes between exposed & unexposed groups are made **to estimate average treatment effects with reduced bias**

- **Emulates analysis of treatment effects in RCTs**

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Techniques In Forming A Matched Sample: I

- **Matching With vs. Without Replacement**
  - With: an unexposed subject can be matched with multiple exposed individuals
  - Without: an unexposed subject is matched with only 1 exposed person

Techniques In Forming A Matched Sample: II

- **Greedy vs. Optimal Matching**
  - **<u>Greedy</u>**
    - Exposed subject selected at random
    - Unexposed subject with closest PS to that of the randomly selected exposed subject is chosen for matching
      - Nearest neighbor matching
      - Nearest neighbor within a pre-specified ***caliper distance***
        - Restricted so that absolute difference in PSs is within threshold
        - If no unexposed subjects meet threshold, then exposed subject is not matched & is discarded
    - At each step, the nearest unexposed subject is chosen to be matched with the exposed subject, even if the unexposed subject has a PS that would better match a different exposed subject
    - **Sequential process until all exposed subjects are matched**

Techniques In Forming A Matched Sample: III

- **Optimal Matching**
  - Subjects are matched to minimize a global distance measure
  - Smallest average absolute distance across all within-pair differences of the PS
  - Greedy & Optimal yield *similar* results (Gu & Rosenbaum 1993)
  - However, Optimal matching is better at minimizing within-pair differences & is preferred when there are fewer control matches for the exposed subjects
  - Greedy is faster, but Optimal is more robust (Gu & Rosenbaum 1993)

Matching Ratios

- 1:1 (pair) matching (most common)
- M:1 (many to one) matching
  - M unexposed subjects matched to a single exposed subject
  - Choice of M is both a science & an art
    - M too small may discard too many unexposed samples (inefficient)
    - M too large may lead to biased samples (PSs may be too dissimilar between groups)

- Matched sets of either:
    - 1 exposed subject to at least 1 unexposed
    - 1 unexposed subject to at least 1 exposed

Balance Diagnostics

- Is the PS model specified appropriately?
- Within the PSM sample:
  - **Are distributions of measured baseline characteristics *similar* between exposed & unexposed subjects with similar PSs?**
  - **Numerical** methods: Are the standardized mean (or prevalence) differences between exposed & unexposed subjects for the covariates small?
    - Although there is no global agreement on threshold for 'small enough', 0.1 units is widely accepted (Normand et al. 2001)
  - **Graphical** methods: boxplots, Q-Q plots, or CDFs

Results of Balance Diagnostics

- If there are still differences, then the model may need modifying
  - Add more covariates
  - Include covariate interactions
- Continue process of modifications & balance-checking until differences are negligible

PSM vs. Regression Adjustment

- For continuous outcomes modeled through linear regression
  - PSM & regression adjustments yield more similar results (Rosenbaum 2005)

- For binary, multi-category, & time-to-event outcomes
  - PSM yields ORs & HRs that reduce bias vs. regression (Austin et al. 2007)

Application in R Statistical Software

- *MatchIt/Matching/PSAgraphics/…*
  - R packages
  - Prepares the observational data for balanced exposure & non-exposure groups prior to parametric analysis (e.g., survival analysis, etc.)
  - Calculate average treatment effect with reduced bias
  - Specify matching method (Greedy/Optimal, Ratio Type, etc.)
  - Balance diagnostics & graphical displays

