W28: Advanced Methods for Matching-Adjusted Indirect Comparison (MAIC)

2024 ISPOR Atlanta

DISCUSSION LEADER

Shannon Cope, MSc

PRECISIONheor, Vancouver, BC, Canada

DISCUSSANTS

Harlan Campbell, PhD

University of British Columbia,

PRECISIONheor, Vancouver, BC, Canada

Antonio Remiro-Azócar, PhD

Novo Nordisk, Madrid, Spain

Speakers

Speaker	Disclosures
Shannon Cope, MSc PRECISIONheor, Vancouver, Canada	No conflicts of interest relevant to the content of this workshop
Harlan Campbell, PhD University of British Columbia PRECISIONheor, Vancouver, Canada	No conflicts of interest relevant to the content of this workshop
Antonio Remiro-Azócar, PhD Novo Nordisk, Madrid, Spain	No conflicts of interest relevant to the content of this workshop

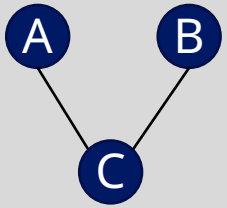
Agenda

Topic	
Part 1 - The main issues involved with existing MAIC methods • When are population-adjusted ITCs needed? • When are MAIC methods possible/useful?	20 min
Part 2 - Alternative weighting approaches for anchored MAICs, featuring two-stage MAIC	15 min
Part 3 - "Augmented MAIC" for doubly-robust estimation	15 min
Audience discussion	10 min

Part 1 Overview

- Background
  - Anchored vs. unanchored indirect treatment comparisons (ITCs)
  - *Example: Anchored ITC (Bucher)*
  - *Example: Availability of individual patient data (IPD)*
  - Effect modifiers (EMs) versus prognostic factors (PFs)
  - Population adjusted indirect comparisons (PAICs)
  - *Example: Anchored PAIC - MAIC*
  - Types of adjustment methods
  - Anchored & unanchored PAICs
  - PAICs in practice & challenges
- Anchored MAIC feasibility:
  - Clinical assessment
  - Numerical assessment
  - *Example: MAIC numerical feasibility*
  - Takeaways for MAIC protocol

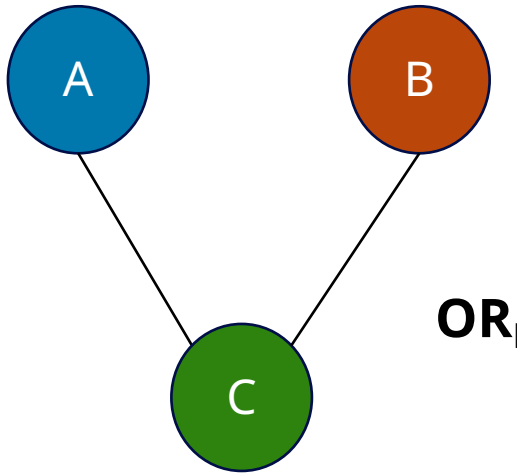
Anchored versus unanchored ITCs

Anchored	Unanchored
Common comparator?  	No connected network of RCTs or only single-arm studies? 
$\widehat{\Delta}_{AB} = \widehat{\Delta}_{AC} - \widehat{\Delta}_{BC}$	$\widehat{\Delta}_{AB} = g(\hat{\mu}_A) - g(\hat{\mu}_B)$

Adapted from: Farinasso et al. 2023 Mapping the characteristics, concepts and methodologies of matching-adjusted indirect comparison studies assessing pharmacological therapies in oncology: a scoping review protocol. BMJ Open (based on NICE DSU Technical Document 18)

Example: Anchored ITC (Bucher)

AC
A 😐
A 😐
A ☺
A ☺
A ☺
C 😐
C 😐
C 😐
C ☺
C ☺



$$\mathbf{OR_{AC}} = \frac{(3/5)/(2/5)}{(2/5)/(3/5)} = 2.25$$

$$\mathbf{OR_{BC}} = \frac{(2/5)/(3/5)}{(1/5)/(4/5)} = 2.67$$

$$\log(\mathbf{OR_{AB}}) = \log(\mathbf{OR_{AC}}) - \log(\mathbf{OR_{BC}})$$
$$= 0.81 - 0.98$$
$$= -0.17$$
$$\mathbf{OR_{AB}} = \exp(-0.17)$$
$$= 0.84$$

Treatment B better than A

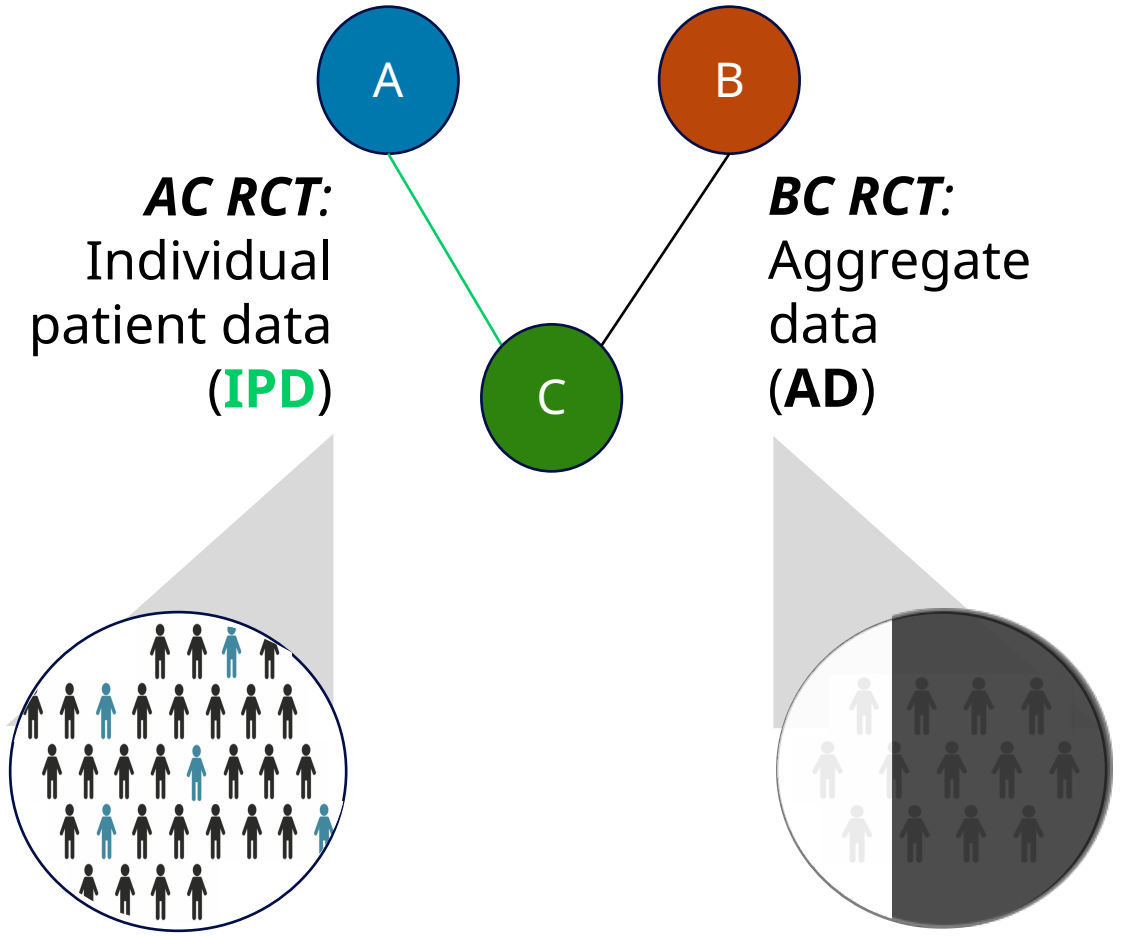
BC
B 😐
B 😐
B 😐
B ☺
B ☺
C 😐
C 😐
C 😐
C 😐
C ☺

☺=Response; 😐=No response

Example: Availability of individual patient data

AC	Age	TSD
A 😐	23	2
A 😐	44	15
A ☺	34	7
A ☺	64	14
A ☺	27	4
C 😐	34	11
C 😐	61	18
C 😐	25	10
C ☺	63	17
C ☺	25	16
Mean	*40*	*11*
SD	*17*	*6*

AC RCT: Individual patient data (**IPD**)

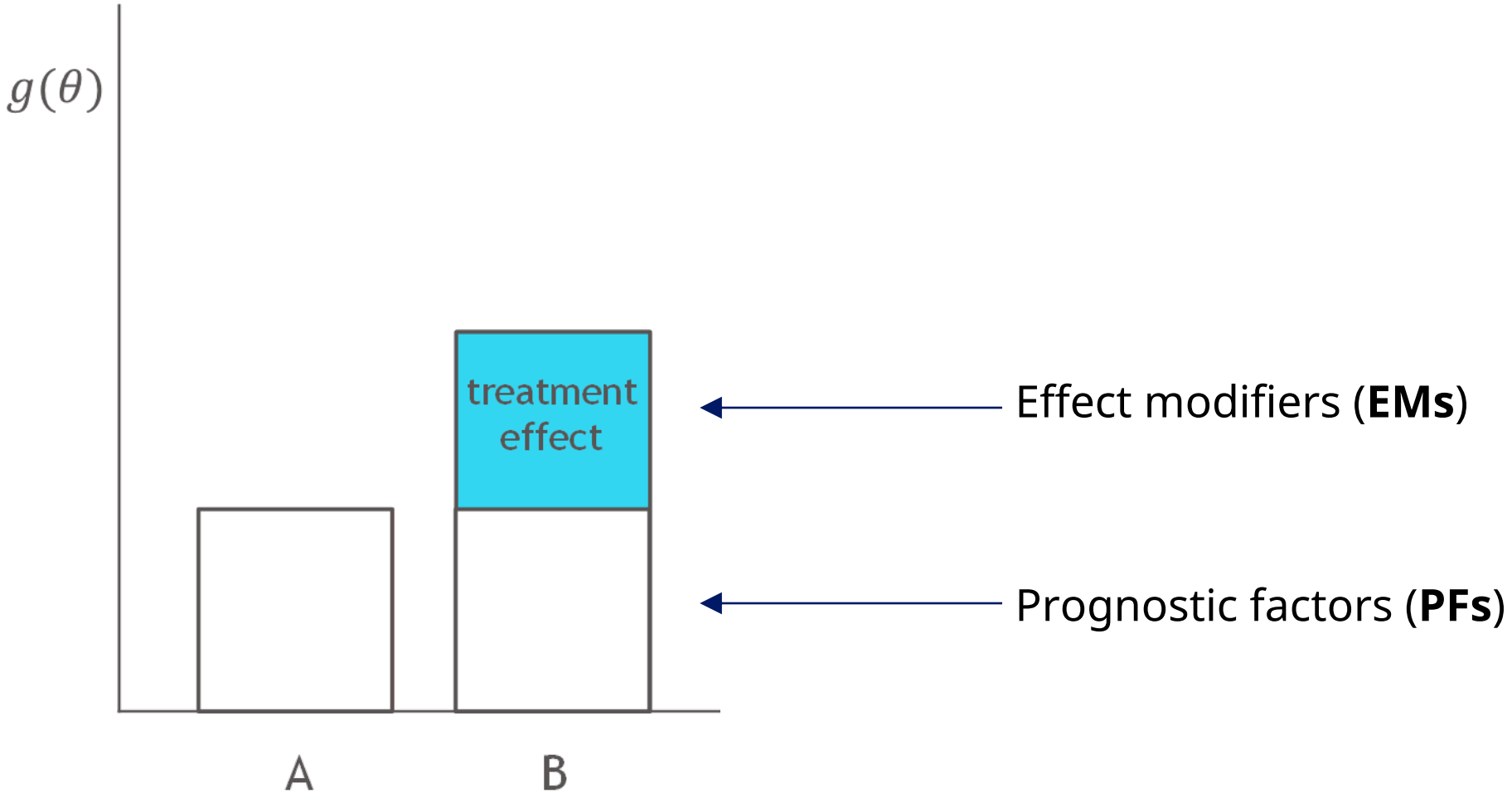


BC RCT: Aggregate data (**AD**)

BC	Age	TSD
B 😐	--	--
B 😐	--	--
B 😐	--	--
B ☺	--	--
B ☺	--	--
C 😐	--	--
C 😐	--	--
C 😐	--	--
C 😐	--	--
C ☺	--	--
Mean	*55*	*8*
SD	*12*	*2*

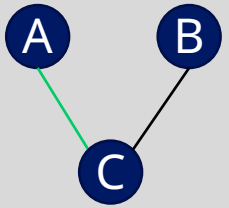
TSD=Time since diagnosis; ☺=Response; 😐=No response

Effect modifiers & prognostic factors



Adapted from: Jansen JP, Trikalinos T, Cappelleri JC, Daw J, al e. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC good practice task force report. Value Health. March 2014;17(2):157-73

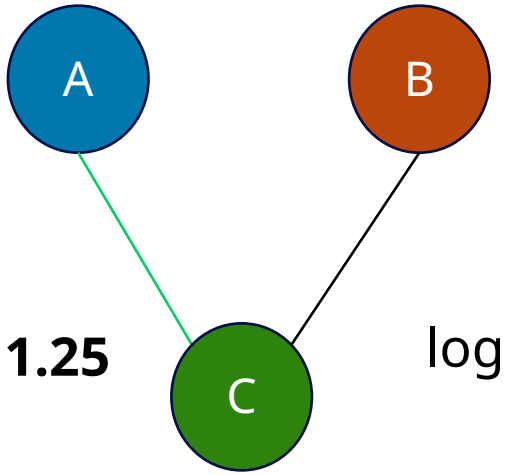
Population-adjusted indirect comparisons

Anchored	Unanchored
Common comparator? Individual patient data (IPD) rather than aggregate data (AD)? 	No connected network of RCTs/ only single- arm studies? Individual patient data (IPD) rather than aggregate data (AD)? 
$\hat{\Delta}_{AB}^{(B)} = \hat{\Delta}_{AC}^{(B)} - \hat{\Delta}_{BC}^{(B)}$	$\hat{\Delta}_{AB}^{(B)} = g\left(\hat{\mu}_{A}^{(B)}\right) - g\left(\hat{\mu}_{B}^{(B)}\right)$
Adjust for **imbalanced EMs** to reduce bias?	Adjust for **PFs** and **EMs** to reduce bias?

