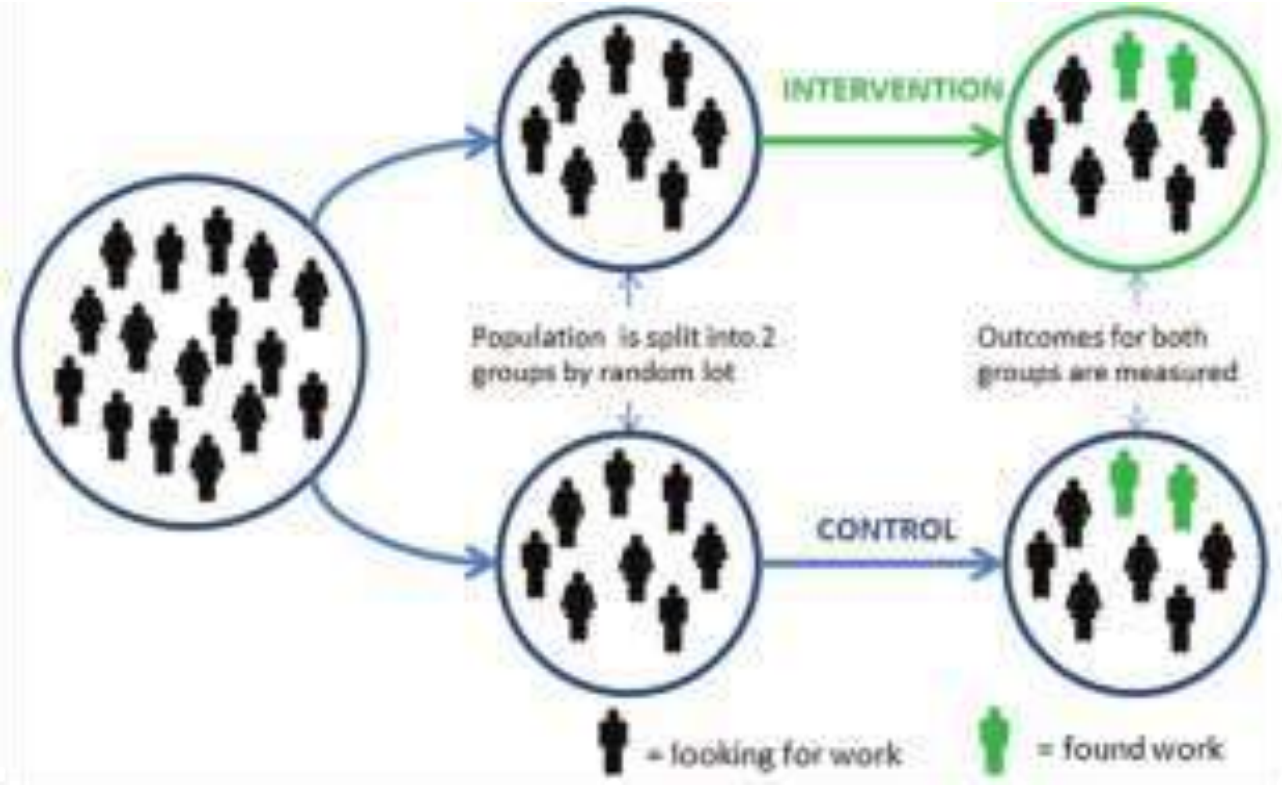
Population-adjusted indirect comparisons: methods, challenges and current practice