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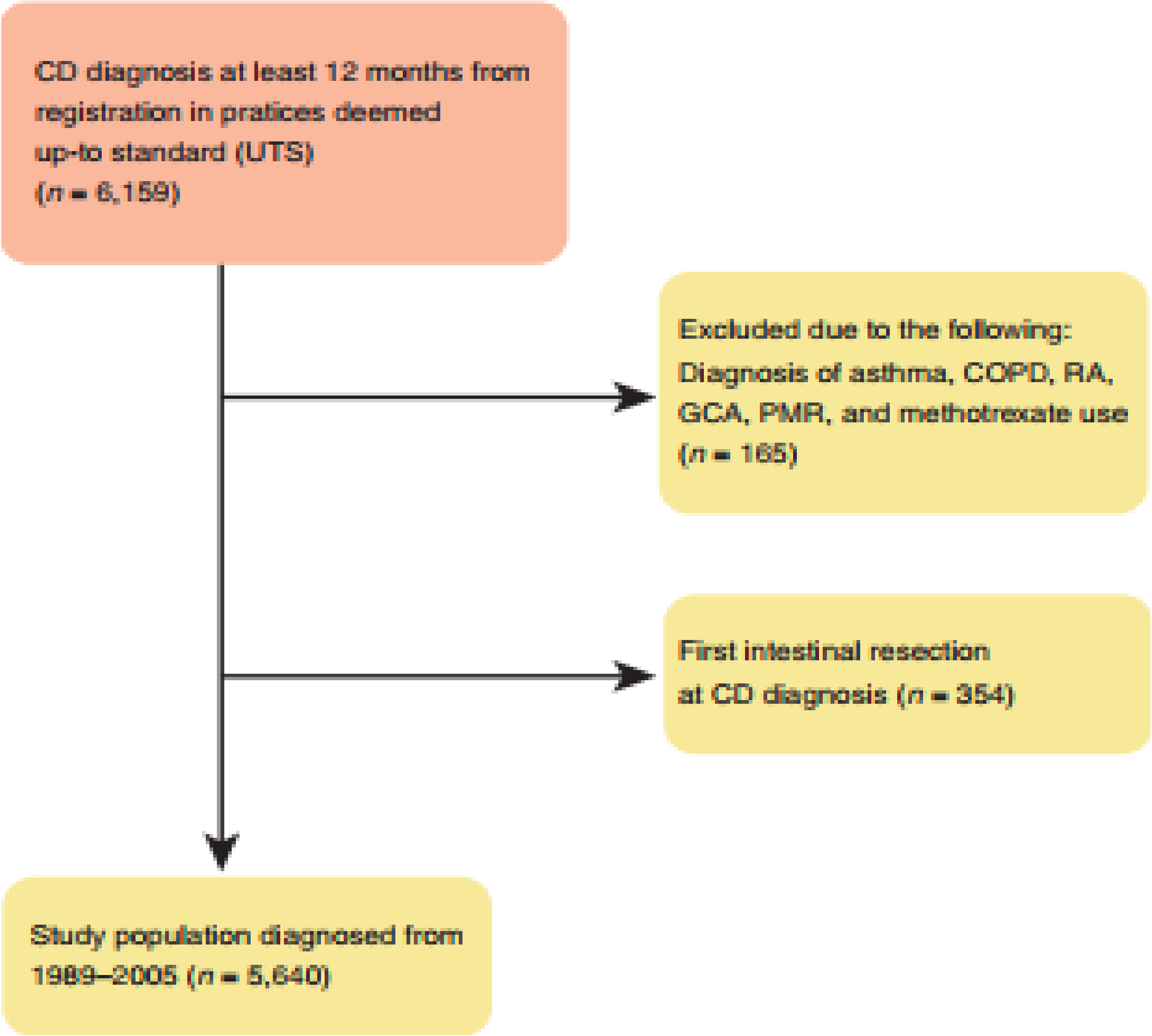
Flow Diagram for UK CPRD Crohn's Cohort Study



CD diagnosis at least 12 months from registration in pratices deemed up-to standard (UTS) (*n* = 6,159)

Excluded due to the following: Diagnosis of asthma, COPD, RA, GCA, PMR, and methotrexate use (*n* = 165)

First intestinal resection at CD diagnosis (*n* = 354)

Study population diagnosed from 1989–2005 (*n* = 5,640)