Adapted from: Farinasso et al. 2023 Mapping the characteristics, concepts and methodologies of matching-adjusted indirect comparison studies assessing pharmacological therapies in oncology: a scoping review protocol. BMJ Open (based on NICE DSU Technical Document 18)

Example: Anchored PAIC - MAIC

AC	Age	Weight
A 😐	23	0.22
A 😐	44	0.79
A ☺	34	0.43
A ☺	64	2.64
A ☺	27	0.28
C 😐	34	0.43
C 😐	61	2.21
C 😐	25	0.25
C ☺	63	2.49
C ☺	25	0.25
Mean	*40*	
SD	*17*	
WMean	***55***	



Weighted log(OR_{AC}) = 1.25

$OR_{BC} = 2.67$

$\log(OR_{BC}) = 0.98$

$$\log(OR_{AB}) = \log(OR_{AC}) - \log(OR_{BC})$$
$$= \mathbf{1.25} - 0.98$$
$$= 0.27$$
$$OR_{AB} = \exp(0.27)$$
$$= 1.31$$

Treatment A better than B

BC	Age
B 😐	--
B 😐	--
B 😐	--
B ☺	--
B ☺	--
C 😐	--
C 😐	--
C 😐	--
C 😐	--
C ☺	--
Mean	*55*
SD	*12*

☺=Response; 😐=No response

Types of population adjustment methods

Description	Model	Assumption
Propensity-score based method	Weights from T | X model Y | T	*Trial/treatment allocation model is correct*
Outcomes-regression based method	Y | T & X	*Outcome model is correct*
Doubly-robust method	Weights from T | X model Y | T & X	*Either trial allocation model or outcome model is correct*

Y = Outcome, T=Treatment/Trial, X=Covariates

Adapted from: Park JE, Campbell H, Towle K, et al. Unanchored Population-Adjusted Indirect Comparison Methods for Time-to-Event Outcomes Using Inverse Odds Weighting, Regression Adjustment, and Doubly Robust Methods With Either Individual Patient or Aggregate Data. Value in Health. 2023-12-01 2023

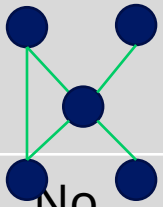
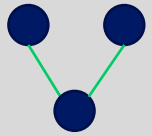
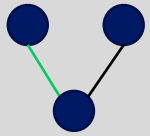
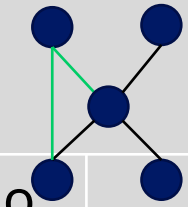
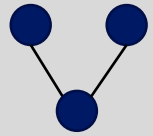
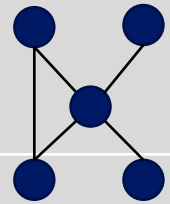
Unanchored ITCs

Unanchored indirect treatment comparisons (ITCs) for 2 treatments*					
IPD-IPD 		IPD [Index trial(s)]-AD [External trial(s)] 		All AD 	
No Cov	PFs and EMs	No Cov	PFs and EMs	No Cov	PFs and EMs
Naïve ITC	External controls (ATE, ATT, ATC): Unanchored IOW Unanchored RA Unanchored DR	Naïve ITC	Unanchored PAICs (ATC): Unanchored MAIC Unanchored STC Unanchored Augmented MAIC	Naïve ITC	--

Abbreviations: AD: Aggregate data; Cov: Covariates; DR: Doubly robust; IOW: Inverse odds weighting; IPD: individual patient data; MAIC: Matching-adjusted indirect comparison; RA: Regression adjustment; STC: Simulated treatment comparison; tx: Treatment

Park JE, et al. Unanchored Population-Adjusted Indirect Comparison Methods for Time-to-Event Outcomes Using Inverse Odds Weighting, Regression Adjustment, and Doubly Robust Methods With Either Individual Patient or Aggregate Data. Value in Health. 2023-12-01 2023

Anchored ITCs

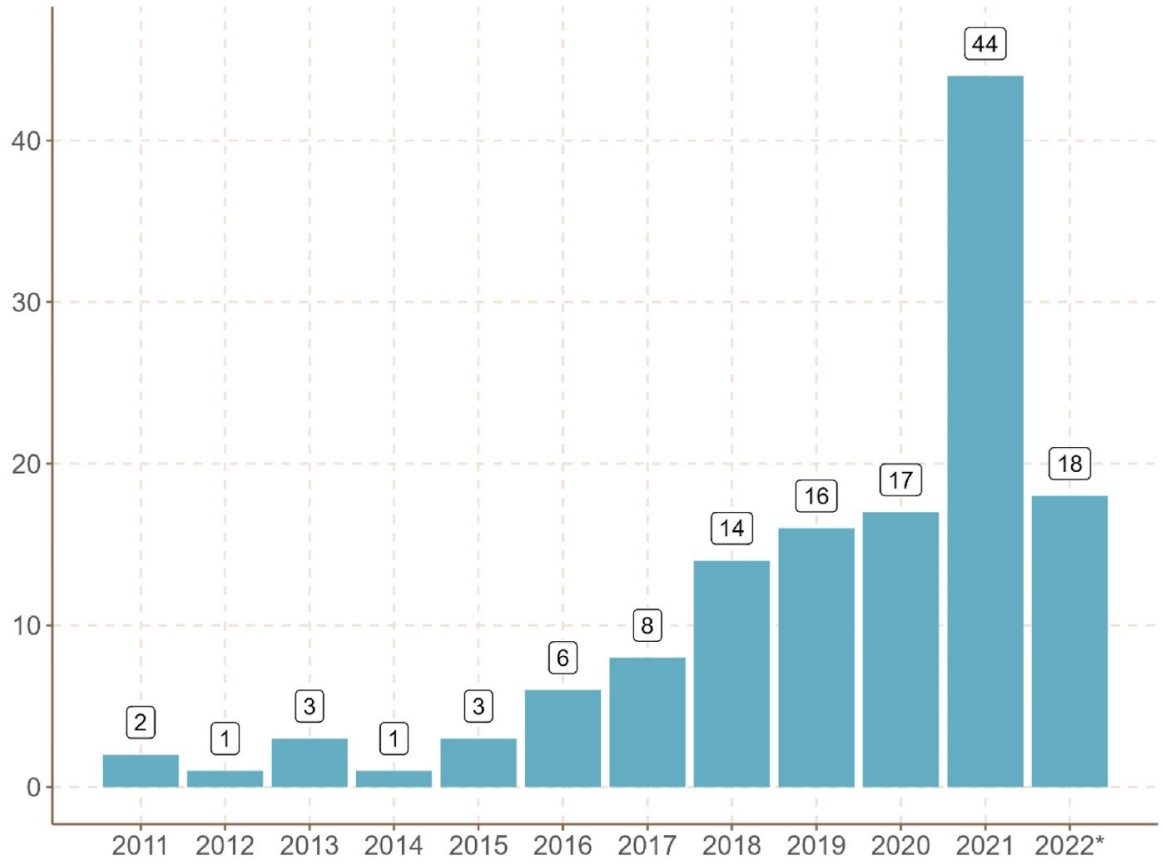
Anchored indirect treatment comparisons (ITCs)							
All **IPD**		Mix **IPD** and **AD**				All **AD**	
Any # comparisons		2 tx comparisons		>2 tx comparisons		Any # comparisons	
 No Cov	 Yes EMs	No Cov	 EMs	No Cov	 EMs	 No Cov	 EMs
ITC or NMA	NMR_{IPD}	ITC	MAIC (ATC) STC (ATC) ML-NMR (Any) Augmented MAIC (ATC)	NMA	ML-NMR (Any)	ITC or NMA	NMR_{AD}

Abbreviations: AD: Aggregate data; Cov: Covariates; DR: Doubly robust; IPD: individual patient data; MAIC: Matching-adjusted indirect comparison; ML-NMR: multi-level network meta-regression; NMA: Network meta-analysis; tx: treatment

PAICs in practice

- Mostly MAIC (89%)
- Mostly unanchored (73%)
- Mostly in oncology (53%)

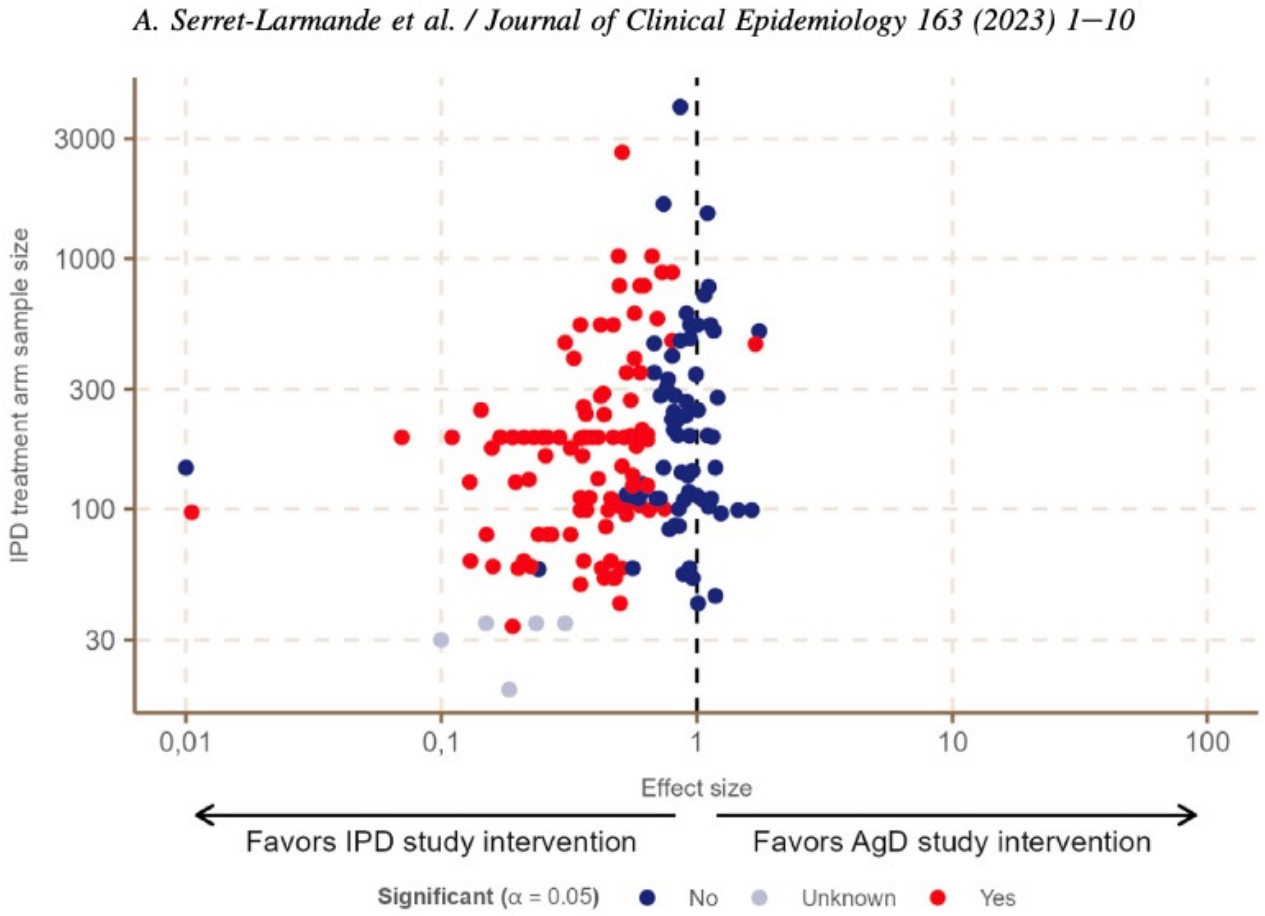
- MAIC weights:
  - **Entropy balancing with method of moments**
    - **Means**
    - Variance