Tat-Thang Vo

University Paris Est Creteil

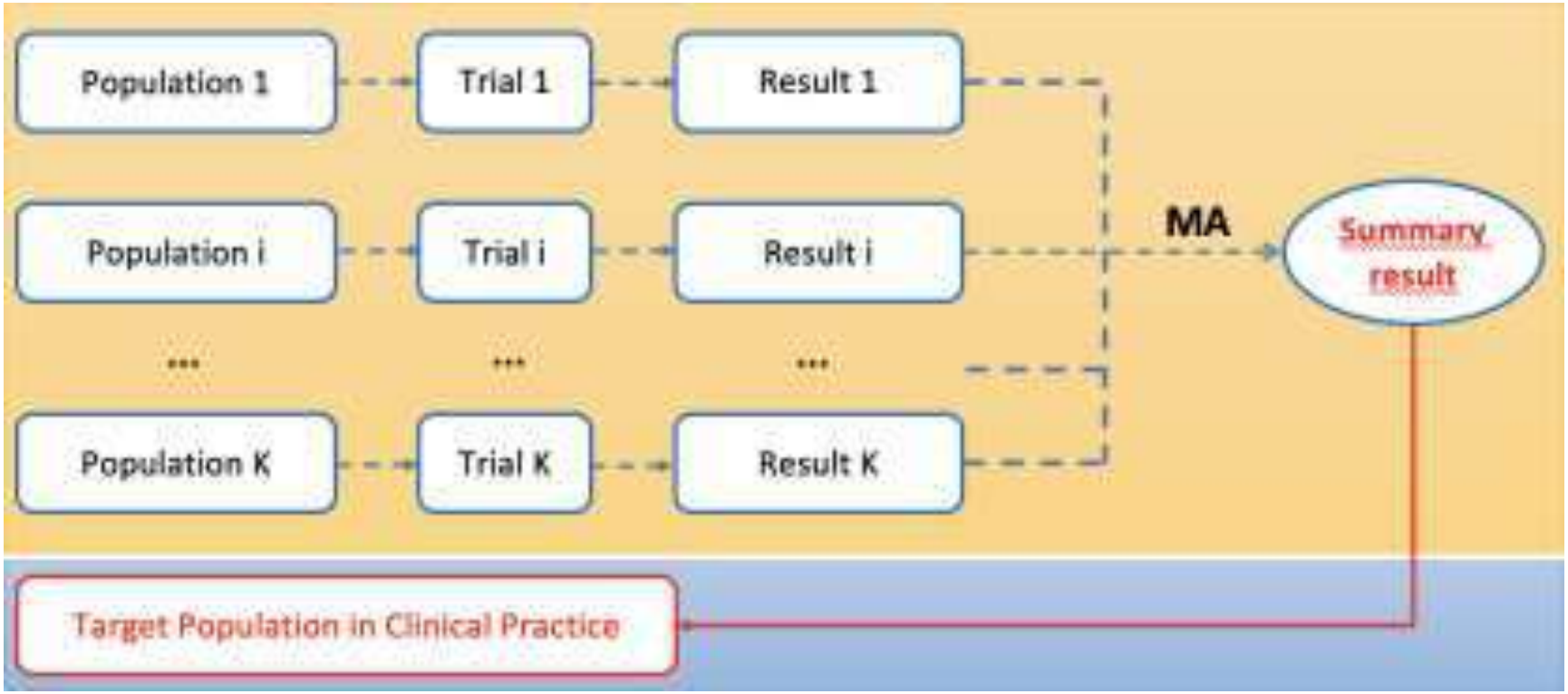
Joint Meeting of Cochrane Skin and EDEN
April 2024