THIOPURINE (TP) PRESCRIPTION

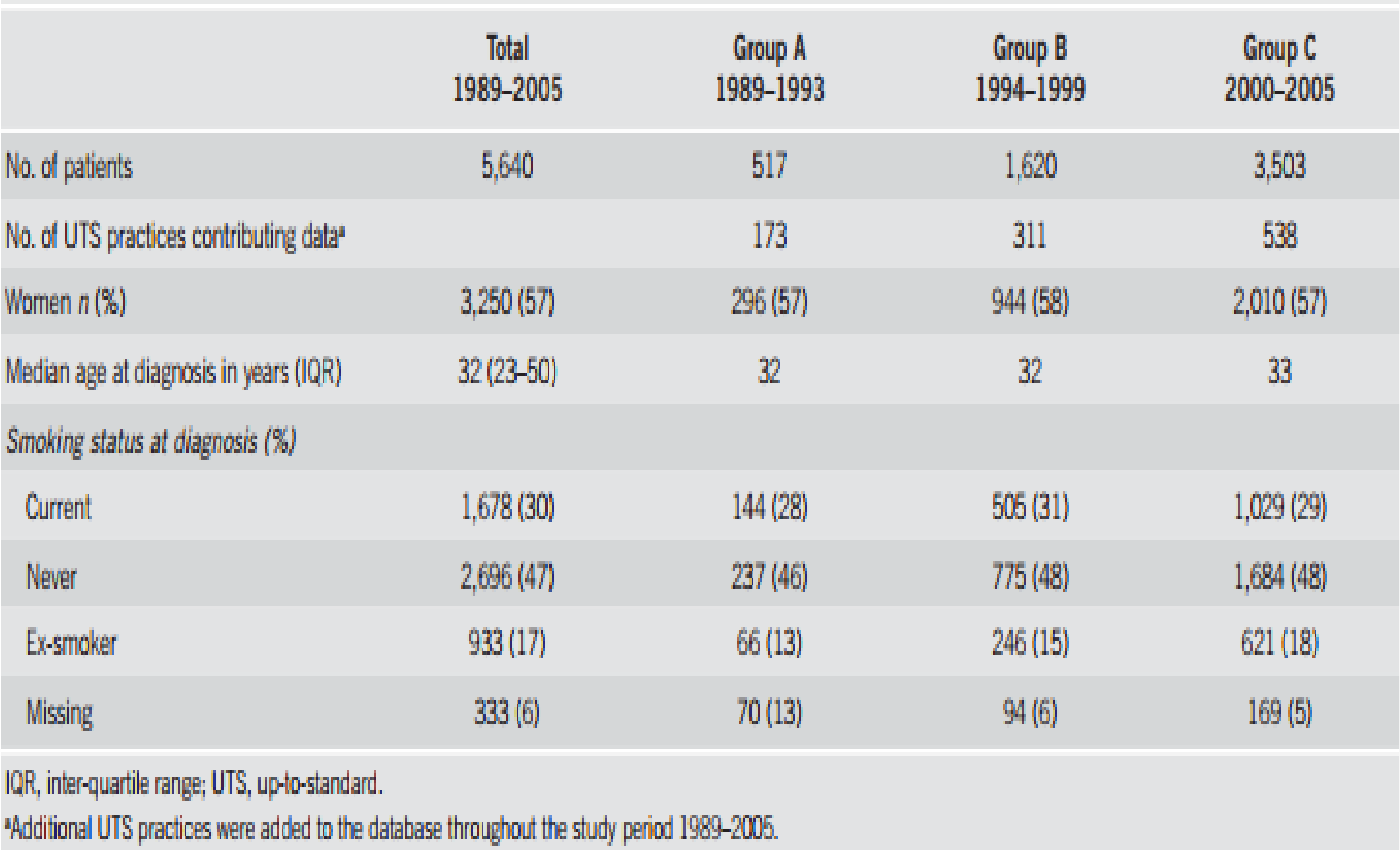
- TP ‘users’
  - ≥ 1 prescription before surgery (or during follow-up, if no surgery)
  - 25% users
- TP ‘non-users’
  - No prescription or 1st prescription after 1st surgical resection
- Early Use
  - Initiated TP within 1st year of diagnosis
- Late Use
  - Initiation after 1st year

- Trends in TP prescribing & first resection
- Compare patients treated with vs. without TPs for:
  - First resection rates
  - Does early or prolonged use impact surgery risk?