Serret-Larmande A, Zenati B, Dechartres A, Lambert J, Hajage D. A methodological review of population-adjusted indirect comparisons reveals inconsistent reporting and suggests publication bias. J Clin Epidemiol. Nov 2023;163:1-10. doi:10.1016/j.jclinepi.2023.09.004

Challenges: Bias, overlap & precision

- Identification of EMs and PFs a priori
- Only 33% of PAICS considered to have included ‘adequate’ covariates
- 25% MAICs N≤50
- Median N reduction 39% after adjustment



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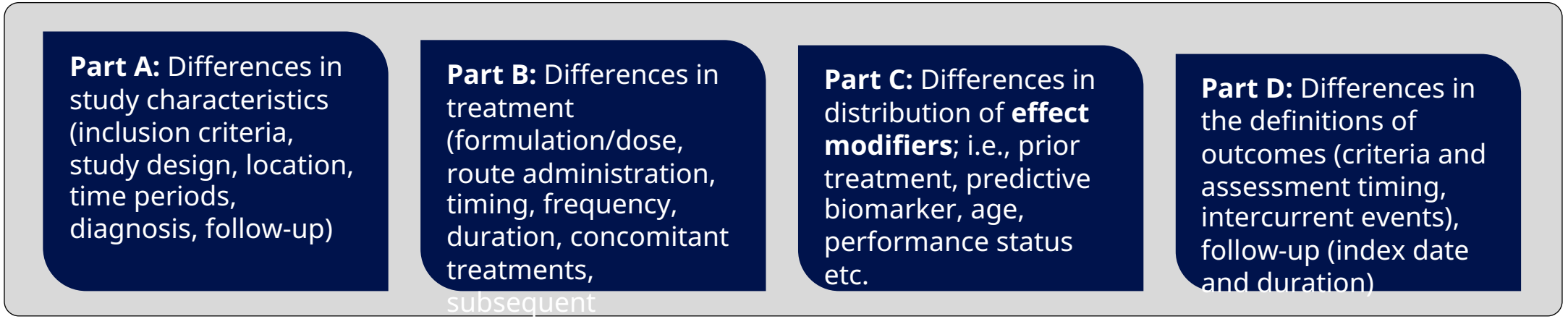
Anchored MAIC feasibility: Clinical assessment



- To align with the external study, should:
  - A: Patients from the index trial be excluded that do not meet inclusion?
  - B: Patient outcomes from the index trial be adjusted given subsequent therapies?
  - C: Patient characteristics from index trial be redefined?
  - D: Outcome definitions from index trial be redefined?

Adapted from: Cope S, Zhang J, Saletan S, Smiechowski B, Jansen JP, Schmid P. A process for assessing the feasibility of a network meta-analysis: a case study of everolimus in combination with hormonal therapy versus chemotherapy for advanced breast cancer. BMC Med. 2014;12:93.

Anchored MAIC feasibility: Numerical feasibility

MAIN PAPER

WILEY

Geometric approaches to assessing the numerical feasibility for conducting matching-adjusted indirect comparisons

Ekkehard Glimm[1,2] | **Lillian Yau**[1]

[1]Novartis Pharma AG, Clinical Development and Analytics, Basel, Switzerland

[2]University of Magdeburg, Medical Faculty, Institute of Biometry and Medical Informatics, Magdeburg, Germany

Correspondence
Ekkehard Glimm, Novartis Pharma AG, Clinical Development and Analytics, Novartis Campus, 4056 Basel, Switzerland.
Email: ekkehard.glimm@novartis.com

Abstract

We discuss how to handle matching-adjusted indirect comparison (MAIC) from a data analyst's perspective. We introduce several multivariate data analysis methods to assess the appropriateness of MAIC for a given set of baseline characteristics. These methods focus on comparing the baseline variables used in the matching of a study that provides the summary statistics or aggregated data (AD) and a study that provides individual patient level data (IPD). The methods identify situations when no numerical solutions are possible with the MAIC method. This helps to avoid misleading results being produced. Moreover, it has been observed that sometimes contradicting results are reported by

Example: Anchored MAIC numerical feasibility

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A ☺	27	0.28	4
C 😐	34	0.43	11
C 😐	61	2.21	18
C 😐	25	0.25	10
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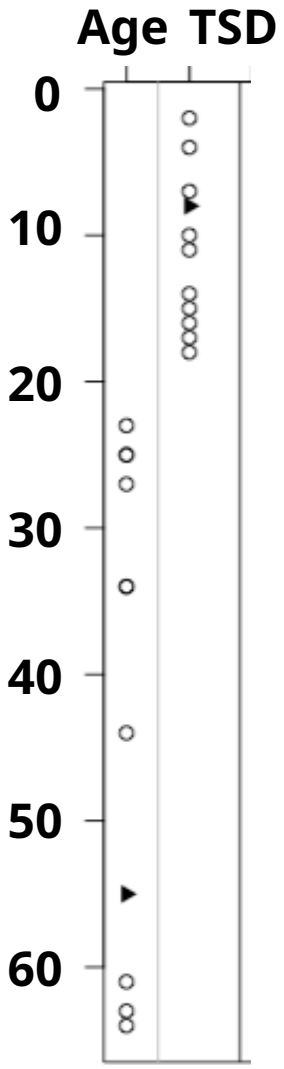
Mean	*40*		*11*
SD	*17*		*6*
WMean	***55***		



BC	Age	TSD
B 😐	--	--
B 😐	--	--
B 😐	--	--
B ☺	--	--
B ☺	--	--
C 😐	--	--
C 😐	--	--
C 😐	--	--
C 😐	--	--
C ☺	--	--
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TSD=Time since diagnosis; ☺=Response; 😐=No response

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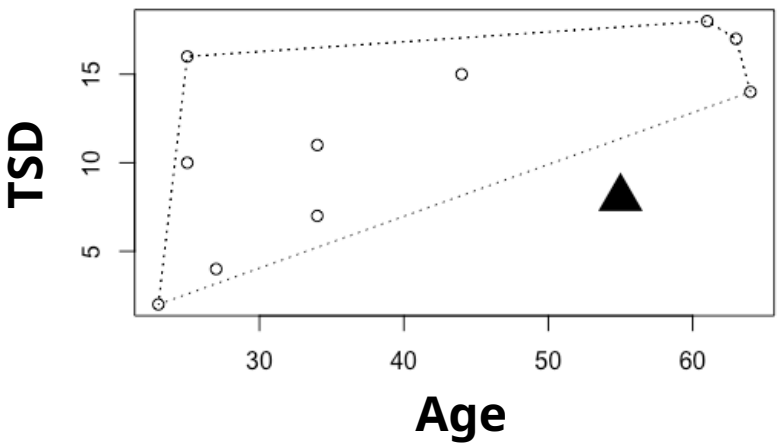

- Not feasible since (55,8) is outside the IPD '*convex hull*'
- Convex hull is the smallest convex shape that encloses all points in a set

BC	Age	TSD
B 😐	--	--
B 😐	--	--
B 😐	--	--
B ☺	--	--
B ☺	--	--
C 😐	--	--
C 😐	--	--
C 😐	--	--
C 😐	--	--
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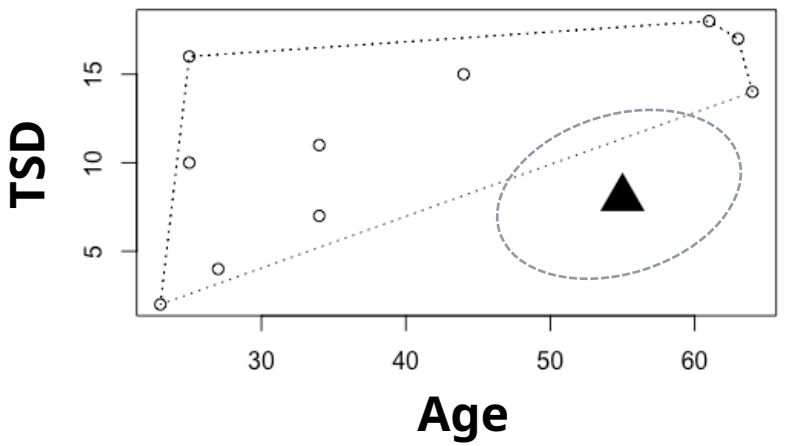

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BC	Age	TSD
B 😐	--	--
B 😐	--	--
B 😐	--	--
B ☺	--	--
B ☺	--	--
C 😐	--	--
C 😐	--	--
C 😐	--	--
C 😐	--	--
C ☺	--	--
Mean	*55*	*8*
SD	*12*	*2*

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Takeaways for MAIC protocol

- Prespecify EMs (and PFs) & feasibility assessment process (clinical & numerical)
- Highlight alternative analyses options:
  - **Part 2: MAICs[1]**
    - Estimation of weights:

Entropy Balancing with method of moments (mean and variance)

Two-stage anchored method

Maximizing the ESS

    - Use of trimming or stabilization
  - **Part 3: Augmented MAIC**
- Interpret results given credibility
  - Inclusion relevant EMs (and PFs) & degree of overlap (ESS & distribution weights) and/or need for extrapolation

1-Jiang Z, Cappelleri JC, Gamalo M, Chen Y, Thomas N, Chu H. A comprehensive review and shiny application on the matching-adjusted indirect comparison. Research Synthesis Methods. 2024-02-21 2024; 2- Thorlund K, Duffield S, Popat S, et al. Quantitative bias analysis for external control arms using real-world data in clinical trials: a primer for clinical researchers. J Comp Eff Res. Mar 2024;13(3):e230147

Advanced methods for matching-adjusted indirect comparison

Antonio Remiro-Azócar, PhD
Methods & Outreach, Novo Nordisk
ISPOR 2024, Atlanta
8th May 2024

Overview

1. Background
2. Matching-adjusted indirect comparison
3. Two-stage matching-adjusted indirect comparison
4. Weight truncation
5. Simulation study
6. Alternative variance reduction approaches
7. Concluding remarks

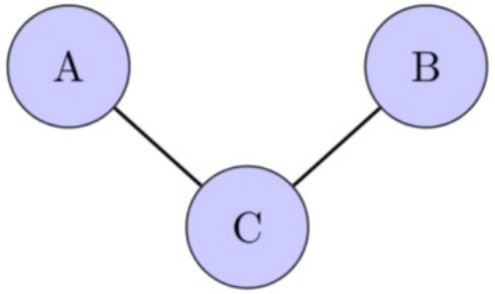
Background

Covariate-adjusted indirect treatment comparisons (ITCs)

The following setting is common in health technology assessment:

- An active treatment (treatment *A*) needs to be compared against a competitor (treatment *B*)
- No head-to-head trial between treatments *A* (*T*=1) and *B* (*T*=2)
- We have individual patient data (IPD) for study *A* ("index" study) but not for study *B* ("competitor" study)
- There are differences in baseline characteristics between study *A* (*S*=1) and study *B* (*S*=2)
- Transportability problem: transfer inferences from study *A* to study *B* for an unbiased ITC in study *B*

ANCHORED COMPARISON



$$\hat{\Delta}_{AB}^{(B)} = \hat{\Delta}_{AC}^{(B)} - \hat{\Delta}_{BC}^{(B)}$$

UNANCHORED COMPARISON

$$\hat{\Delta}_{AB}^{(B)} = g(\hat{\mu}_A^{(B)}) - g(\hat{\mu}_B^{(B)})$$

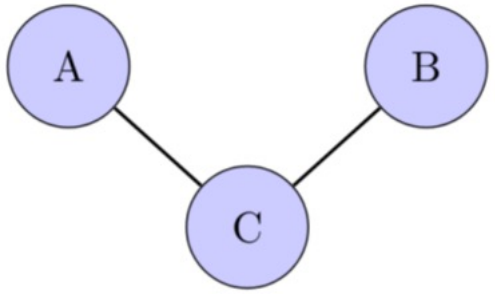
Background

Covariate-adjusted indirect treatment comparisons (ITCs)

Matching-adjusted indirect comparison (MAIC):

- The most widely used covariate-adjusted ITC method
- Weighting approach: the IPD is weighted so that there is cross-study balance in covariate moments
- Vulnerable to poor precision where covariate overlap is poor and the effective sample size after weighting is small, in which case a few extreme weights have an undue impact
- The above scenarios are pervasive in health technology appraisals