Randomized Controlled Trials

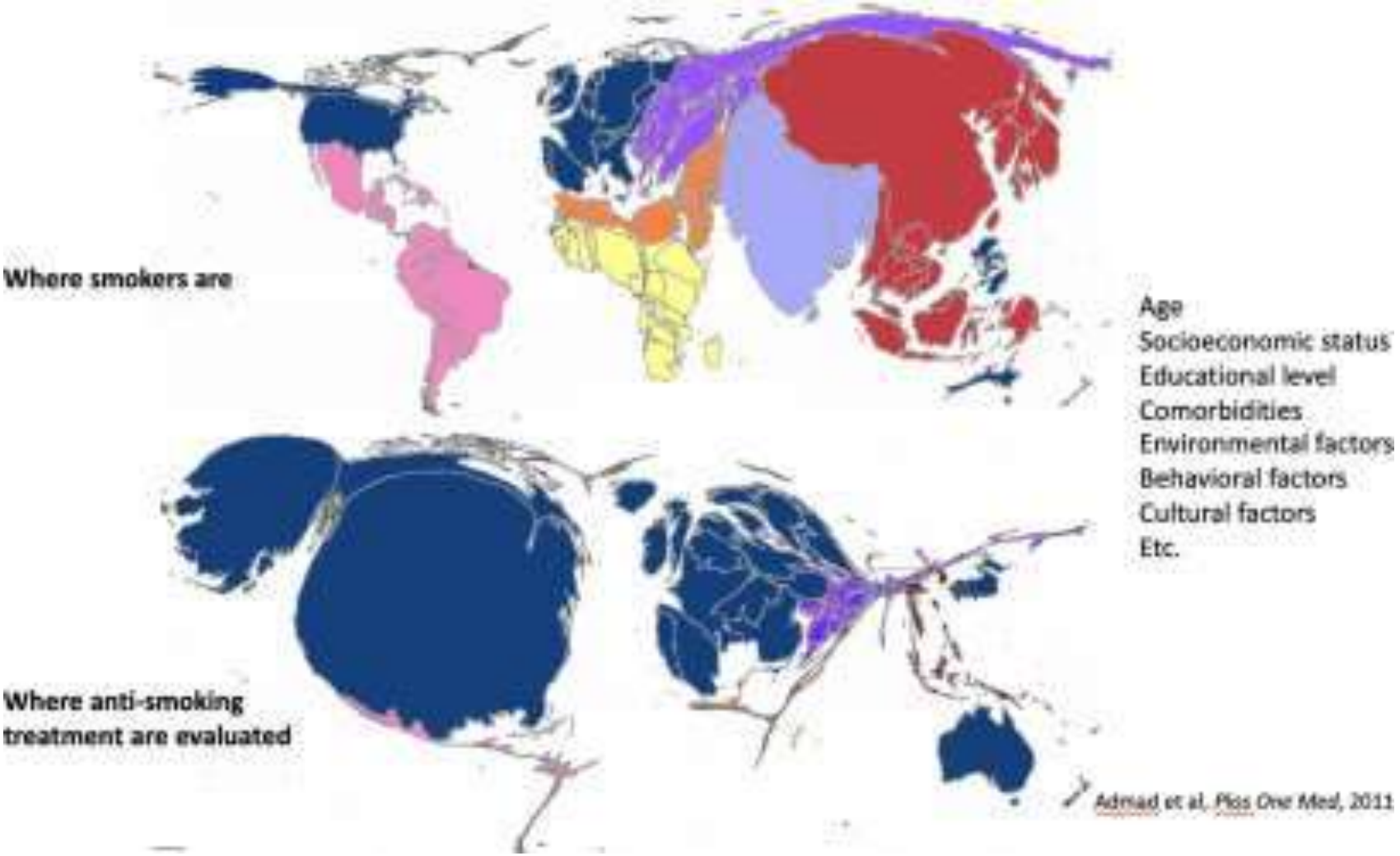


Meta-analysis

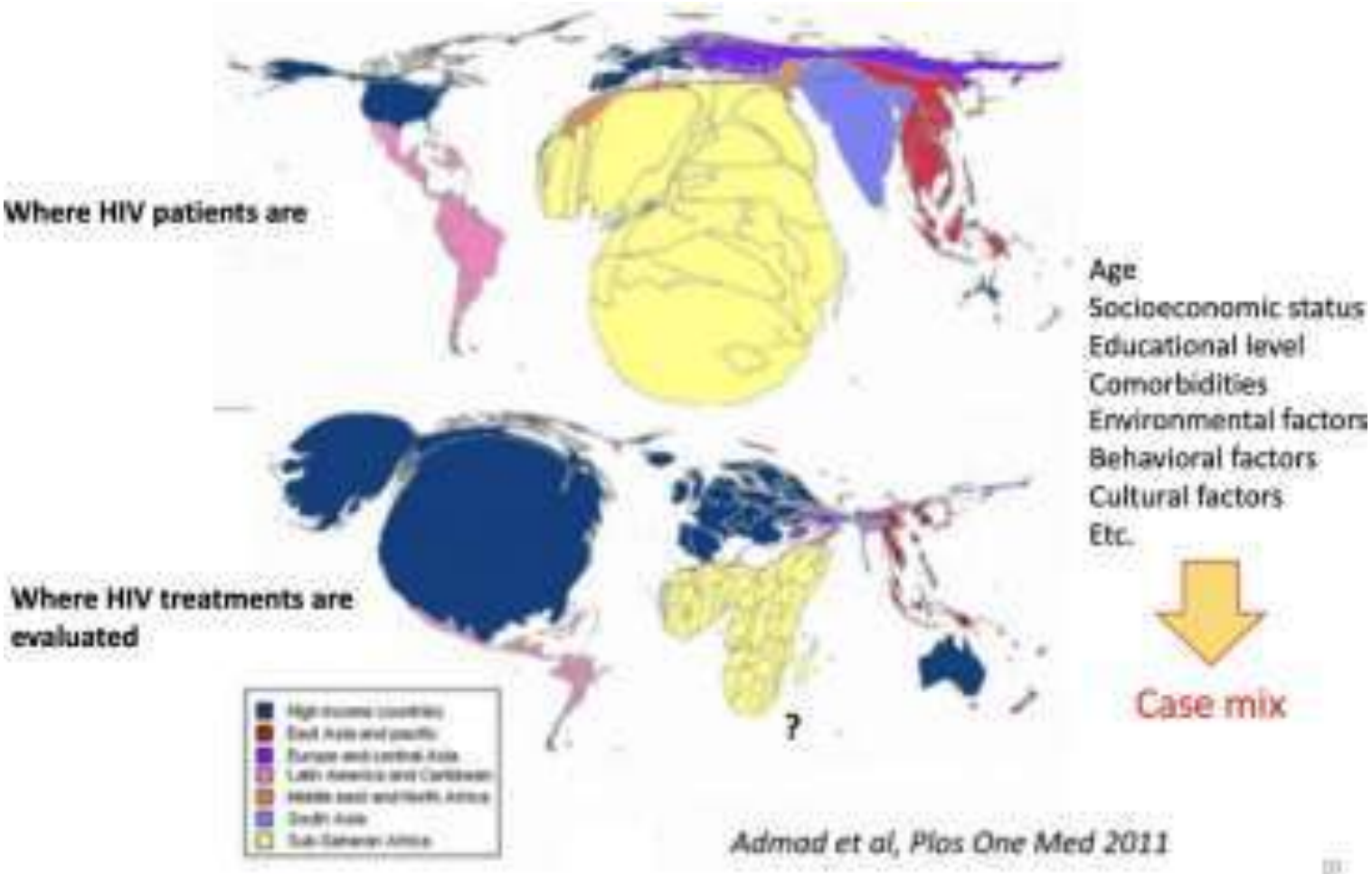
Case-mix heterogeneity in meta-analysis



External validity of RCTs: Anti-smoking treatments



External validity of RCTs: HIV treatments