DATA

- Treatment duration
  - $\geq$ 6 months
  - $\geq$ 12 months
- Primary Outcome: 1st intestinal resection
- Potential Confounders
  - age of diagnosis; gender; year of diagnosis; history of appendectomy; smoking; 5-aminosalicylic acid (5-ASA); corticosteroid
- Missing Data
  - Due to high level of completeness, used a complete case analysis, thus excluding patients with missing information (~5% of data)

Patient Characteristics at CD Diagnosis



	Total 1989–2005	Group A 1989–1993	Group B 1994–1999	Group C 2000–2005
No. of patients	5,640	517	1,620	3,503
No. of UTS practices contributing data[a]		173	311	538
Women *n* (%)	3,250 (57)	296 (57)	944 (58)	2,010 (57)
Median age at diagnosis in years (IQR)	32 (23–50)	32	32	33
Smoking status at diagnosis (%)				
Current	1,678 (30)	144 (28)	505 (31)	1,029 (29)
Never	2,696 (47)	237 (46)	775 (48)	1,684 (48)
Ex-smoker	933 (17)	66 (13)	246 (15)	621 (18)
Missing	333 (6)	70 (13)	94 (6)	169 (5)

IQR, inter-quartile range; UTS, up-to-standard.

[a] Additional UTS practices were added to the database throughout the study period 1989–2005.