ANCHORED COMPARISON



$$\hat{\Delta}_{AB}^{(B)} = \hat{\Delta}_{AC}^{(B)} - \hat{\Delta}_{BC}^{(B)}$$

UNANCHORED COMPARISON

$$\hat{\Delta}_{AB}^{(B)} = g(\hat{\mu}_{A}^{(B)}) - g(\hat{\mu}_{B}^{(B)})$$

Matching-adjusted indirect comparison (MAIC)

- Logistic model for trial assignment

$$\ln(w_i) = \ln[w(\boldsymbol{z}_i)] = \ln\left[\frac{Pr(S=2 \mid \boldsymbol{z}_i)}{1 - Pr(S=2 \mid \boldsymbol{z}_i)}\right] = \alpha_0 + \boldsymbol{z}_i\boldsymbol{\alpha_1}$$

- Entropy balancing approach; covariate balance is viewed as a convex optimization problem

$$Q(\boldsymbol{\alpha_1}) = \sum_{i=1}^{n} \exp\left(\boldsymbol{z}_i^*\boldsymbol{\alpha_1}\right) \qquad \boldsymbol{z}_i^* = \boldsymbol{z}_i - \boldsymbol{\theta}_z$$

- The estimated weights represent the conditional odds of assignment to study *B*

$$\hat{w}_i = \exp(\boldsymbol{z}_i^*\hat{\boldsymbol{\alpha}}_\mathbf{1})$$

- Marginal mean outcomes and/or relative effects for study *A* treatment(s) estimated in study *B*

$$\hat{\mu}_t^{(2)} = \frac{\sum_{i=1}^{n_t} y_{i,t}\hat{w}_{i,t}}{\sum_{i=1}^{n_t} \hat{w}_{i,t}} \qquad \hat{\Delta}_{10}^{(2)} = g\left(\hat{\mu}_1^{(2)}\right) - g\left(\hat{\mu}_0^{(2)}\right)$$

- The objective of the “odds weights” is to account for covariate differences and attain balance **across studies**
- Key assumptions: conditional transportability and overlap **across studies**

Two-stage matching-adjusted indirect comparison (2SMAIC)

Modular extension to MAIC

- Additional logistic model for treatment assignment in the index trial, fitted to the IPD

$$\text{logit}[e_i] = \text{logit}[e(\boldsymbol{x}_i)] = \text{logit}[Pr(T = 1 \mid \boldsymbol{x}_i)] = \beta_0 + \boldsymbol{x}_i\boldsymbol{\beta_1}$$

- Having fitted the model, e.g., using maximum-likelihood, predict propensity scores

$$\hat{e}_i = \text{expit}[\hat{\beta}_0 + \boldsymbol{x}_i\hat{\boldsymbol{\beta}}_{\mathbf{1}}]$$

- Estimate "inverse probability of treatment" weights (IPTWs) and combine them with the odds weights

$$\hat{\omega}_i = \frac{t_i\hat{w}_i}{\hat{e}_i} + \frac{(1-t_i)\hat{w}_i}{(1-\hat{e}_i)}$$

$$\hat{\mu}_t^{(2)} = \frac{\sum_{i=1}^{n_t} y_{i,t}\hat{\omega}_{i,t}}{\sum_{i=1}^{n_t} \hat{\omega}_{i,t}} \qquad \hat{\Delta}_{10}^{(2)} = g\left(\hat{\mu}_1^{(2)}\right) - g\left(\hat{\mu}_0^{(2)}\right)$$

- The IPTWs seek to balance covariates **between the index trial treatment groups**; the combined weights seek to attain balance **between the index trial treatment groups and across studies**
- Limitation: because it relies on a treatment assignment model for the index trial, 2SMAIC is not applicable in the unanchored case

Rationale for 2SMAIC with index RCT

- In an RCT, the true treatment assignment mechanism and propensity scores are fixed and known, due to randomization
- Randomization guarantees covariate balance on expectation, in large samples
- Senn (2004): “over all randomizations the groups are balanced; for a particular randomization they are unbalanced” – there may still be finite-sample imbalances due to chance
- Estimating the propensity scores is beneficial to correct for residual imbalances between treatment arms, particularly where the index trial sample size is small
- Motivation for covariate adjustment: to increase efficiency by gaining precision, not to reduce bias!

Rationale for 2SMAIC with observational index study

- One no longer relies on the internal validity of the index study; covariate adjustment between treatment arms is necessary for confounding control
- Strong assumption #1: conditional exchangeability over treatment assignment → compromised if the treatment assignment model excludes potential confounders
- Strong assumption #2: positivity of treatment assignment → compromised by deterministic positivity violations, such as different selection criteria into the treatment groups
- Randomization is no longer leveraged to meet the strong assumptions above
- Motivation for covariate adjustment: to reduce internal validity bias due to confounding

Truncation

A simple approach for variance reduction

- Restricts the influence of extreme weights by capping the highest estimated weights at a given percentile
- The ideal truncation level will vary on a case-by-case basis and can be set empirically, e.g. by progressively truncating the weights. Density plots are helpful to assess the dispersion of the weights and identify an optimal cutoff point.
- There is a clear trade-off from a bias-variance standpoint: precision improvements always come at the cost of sacrificing balance and accepting bias
- Prior transportability/generalizability literature uses a 95th percentile cutoff; lower thresholds further reduce variance at the cost of more bias and further shifting the target population or estimand
- Limitations:

1. Shifts the target estimand definition (population or analysis set attribute)
2. Requires arbitrary ad hoc decisions on cutoff thresholds

Simulation study

Setting

- Anchored indirect treatment comparison across two RCTs
- Small sample sizes for index trial ($N \in \{140, 200\}$)
- 3 strongly prognostic and effect-modifying covariates
- Varying levels of deterministic overlap between the target populations of the RCTs
- Continuous outcome, linear outcome generating model

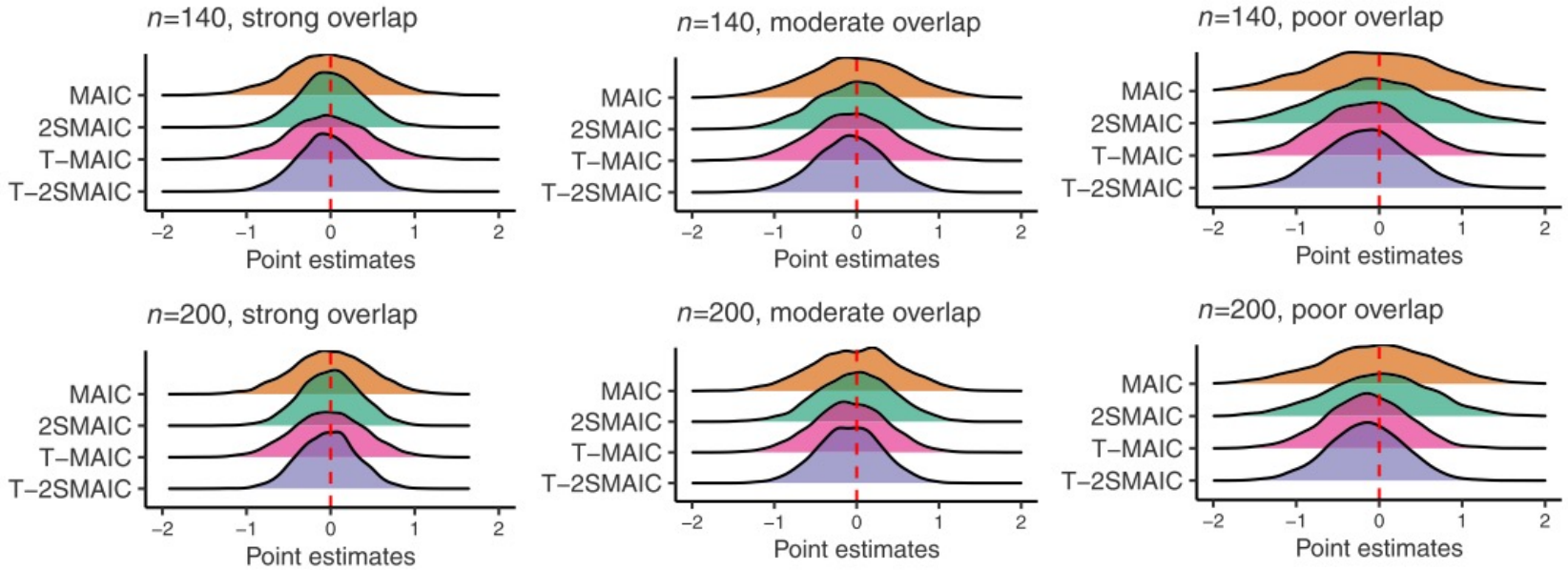
Methods

- Standard matching-adjusted indirect comparison (MAIC)
- Two-stage matching-adjusted indirect comparison (2SMAIC)
- MAIC combined with weight truncation (T-MAIC), capping the estimated weights at the 95th percentile
- 2SMAIC combined with weight truncation (T-2SMAIC), capping the estimated weights at the 95th percentile

No unmeasured covariates and cross-study balance attained for all effect-modifying moments (means)

Simulation study results

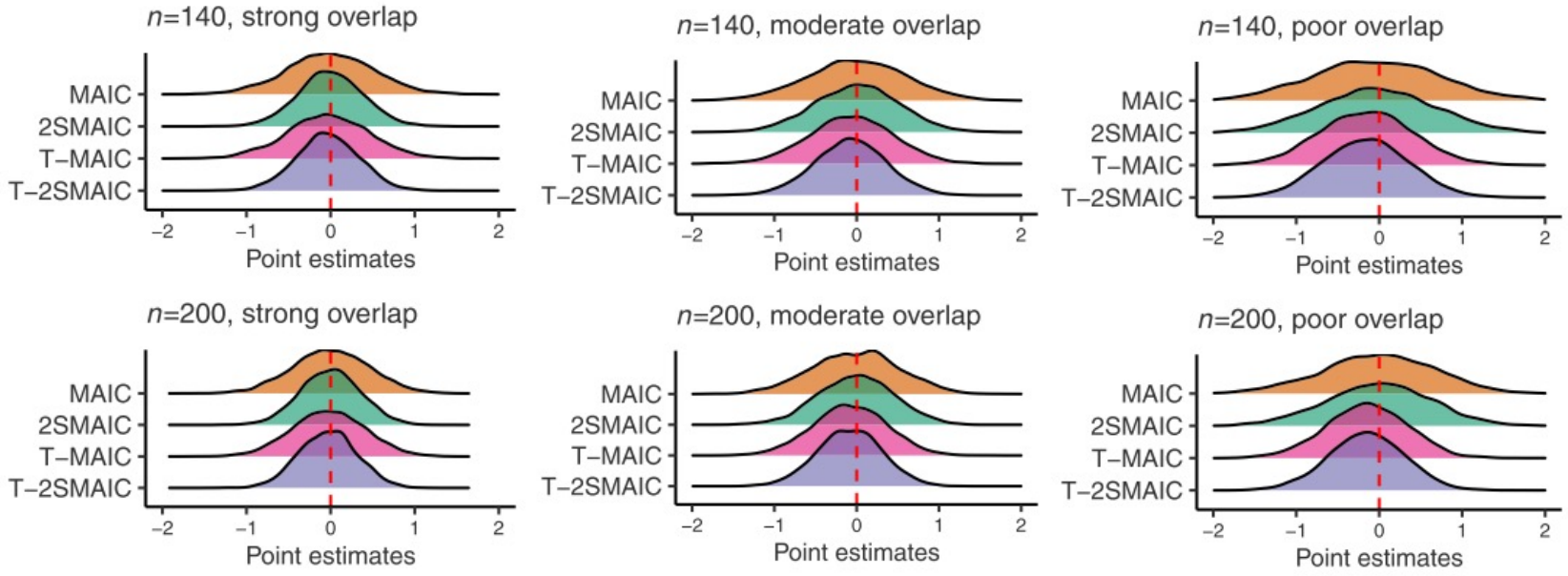
- The two-stage approaches yield improved precision and efficiency with respect to their one-stage counterparts, with similar bias
- The two-stage approaches are more effective with lower index trial sample sizes, due to greater empirical imbalances between treatment arms
- The enhanced performance of the two-stage methods is strongly linked to the prognostic strength of covariates
- Performance gains of the two-stage approaches are attenuated where overlap is poor, due to high extremity of the weights



Remiro-Azócar, A., 2022. Two-stage matching-adjusted indirect comparison. BMC medical research methodology, 22(1), p.217.

Simulation study results

- With strong covariate overlap, truncation offers modest improvements in precision and efficiency, while inducing bias
- As overlap weakens, truncation notably improves precision by reducing the influence of extreme weights, but induces considerable bias
- The combination of the two-stage method and weight truncation (T-2SMAIC) offers the best performance in terms of precision and efficiency, with the increase in precision offsetting the increase in bias
- Truncation is less necessary and bias-variance trade-offs less favorable to variance reduction where there is good overlap, the weights are well-behaved and the effective sample size after weighting is sizeable



Remiro-Azócar, A., 2022. Two-stage matching-adjusted indirect comparison. BMC medical research methodology, 22(1), p.217.