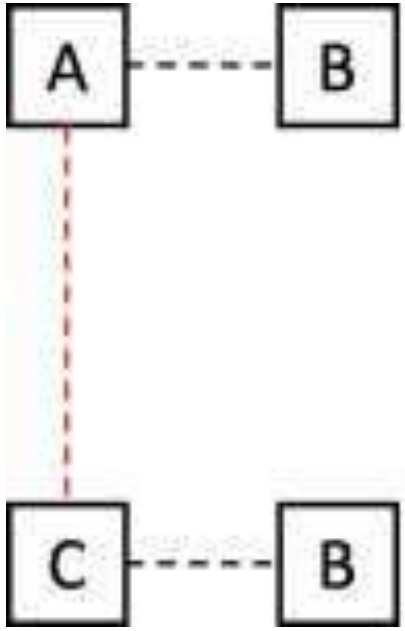


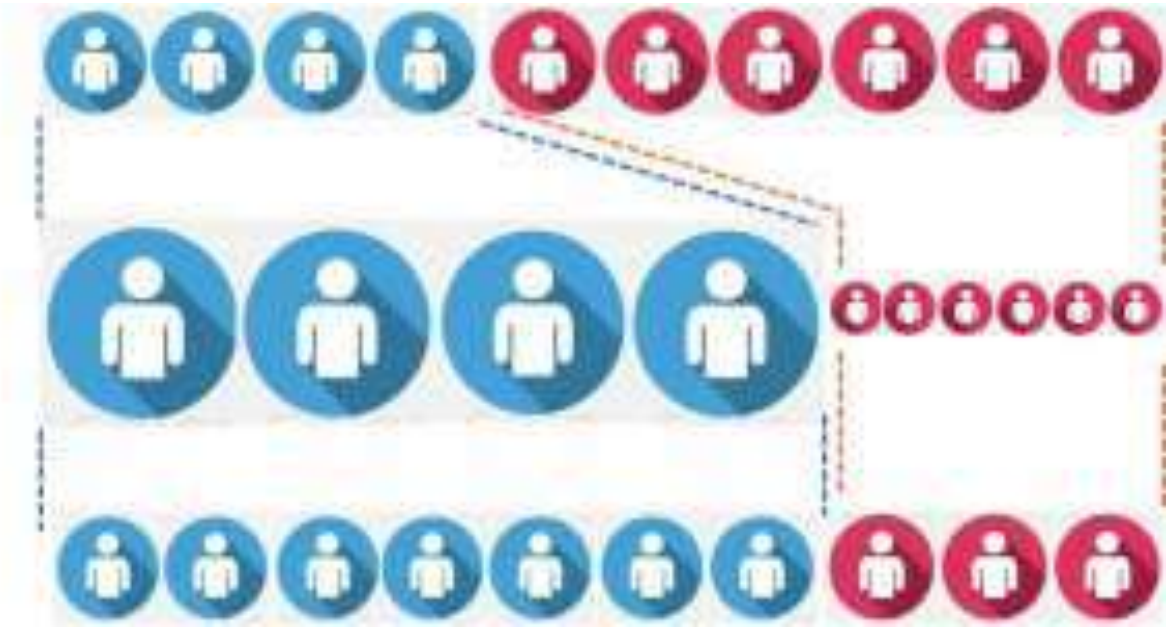
Population-adjusted indirect treatment comparison

A class of statistical methods to adjust for the case-mix difference across different studies prior to evidence synthesis.