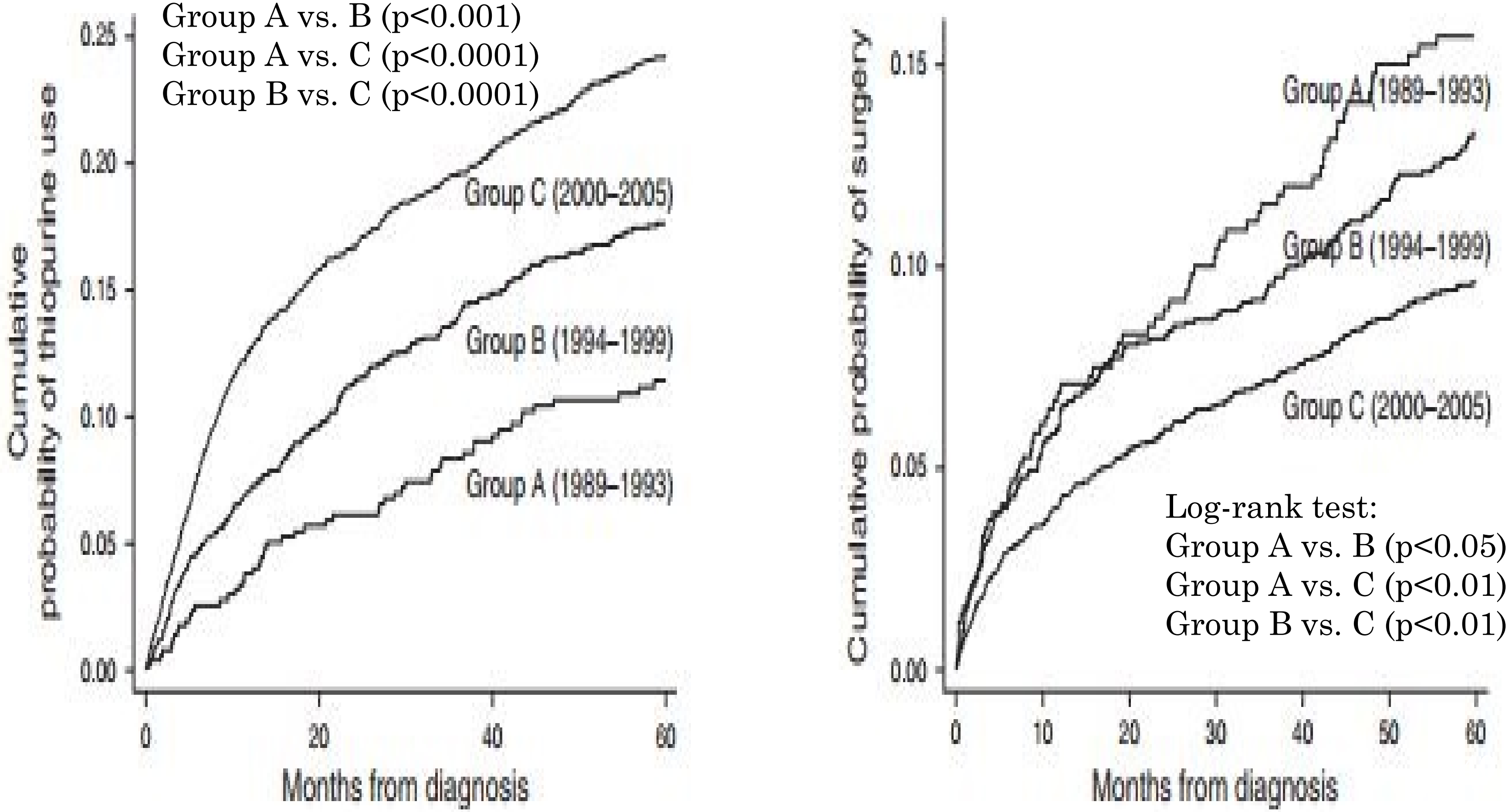
Propensity Score Matching As a Remedy

- To account for inherent selection bias that exists from a historical cohort study
- Calculate PS of thiopurine treatment allocation
- Included all patient-specific covariates into a multivariate logistic regression model to compute PSs for exposed (TP users) & unexposed (non-users)
- 2:1 Optimal matching
- Checked balance diagnostics
- Sensitivity analyses
  - 3:1; 2:1; & 1:1 matching ratios
  - Greedy matching

Cox Proportional Hazards Model

- Applied Cox-PH on **matched data** to determine effect of TP use on 1st intestinal resection in CD patients
- Hazard Ratios (HRs) & 95% CIs
- Sensitivity analysis
  - Greedy matching: *similar* results, however 5-ASA becomes non-significant (p=0.1223) on risk of surgery
    - Nearly 80% of the matched controls were the same in both algorithms
  - Balance diagnostics
    - 1:1 Optimal matching provided best balance diagnostics with all covariate mean & prevalence differences within 0.04 units, however this ratio discards the most data
    - 2:1 Optimal: all differences within 0.06 units except 1 covariate within 0.1 units
    - 3:1 Optimal: all within 0.09 units except 1 covariate within 0.2 units