Alternative variance reduction approaches

Jackson et al. (2021) weighting scheme

- Weight estimation procedure that satisfies the conventional method of moments while explicitly maximizing the effective sample size
- Minimizes dispersion of the weights, with more stable weights improving precision at the expense of inducing bias

Reduce the number of moment-balancing conditions

- Exclude less influential covariates
- Exclude higher-order moments, e.g., only balance means and not variances
- There are bias-variance trade-offs
- These options lead to increased overlap, lower likelihood of extreme weights, less drastic reductions in effective sample size and precision
- These options also lead to residual bias (Vo 2023), particularly as marginal treatment effects generally depend on the full joint covariate distribution, including that of purely prognostic covariates (Remiro-Azócar 2024)

Alternative variance reduction approaches

Weight trimming

- Excludes subjects with outlying weights
- Shares many of the limitations of truncation: arbitrary cutoff points, change in the estimand (target population/analysis set)
- Less appealing than truncation: information directly discarded → precision loss

Weight stabilization

- Not applicable where the covariate-adjusted marginal effect is derived from the treatment coefficient of a weighted model of outcome on time-fixed binary treatment
- The fitted model is “saturated” (cannot be mis-specified)
- For saturated models, stabilized and unstabilized weights give identical results
- Potentially useful where the weighted outcome model is unsaturated, e.g., with dynamic or continuous-valued treatment regimens

Alternative variance reduction approaches

Overlap weighting

- Estimates treatment effects in a subsample with good overlap
- Challenging to implement where subject-level data are unavailable for the competitor study
- Also changes the population or analysis set attribute of the target estimand

Avoid weighting

- With weak overlap, methods based on modeling the outcome expectation, e.g., STC, model-based standardization (G-computation), ML-NMR, exhibit greater precision and efficiency than MAIC…
- …but are prone to extrapolation, which may lead to severe bias under model misspecification (Vo 2023)
- Outcome modeling is a good option where feasible numerical solutions to MAIC do not exist due lack of covariate overlap

Concluding remarks

- We have explored two strategies to improve the precision and efficiency of MAIC:
  1. Modeling the treatment assignment mechanism in the index study
  2. Truncating the weights that are above a certain level

- Weighting is inherently modular:
  1. Just like we have combined the two-stage approach with truncation, other variance reduction approaches can be incorporated, potentially in combination
  2. The estimation procedure for the trial assignment weights does not necessarily need to be entropy balancing or method of moments, alternative methods could be used
  3. Further weighting modules could be incorporated to account for missingness and non-compliance, e.g., dropout or treatment switching, in the index trial

References

- Jackson, D., Rhodes, K. and Ouwens, M., 2021. Alternative weighting schemes when performing matching-adjusted indirect comparisons. Research Synthesis Methods, 12(3), pp.333-346

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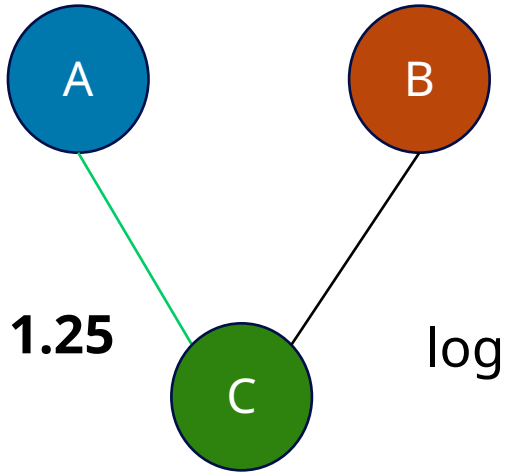
Part 3 Overview

- *Example: MAIC vs. 2SMAIC*
- The implied “trial assignment model”
- Types of adjustment methods
- Augmented-MAIC
- *Example: Augmented-MAIC*
- Simulation study
- Conclusion - Pros and cons of Augmented-MAIC

Example: Anchored PAIC - MAIC

AC	Age	Weight
A 😐	23	0.22
A 😐	44	0.79
A ☺	34	0.43
A ☺	64	2.64
A ☺	27	0.28
C 😐	34	0.43
C 😐	61	2.21
C 😐	25	0.25
C ☺	63	2.49
C ☺	25	0.25
Mean	*40*	
SD	*17*	
WMean	***55***	



Weighted log(OR_{AC}) = 1.25

$OR_{BC} = 2.67$

$\log(OR_{BC}) = 0.98$

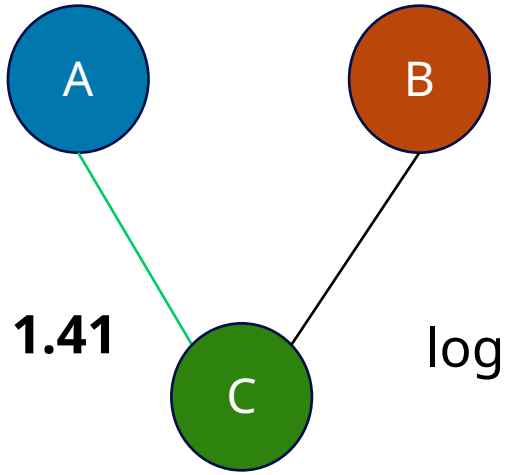
$$\log(OR_{AB}) = \log(OR_{AC}) - \log(OR_{BC})$$
$$= \mathbf{1.25} - 0.98$$
$$= 0.27$$
$$OR_{AB} = \exp(0.27)$$
$$= 1.31$$

BC	Age
B 😐	--
B 😐	--
B 😐	--
B ☺	--
B ☺	--
C 😐	--
C 😐	--
C 😐	--
C 😐	--
C ☺	--
Mean	*55*
SD	*12*

☺=Response; 😐=No response

Example: Anchored PAIC – 2SMAIC

AC	Age	Weight
A 😐	23	0.20
A 😐	44	0.82
A ☺	34	0.42
A ☺	64	3.14
A ☺	27	0.26
C 😐	34	0.45
C 😐	61	1.96
C 😐	25	0.28
C ☺	63	2.19
C ☺	25	0.28
Mean	*40*	
SD	*17*	
WMean	***55***	



Weighted log(OR_{AC}) = 1.41

$OR_{BC} = 2.67$
$\log(OR_{BC}) = 0.98$

$$\log(OR_{AB}) = \log(OR_{AC}) - \log(OR_{BC})$$
$$= \mathbf{1.41} - 0.98$$
$$= 0.43$$
$$OR_{AB} = \exp(0.43)$$
$$= 1.53$$

BC	Age
B 😐	--
B 😐	--
B 😐	--
B ☺	--
B ☺	--
C 😐	--
C 😐	--
C 😐	--
C 😐	--
C ☺	--
Mean	*55*
SD	*12*

☺=Response; 😐=No response

Example: Anchored PAIC – MAIC vs. 2SMAIC

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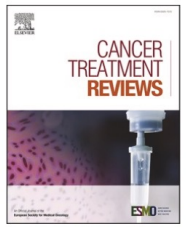


Check for updates

Is tebentafusp superior to combined immune checkpoint blockade and other systemic treatments in metastatic uveal melanoma? A comparative efficacy analysis with population adjustment

Anne Petzold [a,b,c], Theresa Steeb [a,b,c], Anja Wessely [a,b,c], Elias A.T. Koch [a,b,c], Julio Vera [a,b,c], Carola Berking [a,b,c,1], Markus V. Heppt [a,b,c,1,*]

[a] Department of Dermatology, Uniklinikum Erlangen, Friedrich-Alexander University Erlangen-Nürnberg (FAU), Erlangen, Germany
[b] Comprehensive Cancer Center Erlangen-European Metropolitan Area of Nuremberg (CCC ER-EMN), Erlangen, Germany
[c] Deutsches Zentrum Immuntherapie (DZI), Uniklinikum Erlangen, Erlangen, Germany

ARTICLE INFO

Keywords:
Uveal melanoma
Survival
Immune checkpoint blockade
Tebentafusp
Individual patient data

ABSTRACT

Background: Distinct systemic treatments exist for metastatic uveal melanoma. Tebentafusp and combined immune checkpoint blockade (ICB) with ipilimumab plus anti-PD-1 antibodies are the most commonly used treatment options but their comparative efficacy is unclear. The aim of this study is to compare currently available systemic treatments regarding overall survival (OS) and progression-free survival (PFS) with a focus on the comparison of tebentafusp versus combined ICB.

MAIC:

HR: 0.386 (95% CI: 0.236–0.631)

CI width = 0.395

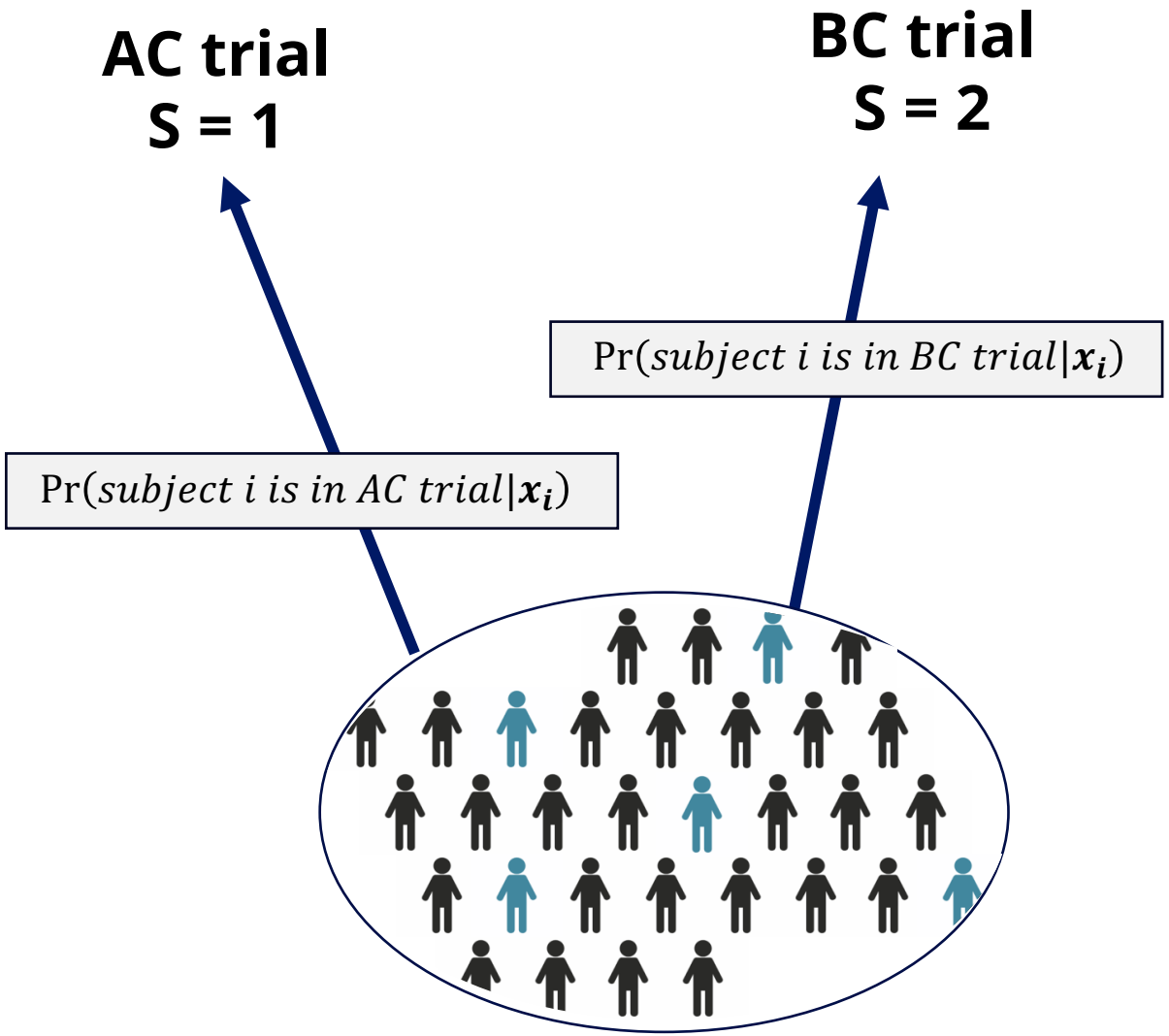
2SMAIC:

HR: 0.378 (95% CI: 0.234–0.612)

CI width = 0.378

Petzold, A., Steeb, T., Wessely, A., Koch, E. A., Vera, J., Berking, C., & Heppt, M. V. (2023). Is tebentafusp superior to combined immune checkpoint blockade and other systemic treatments in metastatic uveal melanoma? A comparative efficacy analysis with population adjustment. *Cancer Treatment Reviews*, 102543.