Matching-Adjusted Indirect Comparison (MAIC)

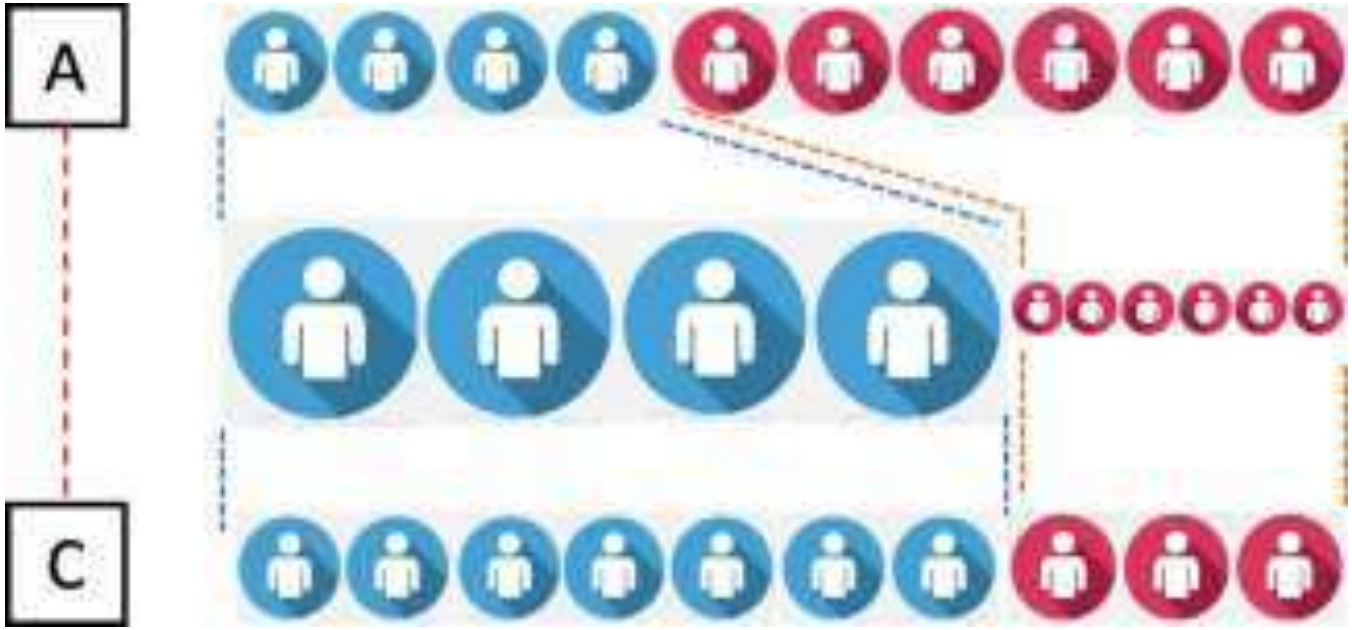
To compare A and C indirectly via B in the target population of trial BC.





MAIC: unanchored comparison

To directly compare A and C in the target population of the single-arm trial C.



A catalogue of different methods

- Matching-Adjusted Indirect Comparison (MAIC)
  - Vulnerable to extreme weights when populations are very different in case-mix.
- Two-Stage Matching-Adjusted Indirect Comparison (TS-MAIC)
  - More powerful than standard MAIC.
  - Also vulnerable to extreme weights.
- Simulated treatment comparison (STC)
  - More powerful than standard MAIC.
  - But may hidden the risk of extrapolation.
- Multi-level network meta-regression (ML-NMR)
  - An extension of STC.
  - To do population adjustment when the network of treatments is complex.
  - Also vulnerable to extrapolation.

Population adjustment in practice

Received: 13 November 2022 | Revised: 19 June 2023 | Accepted: 20 June 2023

DOI: 10.1002/jrsm.1655

REVIEW

Research Synthesis Methods WILEY

Population adjusted-indirect comparisons in health technology assessment: A methodological systematic review

Bang Truong[1,2] | Lan-Anh T. Tran[3] | Tuan Anh Le[4] | Thi Thu Pham[5] | Tat-Thang Vo[6]

Method

- Objective: to assess the conduct and reporting of PAICs in recent practice
- Eligibility: studies implementing PAICs from PubMed, EMBASE Classic, Embase/Ovid Medline All, and Cochrane databases.
- Date: from January 1, 2010 to Feb 13, 2023.

Characteristics of eligible studies

Characteristics (N = 162)	Statistic
Year of publication, N (%)	
2011–2015	10 (6.2)
2016–2020	65 (40.1)
2021	38 (23.5)
2022	40 (24.7)
2023	9 (5.5)
Source of funding, N (%)	
Industry	157 (96.9)
Academia	5 (3.1)
Number of studies with IPD, N (%)	
One	120 (74.1)
Two	30 (18.5)
Three or more	12 (7.4)
Number of studies with AgD, N (%)	
One	125 (77.2)
Two	23 (14.2)
Three or more	14 (8.6)
Type of treatment/exposures, N (%)	
Medication	156 (96.3)
Non-pharmacological treatments	6 (3.7)
Type of outcome, N (%)	
Continuous	20 (12.4)
Binary	36 (46.9)
Time-to-event	66 (40.7)
Number of studies included in the analysis, N (%)	
Two studies	74 (45.7)
Three studies	26 (16.0)
More	62 (38.3)
Number of treatment arms, N (%)	
Two	108 (66.7)
Three	23 (14.2)
More	31 (19.1)