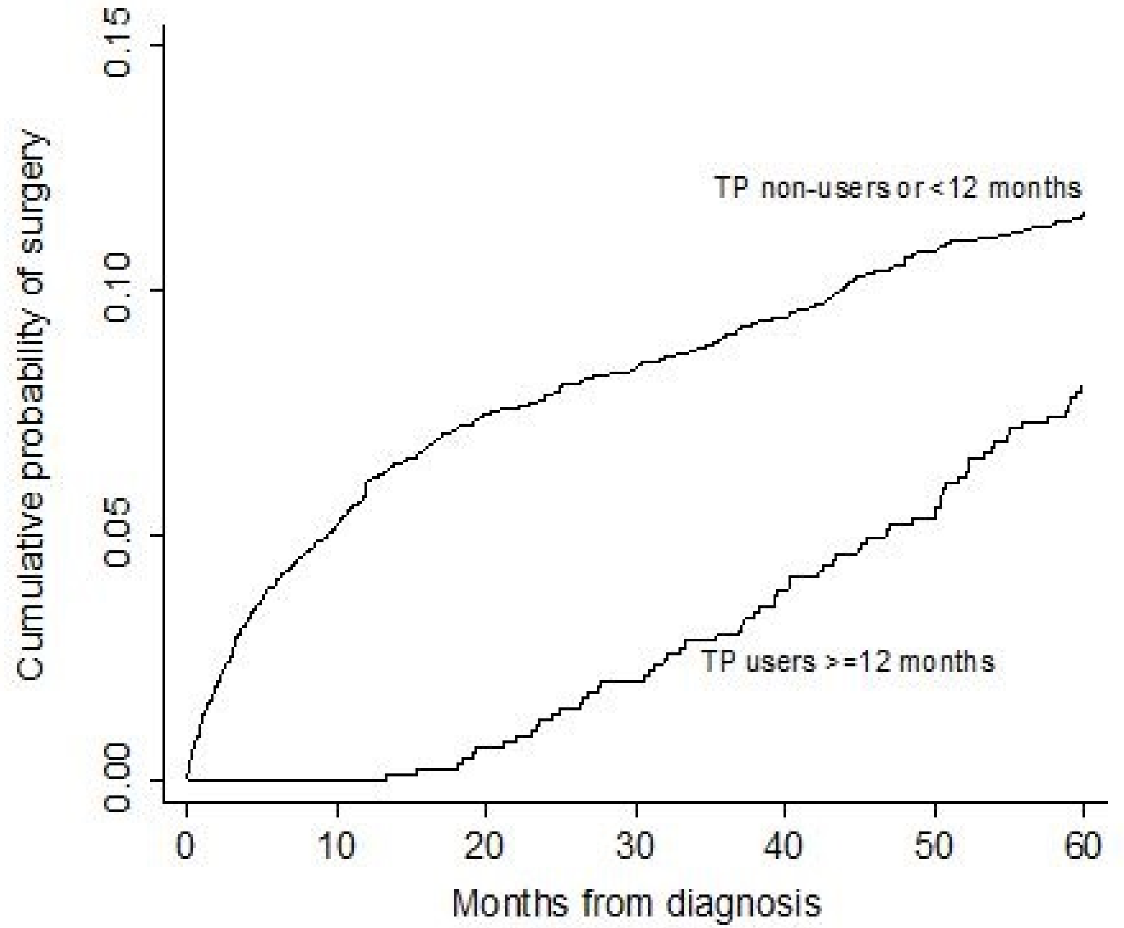
Kaplan- Meier Curve Comparing Cumulative Probability of: TP Use (left) & 1st Intestinal Surgery (right) after CD Diagnosis by Period of Diagnosis



Log-rank test:
Group A vs. B ($p<0.001$)
Group A vs. C ($p<0.0001$)
Group B vs. C ($p<0.0001$)

Log-rank test:
Group A vs. B ($p<0.05$)
Group A vs. C ($p<0.01$)
Group B vs. C ($p<0.01$)