The implied "trial assignment model"



Using the entropy balancing approach for weights:

$$\frac{\sum_{S=1} \boldsymbol{x_i} w_i}{\sum_{S=1} w_i} = \overline{\boldsymbol{x}}_{S=2}$$

This implies that the weights are equal to the odds:

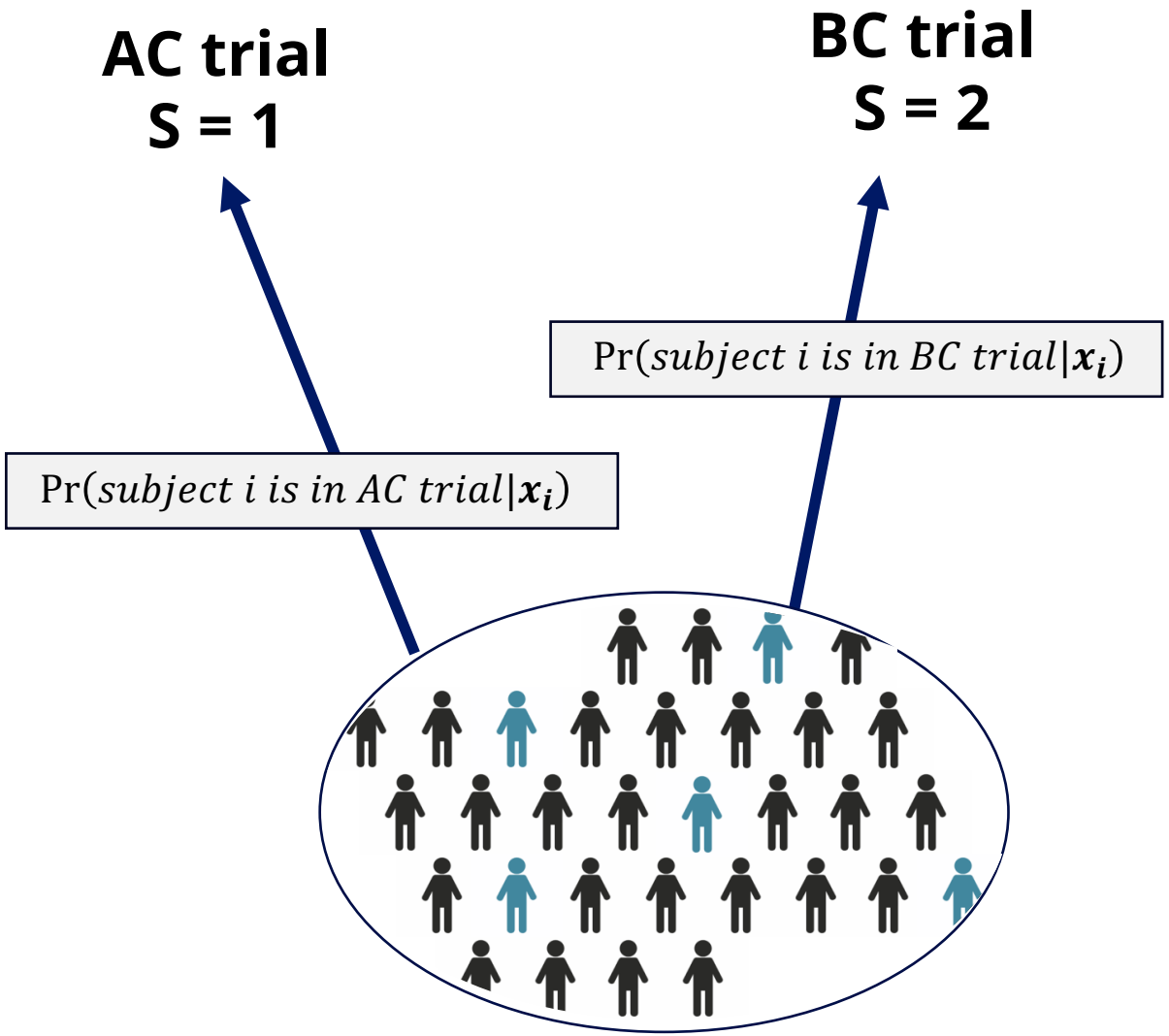
$$w_i = \text{Odds}(subject\ i\ is\ in\ BC\ trial|\boldsymbol{x_i}) = \exp(\boldsymbol{\beta x_i})$$

and that the **true trial assignment model** is the logistic regression model:

$$\Pr(subject\ i\ is\ in\ BC\ trial|\boldsymbol{x_i}) = \text{logit}^{-1}(\boldsymbol{\beta x_i})$$

Cheng, D., Ayyagari, R., & Signorovitch, J. (2020). The statistical performance of matching-adjusted indirect comparisons: estimating treatment effects with aggregate external control data. Ann. Appl. Stat. 14(4): 1806-1833 (December 2020). DOI: 10.1214/20-AOAS1359

The implied “trial assignment model”



Cheng et al. (2020):

“Even when all confounders [i.e., effect modifiers and prognostic factors] are observed, MAIC still **relies on the trial assignment model being at least approximately correct** […] to make appropriate adjustments.”

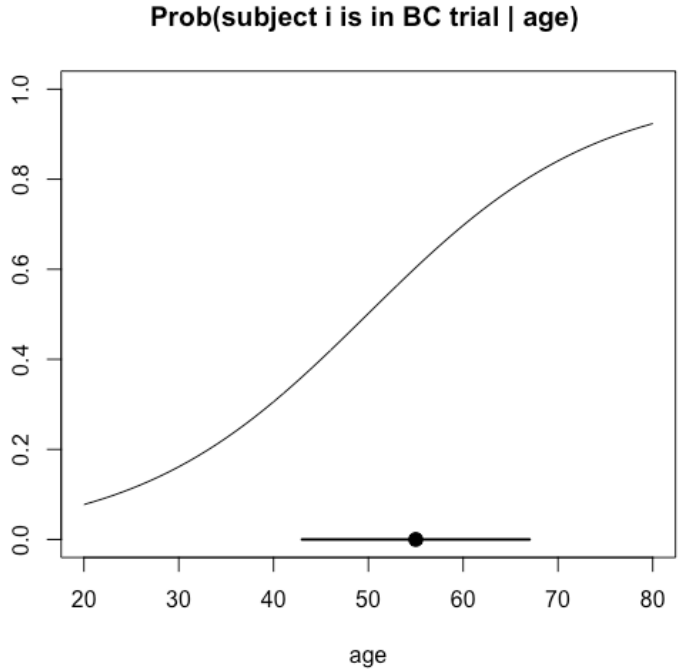
Ways in which the trial assignment model could be incorrectly specified:

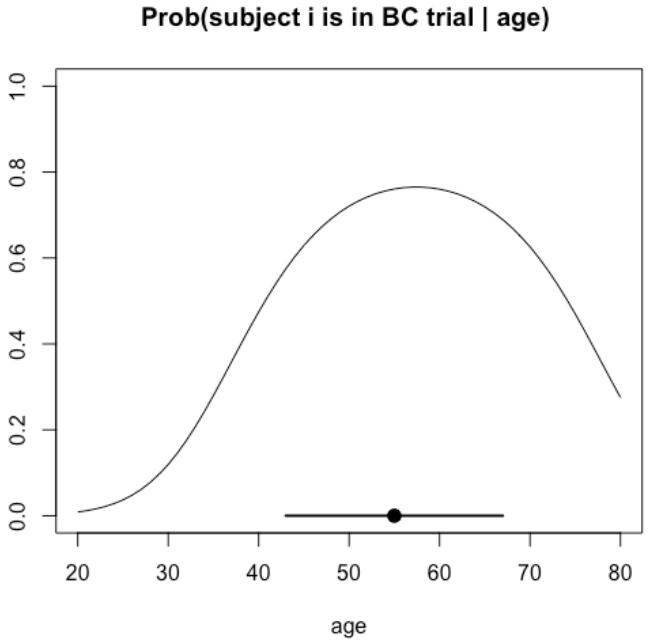
- Missed important covariates
- Failed to account for specific interactions
- Failed to match for higher moments

Cheng, D., Ayyagari, R., & Signorovitch, J. (2020). The statistical performance of matching-adjusted indirect comparisons: estimating treatment effects with aggregate external control data. Ann. Appl. Stat. 14(4): 1806-1833 (December 2020). DOI: 10.1214/20-AOAS1359

The implied “trial assignment model”

Weighting	Implied trial assignment model
Entropy balancing matching on first moment	$\Pr(subject\ i\ is\ in\ BC\ trial \mid age) = \text{logit}^{-1}(\beta_0 + \beta_1 age) = \frac{1}{1 + \exp(\beta_0 + \beta_1 age)}$
Entropy balancing matching on first and second moments	$\Pr(subject\ i\ is\ in\ BC\ trial \mid age) = \text{logit}^{-1}(\beta_0 + \beta_1 age + \beta_2 age^2) = \frac{1}{1 + \exp(\beta_0 + \beta_1 age + \beta_2 age^2)}$

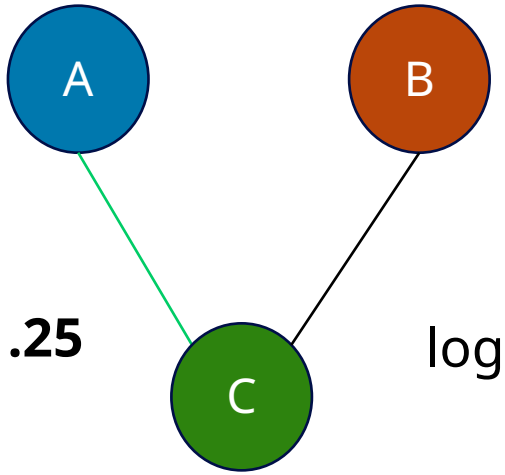




Example: Anchored PAIC - MAIC

Matching on first moment

AC	Age	Weight
A 😐	23	0.22
A 😐	44	0.79
A ☺	34	0.43
A ☺	64	2.64
A ☺	27	0.28
C 😐	34	0.43
C 😐	61	2.21
C 😐	25	0.25
C ☺	63	2.49
C ☺	25	0.25
Mean	*40*	
SD	*17*	
WMean	***55***	



Weighted log(OR_{AC}) = 1.25

$OR_{BC} = 2.67$

$\log(OR_{BC}) = 0.98$

$$\log(OR_{AB}) = \log(OR_{AC}) - \log(OR_{BC})$$
$$= \mathbf{1.25} - 0.98$$
$$= 0.27$$
$$OR_{AB} = \exp(0.27)$$
$$= 1.31$$

Treatment A better than B

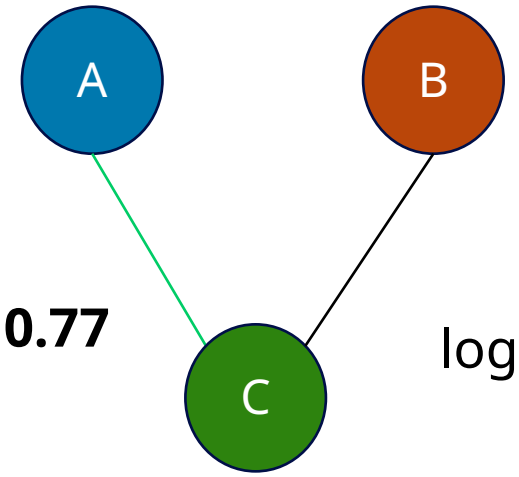
BC	Age
B 😐	--
B 😐	--
B 😐	--
B ☺	--
B ☺	--
C 😐	--
C 😐	--
C 😐	--
C 😐	--
C ☺	--
Mean	*55*
SD	*12*

☺=Response; 😐=No response

Example: Anchored PAIC - MAIC

Matching on first and second moments

AC	Age	Weight
A 😐	23	0.07
A 😐	44	1.64
A ☺	34	0.52
A ☺	64	2.16
A ☺	27	0.15
C 😐	34	0.52
C 😐	61	2.46
C 😐	25	0.10
C ☺	63	2.27
C ☺	25	0.10
Mean	*40*	
SD	*17*	
WMean	***55***	



Weighted log(OR_{AC}) = 0.77

$OR_{BC} = 2.67$

$\log(OR_{BC}) = 0.98$

$$\log(OR_{AB}) = \log(OR_{AC}) - \log(OR_{BC})$$
$$= \mathbf{0.77} - 0.98$$
$$= -0.21$$
$$OR_{AB} = \exp(-0.21)$$
$$= 0.81$$