Methods used for population adjustment

Characteristics	Statistics
Population adjustment methods, *N* (%)	
Matching-Adjusted Indirect Comparison (MAIC)	144 (88.9)
Simulated Treatment Comparison (STC)	11 (6.8)
Both MAIC and STC	6 (3.7)
Multilevel Network Meta Regression (ML-NMR)	1 (0.6)
Type of comparison, *N* (%)	
Anchored	57 (35.2)
Unanchored	105 (64.8)
Handling multiple treatments (>2 for unanchored and >3 for anchored comparisons), *N* (%)	50 (30.9)
Separate PAIC analysis for each pair (or each group of three) of treatments	48 (29.6)
One common analysis for the entire treatment network (e.g., by using ML-NMR)	2 (1.2)
Handling multiple studies (>2) with IPD, *N* (%)	42 (25.9)
Studies with IPD merged	41 (25.3)
Studies with IPD kept apart (by using ML-NMR)	1 (0.6)
Handling multiple studies (>2) with AgD, *N* (%)	37 (22.8)
Studies with AgD pooled	34 (21.0)
Separate PAIC analysis for each AgD study	3 (1.8)
Before adjustment, the eligibility criteria of one study (i.e., the one with AgD) were used to refine the patient sample of other studies (with IPD), *N* (%)	
No	90 (55.5)
Partially	33 (20.4)
Fully	39 (24.1)

Bias and heterogeneity assessment

Characteristics	Statistics
Bias/quality assessment of each study included in the PAIC analysis	
Yes	15 (9.3)
No	147 (90.7)
Heterogeneity assessment, *N* (%)	
No description/discussion about potential heterogeneity	18 (11.1)
No formal assessment, but the authors mentioned/discussed (informally) the potential difference between studies in:	40 (24.7)
Inclusion/exclusion criteria	26 (16.0)
Common comparator (only for anchored comparison)	2 (1.2)
Outcome definition/measurement	20 (12.3)
Follow-up time	19 (11.7)

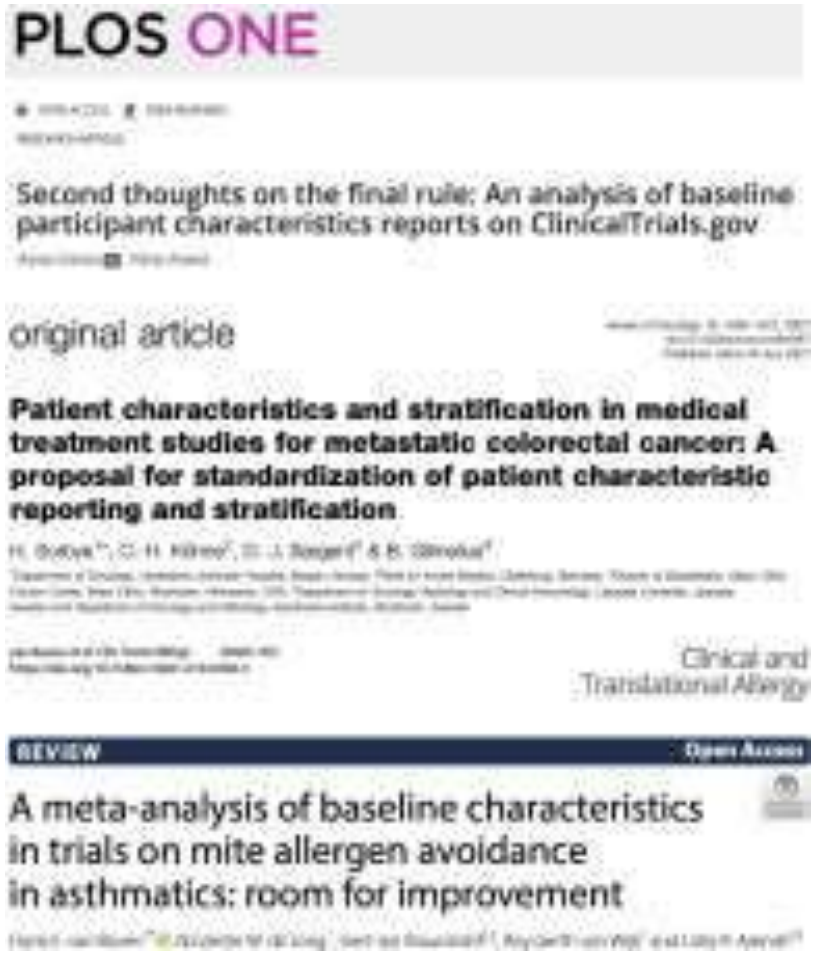
Characteristics	Statistics
The authors conducted a (partially) formal and systematic assessment of heterogeneity between studies in:	104 (64.2)
Inclusion/exclusion criteria	98 (60.5)
Common comparator (only for anchored comparison)	8 (4.9)
Outcome definition/measurement	81 (50.0)
Follow-up time	77 (47.5)