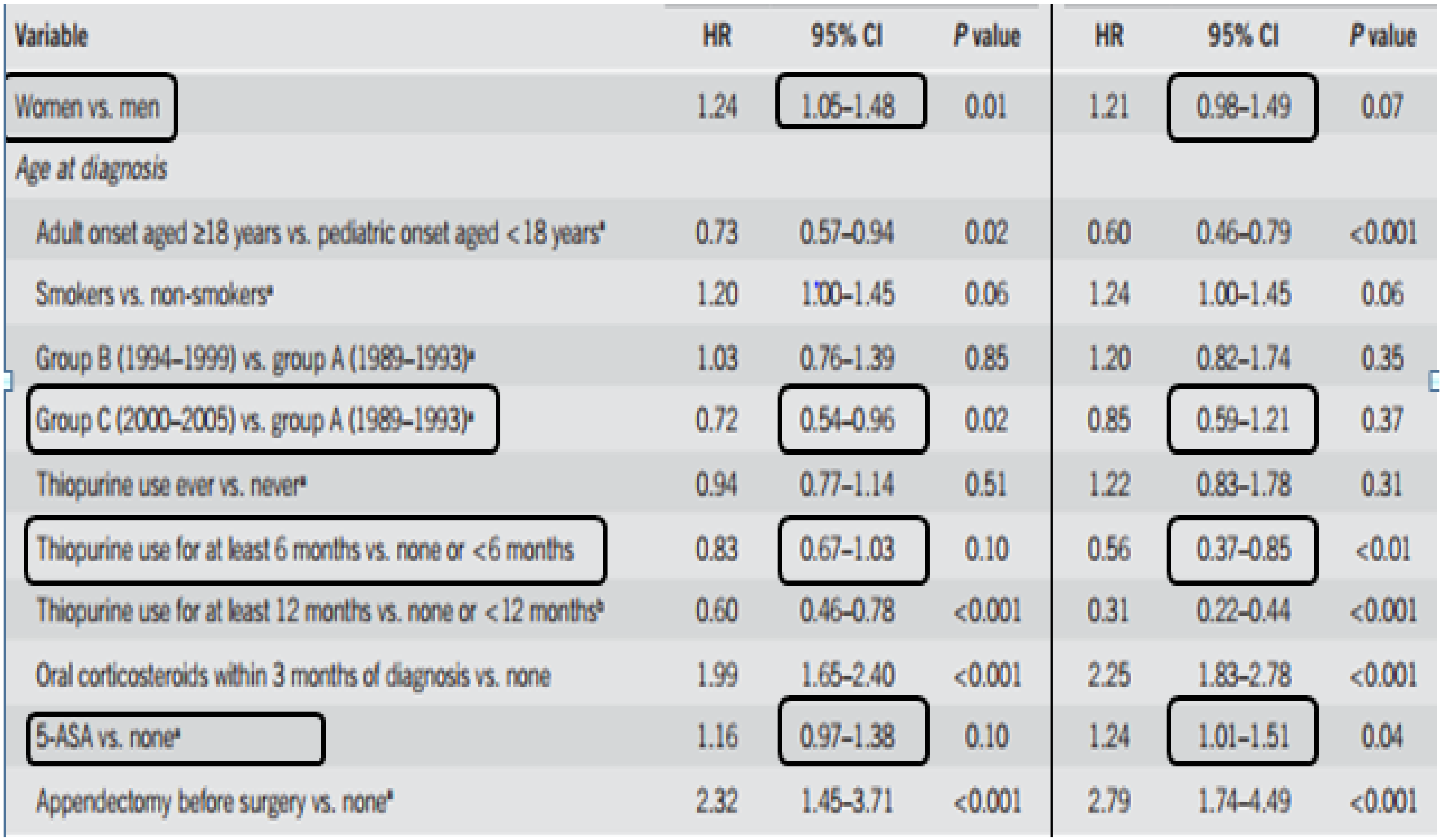
K-M Curve Comparing 5-Year Cumulative Probability of Surgery in CD Patients Receiving ≥12 Months of Thiopurine (TP) vs. Non-Users or Those Who Receiving <12 Months of therapy



Log-rank test:
p<0.001

What are Risk & Protective Factors for Surgery?