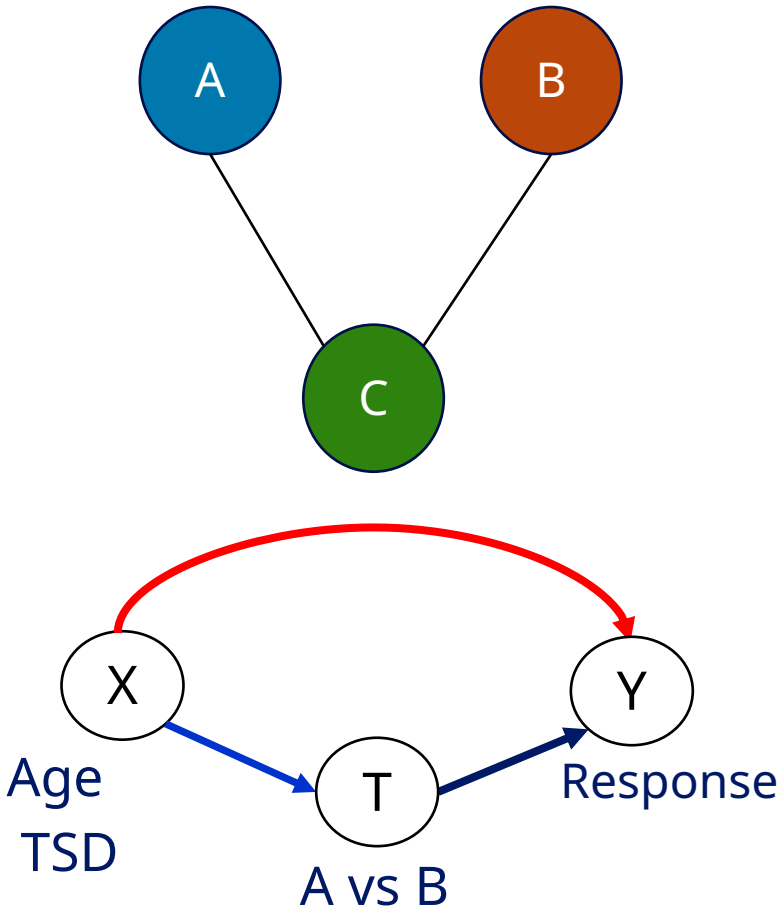
Treatment B better than A

BC	Age
B 😐	--
B 😐	--
B 😐	--
B ☺	--
B ☺	--
C 😐	--
C 😐	--
C 😐	--
C 😐	--
C ☺	--
Mean	*55*
SD	*12*

☺=Response; 😐=No response

Types of population-adjustment methods

ITCs are “essentially observational findings across trials” (Higgins and Green, 2011).



Method	Description	Model	Assumption
Matching Adjusted Indirect Comparison (MAIC)	Propensity-score based method	Weights from T | X model Y | T	*Trial assignment model is correct*
Simulated Treatment Comparison (STC)	Outcomes-regression based method	Y | T & X	*Outcome model is correct*
Augmented Matching Adjusted Indirect Comparison (AMAIC)	Doubly-robust method	Weights from T | X model Y | T & X	*Either trial assignment model or outcome model is correct*

Y = Outcome, T=Treatment/Trial, X=Covariates

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org

Augmented-MAIC in 4 steps

Step 1. Obtain weights from MAIC.

Step 2. Fit weighted adjusted logistic regression outcome model to weighted IPD:

$$\Pr(Y = 1|T = t, X = x) = \text{logit}^{-1}(\beta_0 + \beta_1 t + \beta_2 x + \beta_3 tx) = \frac{1}{1 + \exp(\beta_0 + \beta_1 t + \beta_2 x + \beta_3 tx)}$$

Step 3. Use standardization over the covariate distribution of the target population (i.e., AD trial) to obtain the "marginal log-odds ratio" for A vs. C: $\log(OR_{AC})$.

Step 4. $\log(OR_{AB}) = \log(OR_{AC}) - \log(OR_{BC})$.

Augmented-MAIC: Step 3 details

Step 3a: Simulate a large number of IPD covariate values to match the covariate distribution in the BC trial.

Step 3b: Obtain predicted probabilities based on estimates from the outcome model and simulated IPD:

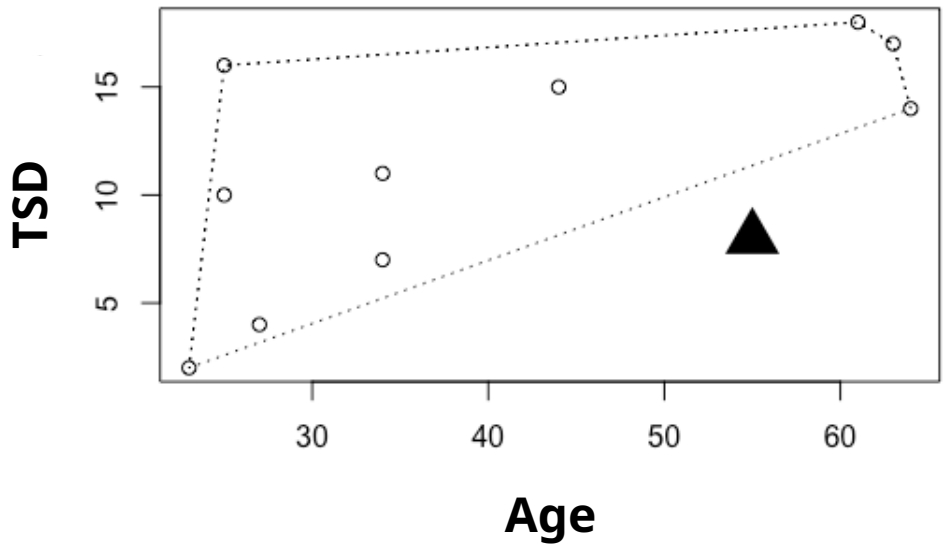
$$\hat{\Pr}(Y=1|T=0)=\frac{1}{N}\sum_{i=1}^{N}\text{logit}^{-1}\left(\hat{\beta}_0+\hat{\beta}_2 x_i\right), \quad \text{and} \quad \hat{\Pr}(Y=1|T=1)=\frac{1}{N}\sum_{i=1}^{N}\text{logit}^{-1}\left(\hat{\beta}_0+\hat{\beta}_1+\hat{\beta}_2 x_i+\beta_3 x_i\right)$$

Step 3c: Calculate the covariate-adjusted estimator of the marginal OR for A vs. C :

$$\log(\text{ORAC})=\log\left[\left(\frac{\hat{\Pr}(Y=1|T=1)}{1-\hat{\Pr}(Y=1|T=1)}\right)/\left(\frac{\hat{\Pr}(Y=1|T=0)}{1-\hat{\Pr}(Y=1|T=0)}\right)\right]$$

Example: Anchored MAIC numerical feasibility

AC	Age	TSD
A 😐	23	2
A 😐	44	15
A ☺	34	7
A ☺	64	14
A ☺	27	4
C 😐	34	11
C 😐	61	18
C 😐	25	10
C ☺	63	17
C ☺	25	16
Mean	*40*	*11*
SD	*17*	*6*



- Not feasible since (55,8) is outside the IPD '*convex hull*'
- Convex hull is the smallest convex shape that encloses all points in a set

BC	Age	TSD
B 😐	--	--
B 😐	--	--
B 😐	--	--
B ☺	--	--
B ☺	--	--
C 😐	--	--
C 😐	--	--
C 😐	--	--
C 😐	--	--
C ☺	--	--
Mean	*55*	*8*
SD	*12*	*2*

TSD=Time since diagnosis; ☺=Response; 😐=No response

Augmented-MAIC: Example

AC	Age	Weight	TSD
A 😐	23	0.22	2
A 😐	44	0.79	15
A ☺	34	0.43	7
A ☺	64	2.64	14
A ☺	27	0.28	4
C 😐	34	0.43	11
C 😐	61	2.21	18
C 😐	25	0.25	10
C ☺	63	2.49	17
C ☺	25	0.25	16
Mean	*40*		*11*
SD	*17*		*6*
WMean	***55***		***15***

1. Obtain weights from MAIC

Matching on the first moment of age.

weighted
mean of Age
= (23x0.22 + 44x0.79 +
+ … +
25x0.25)/10
= 55

weighted
mean of TSD
= (2x0.22 + 15x0.79 +
+ … +
16x0.25)/10
= 15

BC	Age	TSD
B 😐	--	--
B 😐	--	--
B 😐	--	--
B ☺	--	--
B ☺	--	--
C 😐	--	--
C 😐	--	--
C 😐	--	--
C 😐	--	--
C ☺	--	--
Mean	*55*	*8*
SD	*12*	*2*

Augmented-MAIC: Example

AC	Age	Weight	TSD
A 😐	23	0.22	2
A 😐	44	0.79	15
A ☺	34	0.43	7
A ☺	64	2.64	14
A ☺	27	0.28	4
C 😐	34	0.43	11
C 😐	61	2.21	18
C 😐	25	0.25	10
C ☺	63	2.49	17
C ☺	25	0.25	16
Mean	*40*		*11*
SD	*17*		*6*
WMean	***55***		***15***

2. Fit weighted outcome model:

Weighted logistic regression model:

$$\Pr(Y = 1|T = t, age, tsd)$$

$$= \text{logit}^{-1}\begin{pmatrix}\beta_0 + \beta_1 t + \beta_2 age + \\ \beta_3 tsd + \beta_4(t \times age_i) + \beta_5(t \times tsd_i)\end{pmatrix}$$

$$= \frac{1}{1 + \exp(\beta_0 + \beta_1 t + \beta_2 age + \beta_3 tsd + \beta_4(t \times age_i) + \beta_5(t \times tsd_i))}$$

Parameter estimates:

$$\widehat{\beta_0} = -0.99$$
$$\widehat{\beta_1} = -938.64$$
$$\widehat{\beta_2} = 0.08$$
$$\widehat{\beta_3} = -0.20$$
$$\widehat{\beta_4} = 46.58$$
$$\widehat{\beta_5} = -75.43$$

BC	Age	TSD
B 😐	--	--
B 😐	--	--
B 😐	--	--
B ☺	--	--
B ☺	--	--
C 😐	--	--
C 😐	--	--
C 😐	--	--
C 😐	--	--
C ☺	--	--
Mean	*55*	*8*
SD	*12*	*2*

Augmented-MAIC: Example

AC	Age	Weight	TSD
A 😐	23	0.22	2
A 😐	44	0.79	15
A ☺	34	0.43	7
A ☺	64	2.64	14
A ☺	27	0.28	4
C 😐	34	0.43	11
C 😐	61	2.21	18
C 😐	25	0.25	10
C ☺	63	2.49	17
C ☺	25	0.25	16
Mean	*40*		*11*
SD	*17*		*6*
WMean	***55***		***15***

cor(age, TSD) = 0.69

3a. Simulate BC covariate data:

ID	Age	TSD
1	45	9
2	29	8
3	60	11
⋮	--	--
100000	44	7
Mean	*55*	*8*
SD	*12*	*2*

cor(simulated age, simulated TSD) = 0.69

BC	Age	TSD
B 😐	--	--
B 😐	--	--
B 😐	--	--
B ☺	--	--
B ☺	--	--
C 😐	--	--
C 😐	--	--
C 😐	--	--
C 😐	--	--
C ☺	--	--
Mean	*55*	*8*
SD	*12*	*2*

Augmented-MAIC: Example

AC	Age	Weight	TSD
A 😐	23	0.22	2
A 😐	44	0.79	15
A ☺	34	0.43	7
A ☺	64	2.64	14
A ☺	27	0.28	4
C 😐	34	0.43	11
C 😐	61	2.21	18
C 😐	25	0.25	10
C ☺	63	2.49	17
C ☺	25	0.25	16
Mean	*40*		*11*
SD	*17*		*6*
WMean	***55***		***15***

3b. Obtain predicted probabilities:

$$\hat{\Pr}(Y = 1|T = 0) = \frac{1}{100000}\sum_{i=1}^{100000} \text{logit}^{-1}(\hat{\beta}_0 + \hat{\beta}_2 age_i + \hat{\beta}_3 tsd_i)$$

$$\hat{\Pr}(Y = 1|T = 1) = \frac{1}{100000}\sum_{i=1}^{100000} \text{logit}^{-1}\begin{pmatrix}\hat{\beta}_0 + \hat{\beta}_1 + \hat{\beta}_2 age_i \\ +\hat{\beta}_3 tsd_i + \hat{\beta}_4 age_i + \hat{\beta}_5 tsd_i\end{pmatrix}$$

BC	Age	TSD
B 😐	--	--
B 😐	--	--
B 😐	--	--
B ☺	--	--
B ☺	--	--
C 😐	--	--
C 😐	--	--
C 😐	--	--
C 😐	--	--
C ☺	--	--
Mean	*55*	*8*
SD	*12*	*2*

Augmented-MAIC: Example

AC	Age	Weight	TSD
A 😐	23	0.22	2
A 😐	44	0.79	15
A ☺	34	0.43	7
A ☺	64	2.64	14
A ☺	27	0.28	4
C 😐	34	0.43	11
C 😐	61	2.21	18
C 😐	25	0.25	10
C ☺	63	2.49	17
C ☺	25	0.25	16
Mean	*40*		*11*
SD	*17*		*6*
WMean	***55***		***15***