Sensitivity analysis

Sensitivity analysis to assess the robustness of PAIC results	
No sensitivity analysis	77 (47.5)
Adjusting for different sets of covariates	55 (34.0)
Applying additional inclusion/exclusion criteria to the IPD study	19 (11.7)
Using different outcome definitions	7 (4.3)
Using different follow-up time	11 (6.8)
Other (e.g., using different approaches for handling missing data, implementing additional anchored/unanchored comparisons)	12 (7.4)

Heterogeneity in reporting patient characteristics

- In PAIC, variable selection is affected by the availability of covariates data in individual studies.
- In practice, the collection and reporting of patient characteristics data among clinical studies in the same field remain very inconsistent


PLOS ONE

Second thoughts on the final rule: An analysis of baseline participant characteristics reports on ClinicalTrials.gov

original article

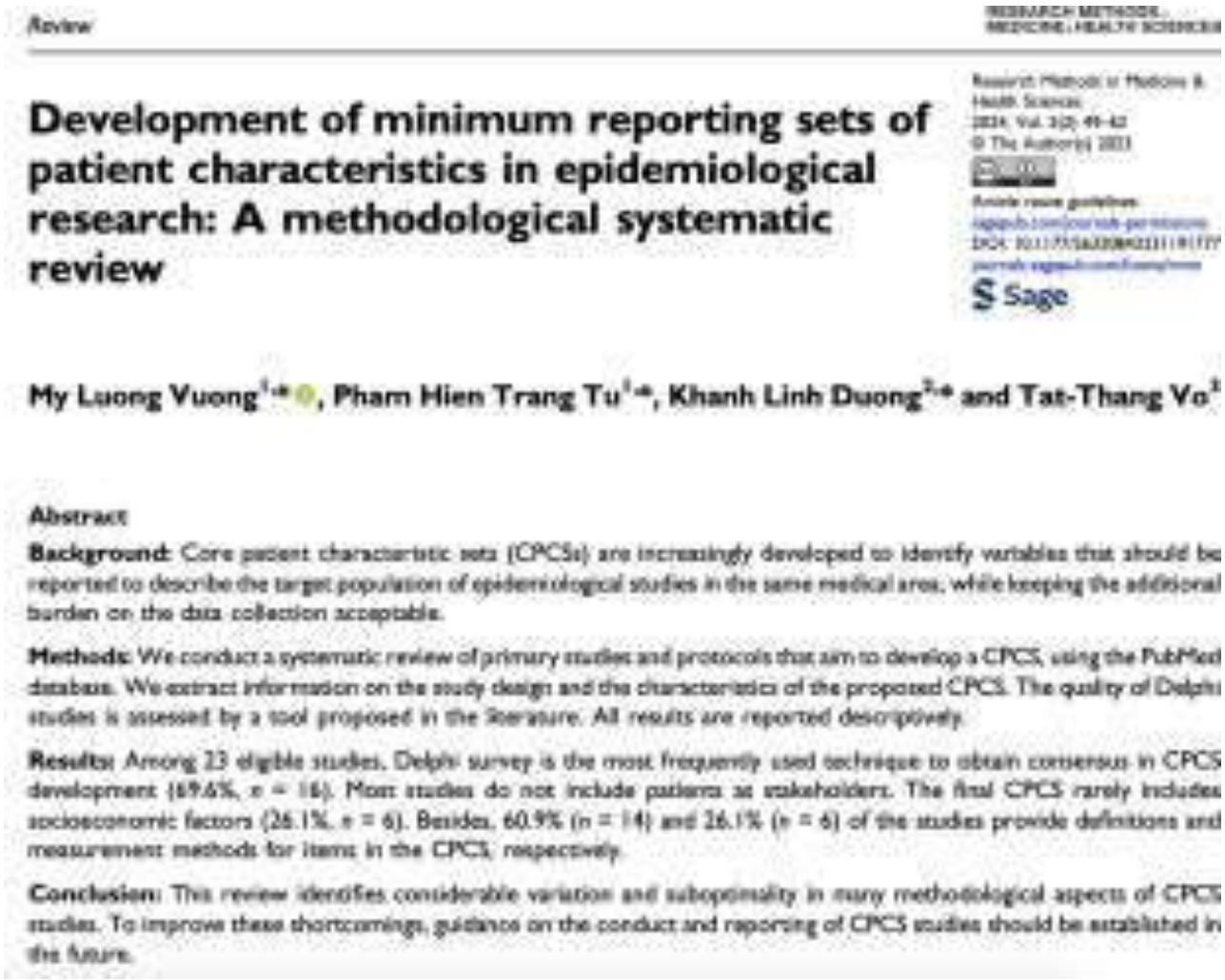
Patient characteristics and stratification in medical treatment studies for metastatic colorectal cancer: A proposal for standardization of patient characteristic reporting and stratification