Cox Regression after Adjusting for 2:1 Optimal Propensity Score Matching (right), Showing Hazard Ratios (HRs) for Risk of Surgery within 5 Years of CD Diagnosis



	Before PSM			After PSM		
Variable	HR	95% CI	*P* value	HR	95% CI	*P* value
Women vs. men	1.24	1.05–1.48	0.01	1.21	0.98–1.49	0.07
Age at diagnosis						
Adult onset aged ≥18 years vs. pediatric onset aged <18 years[a]	0.73	0.57–0.94	0.02	0.60	0.46–0.79	<0.001
Smokers vs. non-smokers[a]	1.20	1.00–1.45	0.06	1.24	1.00–1.45	0.06
Group B (1994–1999) vs. group A (1989–1993)[a]	1.03	0.76–1.39	0.85	1.20	0.82–1.74	0.35
Group C (2000–2005) vs. group A (1989–1993)[a]	0.72	0.54–0.96	0.02	0.85	0.59–1.21	0.37
Thiopurine use ever vs. never[a]	0.94	0.77–1.14	0.51	1.22	0.83–1.78	0.31
Thiopurine use for at least 6 months vs. none or <6 months	0.83	0.67–1.03	0.10	0.56	0.37–0.85	<0.01
Thiopurine use for at least 12 months vs. none or <12 months[a]	0.60	0.46–0.78	<0.001	0.31	0.22–0.44	<0.001
Oral corticosteroids within 3 months of diagnosis vs. none	1.99	1.65–2.40	<0.001	2.25	1.83–2.78	<0.001
5-ASA vs. none[a]	1.16	0.97–1.38	0.10	1.24	1.01–1.51	0.04
Appendectomy before surgery vs. none[a]	2.32	1.45–3.71	<0.001	2.79	1.74–4.49	<0.001

[1]Reference group. Analysis based on 2:1 optimal matching between TP users and non-users (n=3,693),

*All multivariate results are shown for the model including TP use for ≥12 months (omitting 6 months duration). TP use for ≥6 months was added separately when the 12 months duration was removed; this was due to substantial multicollinearity present in the model.

- *When should therapy be initiated?*
  - *Sub-analysis of 879 CD patients with ≥ 12 months of therapy showed that both early (within 1 yr of diagnosis) & late (after 1 yr of diagnosis) initiation reduced risk of surgery*
  - *Early: HR=0.41; 95% CI: (0.27,0.61)*
  - *Late: HR=0.21; 95% CI: (0.13,0.34)*

More Application Details Available In:

- The Impact of Timing and Duration of Thiopurine Treatment on First Intestinal Resection in Crohn's Disease: National UK Population-Based Study 1989-2010.
- *American Journal of Gastroenterology*. 2014;109:409-16. https://www.nature.com/articles/ajg2013462
- Joint work with:
  - Sukh Chatu
    - Consultant Gastroenterologist & Physician, King's College Hospital, London
  - Richard Pollok
    - Dept. of Gastroenterology, St. George's University Hospital, London
  - Azeem Majeed
    - Professor & Dept. Head, Primary Care & Public Health, Imperial College London
  - Sonia Saxena
    - Professor, Primary Care & Public Health, Child Health Unit, Imperial College London
  - Ghasem Yadegarfar
    - Dept. of Primary Care and Public Health, Imperial College London
  - Venkat Subramanian
    - Clinical Associate Professor & Honorary Consultant Gastroenterologist, Leeds Institute of Biomedical & Clinical Sciences, University of Leeds;
      Dept. of Gastroenterology, St. James's University Hospital, Leeds
  - Vasa Curcin
    - Dept. of Computing, Imperial College London

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NEXT STEPS: BIG DATA & STATISTICS

- Multi-year cohort study on U.K. diabetic population to assess effect of exposure status (meeting QOF/NDA targets) on hospital admissions & mortality
  - Propensity score matching methods needed
- U.K. Population data with tens of millions of observations
  - CPRD diabetic population (2010-2017)
  - Joint work with colleagues at School of Public Health, Faculty of Medicine, Imperial College London
  - Big Data & Analytical Unit, Imperial College London
- New wave of data management & methods
  - Statistical methods to handle increasingly large data
  - Messy data from multiple sources require combining & cleaning

THANK YOU

- **Questions?**

- **References**

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