3b. Obtain predicted probabilities:

$$\hat{\Pr}(Y = 1|T = 0) =$$

$$0.803$$

$$\hat{\Pr}(Y = 1|T = 1) =$$

$$0.985$$

BC	Age	TSD
B 😐	--	--
B 😐	--	--
B 😐	--	--
B ☺	--	--
B ☺	--	--
C 😐	--	--
C 😐	--	--
C 😐	--	--
C 😐	--	--
C ☺	--	--
Mean	*55*	*8*
SD	*12*	*2*

Augmented-MAIC: Example

AC	Age	Weight	TSD
A 😐	23	0.22	2
A 😐	44	0.79	15
A ☺	34	0.43	7
A ☺	64	2.64	14
A ☺	27	0.28	4
C 😐	34	0.43	11
C 😐	61	2.21	18
C 😐	25	0.25	10
C ☺	63	2.49	17
C ☺	25	0.25	16
Mean	*40*		*11*
SD	*17*		*6*
WMean	***55***		***15***

3c. Calculate the covariate-adjusted estimator of the marginal OR for A vs. C:

$$\log(\mathrm{OR}_{AC})$$

$$= \log\left[\left(\frac{\hat{\Pr}(Y=1|T=1)}{1-\hat{\Pr}(Y=1|T=1)}\right)/\left(\frac{\hat{\Pr}(Y=1|T=0)}{1-\hat{\Pr}(Y=1|T=0)}\right)\right]$$

$$= \log\left[\left(\frac{0.985}{1-0.985}\right)/\left(\frac{0.803}{1-0.803}\right)\right]$$

$$= 2.80$$

BC	Age	TSD
B 😐	--	--
B 😐	--	--
B 😐	--	--
B ☺	--	--
B ☺	--	--
C 😐	--	--
C 😐	--	--
C 😐	--	--
C 😐	--	--
C ☺	--	--
Mean	*55*	*8*
SD	*12*	*2*

Augmented-MAIC: Example

AC	Age	Weight	TSD
A 😐	23	0.22	2
A 😐	44	0.79	15
A ☺	34	0.43	7
A ☺	64	2.64	14
A ☺	27	0.28	4
C 😐	34	0.43	11
C 😐	61	2.21	18
C 😐	25	0.25	10
C ☺	63	2.49	17
C ☺	25	0.25	16
Mean	*40*		*11*
SD	*17*		*6*
WMean	***55***		***15***

4. Calculate estimate of OR_{AB} :

$$\log(\mathrm{OR}_{AB}) = \log(\mathrm{OR}_{AC}) - \log(\mathrm{OR}_{BC})$$

$$= 2.80 - 0.98$$

$$= 1.82$$

$$\mathrm{OR}_{AB} = \exp(1.82) = 6.19$$

Treatment A much better than B

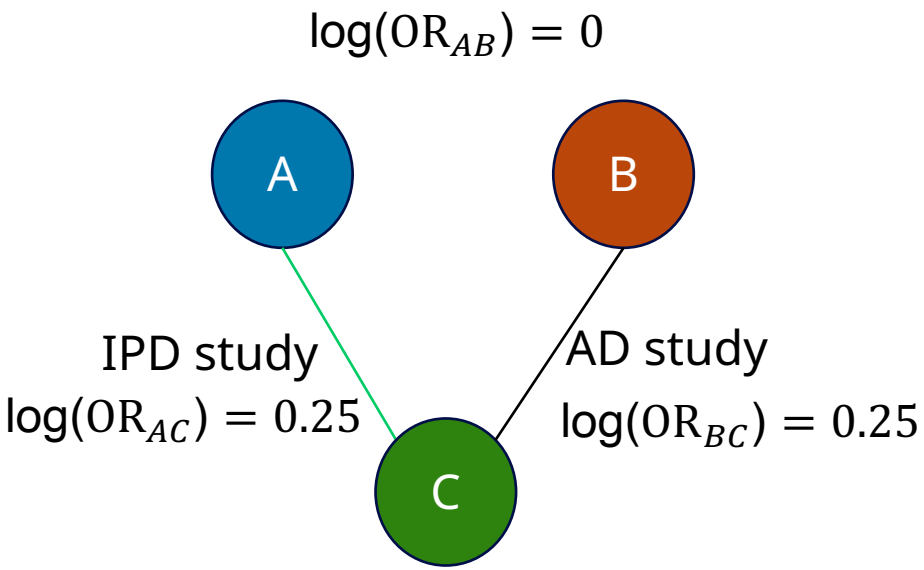
BC	Age	TSD
B 😐	--	--
B 😐	--	--
B 😐	--	--
B ☺	--	--
B ☺	--	--
C 😐	--	--
C 😐	--	--
C 😐	--	--
C 😐	--	--
C ☺	--	--
Mean	*55*	*8*
SD	*12*	*2*

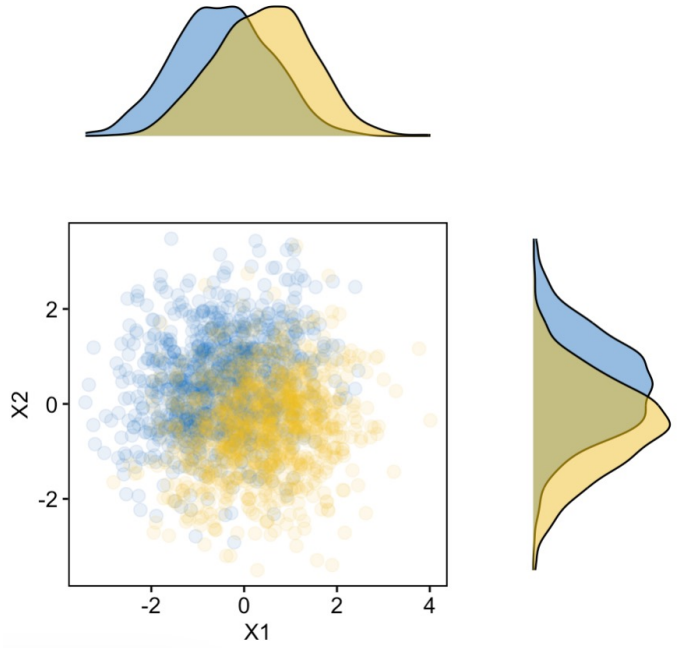
Simulation study - setup

Trial assignment model: $\Pr(i\ is\ in\ BC\ trial|X_1 = x_1, X_2 = x_2) = \text{logit}^{-1}(\kappa_1 x_1 + \kappa_2 x_2); \quad \kappa_1 = 1, \kappa_2 = -1$

Outcome model: $\Pr(Y = 1|T = t, X_1 = x_1) = \text{logit}^{-1}\begin{pmatrix}\beta_0 + \beta_1 I(t = A) + \beta_2 I(t = B) + \beta_3 x_1 + \beta_4 t x_1 + \\ +\beta_5 x_2 + \beta_6 t x_2 + \beta_7 t x_2^2\end{pmatrix};$

$\beta_0 = 1, \beta_1 = 0.25, \beta_2 = 0.25, \beta_3 = 1, \beta_4 = 0.25, \beta_5 = -1, \beta_6 = -0.25, \beta_7 = -0.15$





Simulation study - results

Anchored ITC with **large** sample sizes (*N* = 2000)

Method	Trial assignment model	Outcome model	Mean log-OR	SD
Unadjusted	Trial ~ 1	y ~ trt	-0.180	0.145

Incorrect model / Correct model

Simulation study - results

Anchored ITC with **large** sample sizes (*N* = 2000)

Method	Trial assignment model	Outcome model	Mean log-OR	SD
Unadjusted	Trial ~ 1	y ~ trt	-0.180	0.145
MAIC	Trial ~ X1	y ~ trt	-0.155	0.169

Incorrect model / Correct model

Simulation study - results

Anchored ITC with **large** sample sizes (*N* = 2000)

Method	Trial assignment model	Outcome model	Mean log-OR	SD
Unadjusted	Trial ~ 1	y ~ trt	-0.180	0.145
MAIC	Trial ~ X1	y ~ trt	-0.155	0.169
MAIC	Trial ~ X1 + X2	y ~ trt	0.006	0.213

Incorrect model / Correct model

Simulation study - results

Anchored ITC with **large** sample sizes (*N* = 2000)

Method	Trial assignment model	Outcome model	Mean log-OR	SD
Unadjusted	Trial ~ 1	y ~ trt	-0.180	0.145
MAIC	Trial ~ X1	y ~ trt	-0.155	0.169
MAIC	Trial ~ X1 + X2	y ~ trt	0.006	0.213
STC	Trial ~ 1	y ~ trt + X1 + X2 + trt*X1 + trt*X2	0.022	0.160

Incorrect model / Correct model

Simulation study - results

Anchored ITC with **large** sample sizes (*N* = 2000)

Method	Trial assignment model	Outcome model	Mean log-OR	SD
Unadjusted	Trial ~ 1	y ~ trt	-0.180	0.145
MAIC	Trial ~ X1	y ~ trt	-0.155	0.169
MAIC	Trial ~ X1 + X2	y ~ trt	0.006	0.213
STC	Trial ~ 1	y ~ trt + X1 + X2 + trt*X1 + trt*X2	0.022	0.160
Augmented-MAIC	Trial ~ X1	y ~ trt + X1 + X2 + trt*X1 + trt*X2	0.061	0.171
Augmented-MAIC	Trial ~ X1 + X2	y ~ trt + X1 + X2 + trt*X1 + trt*X2	0.002	0.177
Augmented-MAIC	Trial ~ X1	y ~ trt + X1 + X2+ trt*X1+ trt*X2 + trt*$X2^2$	0.001	0.174

Incorrect model / Correct model

Simulation study - results

Anchored ITC with **moderate** sample sizes (*N* = 200)

Method	Trial assignment model	Outcome model	Mean log-OR	SD
Unadjusted	Trial ~ 1	y ~ trt	-0.190	0.472
MAIC	Trial ~ X1	y ~ trt	-0.163	0.550
MAIC	Trial ~ X1 + X2	y ~ trt	0.019	0.702
STC	Trial ~ 1	y ~ trt + X1 + X2 + trt*X1 + trt*X2	0.024	0.523
Augmented-MAIC	Trial ~ X1	y ~ trt + X1 + X2 + trt*X1 + trt*X2	0.062	0.559
Augmented-MAIC	Trial ~ X1 + X2	y ~ trt + X1 + X2 + trt*X1 + trt*X2	0.007	0.571
Augmented-MAIC	Trial ~ X1	y ~ trt + X1 + X2+ trt*X1+ trt*X2 + trt*$X2^2$	-0.008	0.573

Incorrect model / Correct model

Simulation study - results

Anchored ITC with **small** sample sizes (*N* = 100)

Method	Trial assignment model	Outcome model	Mean log-OR	SD
Unadjusted	Trial ~ 1	y ~ trt	-0.200	0.698
MAIC	Trial ~ X1	y ~ trt	-0.175	0.815
MAIC	Trial ~ X1 + X2	y ~ trt	0.012	1.130
STC	Trial ~ 1	y ~ trt + X1 + X2 + trt*X1 + trt*X2	0.004	0.780
Augmented-MAIC	Trial ~ X1	y ~ trt + X1 + X2 + trt*X1 + trt*X2	0.044	0.826
Augmented-MAIC	Trial ~ X1 + X2	y ~ trt + X1 + X2 + trt*X1 + trt*X2	-0.012	0.852
Augmented-MAIC	Trial ~ X1	y ~ trt + X1 + X2+ trt*X1+ trt*X2 + trt*$X2^2$	-0.040	0.865

Incorrect model / Correct model

Conclusion – Pros and cons of Augmented-MAIC

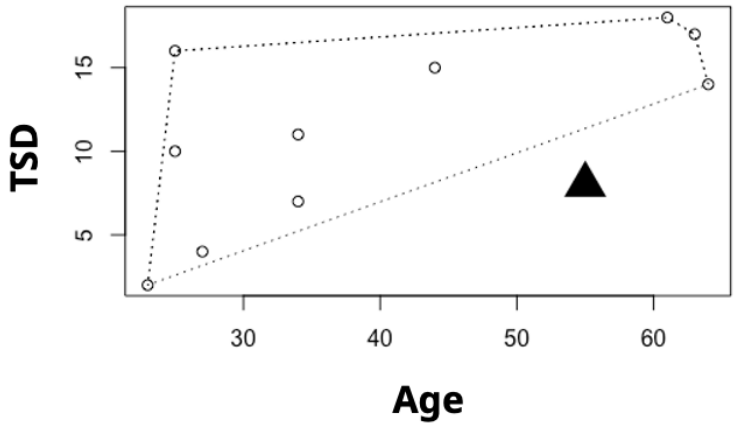
Pros

Robust to model misspecification

Able to adjust for variables for which there is no overlap

Potential efficiency gains

Useful for both anchored and unanchored ITCs



Cons

Requires some degree of extrapolation

Requires parametric assumptions about the distribution of covariates

Potential small sample bias

Too many choices? (researcher degrees of freedom)