Clinical and Translational Allergy

REVIEW

A meta-analysis of baseline characteristics in trials on mite allergen avoidance in asthmatics: room for improvement

Standardizing patient characteristics reporting



Review

Development of minimum reporting sets of patient characteristics in epidemiological research: A methodological systematic review

My Luong Vuong[1,*], Pham Hien Trang Tu[1,*], Khanh Linh Duong[2,*] and Tat-Thang Vo[1]

Abstract

Background: Core patient characteristic sets (CPCSs) are increasingly developed to identify variables that should be reported to describe the target population of epidemiological studies in the same medical area, while keeping the additional burden on the data collection acceptable.

Methods: We conduct a systematic review of primary studies and protocols that aim to develop a CPCS, using the PubMed database. We extract information on the study design and the characteristics of the proposed CPCS. The quality of Delphi studies is assessed by a tool proposed in the literature. All results are reported descriptively.

Results: Among 23 eligible studies, Delphi survey is the most frequently used technique to obtain consensus in CPCS development (69.6%, n = 16). Most studies do not include patients as stakeholders. The final CPCS rarely includes socioeconomic factors (26.1%, n = 6). Besides, 60.9% (n = 14) and 26.1% (n = 6) of the studies provide definitions and measurement methods for items in the CPCS, respectively.

Conclusion: This review identifies considerable variation and suboptimality in many methodological aspects of CPCS studies. To improve these shortcomings, guidance on the conduct and reporting of CPCS studies should be established in the future.

Some conclusions

- Population-adjusted indirect comparison is increasingly popular in practice.
- However, the conduct and reporting of these analyses are often suboptimal, with much room left for further improvement.
- Heterogeneity in reporting patient characteristics is an important challenge to PAIC.
- More guidance is needed to improve current practice.

Recommendations on PAIC (Truong et al, 2023)

TABLE 4 Methodological recommendations for population-adjusted indirect comparisons (PAICs).

Conduct	• Decide carefully which variables to adjust for in the PAIC. ◦ Based on the type of comparison (anchored or unanchored), subject-matter knowledge and the availability of covariates across studies. For a more detailed guidance, see Reference 3. • Assess the risk of bias in each eligible study. ◦ For instance, by the RoB-2 tool for RCTs, by the ROBINS-I tool for observational controlled studies, by the NIH quality appraisal tool (or many other tools) for case-series/single-arm studies.[29] • Assess clinical and methodological heterogeneity across eligible studies. ◦ For instance, by comparing the characteristics of included studies (i.e., eligibility criteria, common control (in anchored comparisons), outcome definition and follow-up time) in a table.[12] ◦ PAICs should only be implemented when individual studies can be judged as sufficiently similar. • On many occasions, the eligibility criteria of different studies can be aligned to reduce heterogeneity and/or to avoid positivity violation. • Choose an appropriate statistical method to implement PAIC. ◦ Anchored comparisons should be prioritized whenever possible.[3] ◦ In the standard setting of PAIC where two treatments are indirectly compared (possibly via a common control), MAIC is still the primary method to use. However, extreme weights may arise and bias the effect estimate by MAIC when there is limited overlapping among study populations.[11,14] ◦ In contrast, STC only provides estimates for the conditional treatment effect, which does not coincide with the population-level treatment effect when the effect measure is non-collapsible (e.g., odds ratio or hazard ratio).[3,7] Because PAIC findings are often used for reimbursement decision making on the population level, STC may not be suitable for binary and time-to-event outcomes. ◦ Recently, enhancements to the standard versions of MAIC and STC have been proposed in the literature, with aims to improve statistical performance and to overcome the above-mentioned limitations.[11,16,28] ◦ In complex settings where a connected network of treatments is evaluated across multiple trials, new methods such as ML-NMR should be used.[3] However, ML-NMR, as currently conceptualized, is not readily extended to disconnected networks/unanchored comparisons of multiple treatments, or to time-to-event outcomes. This leaves room for future methodological research. ◦ When there are multiple studies with IPD, combining the IPD of different studies into one and then using a single method such as MAIC or STC for population adjustment is suboptimal. This overlooks potential heterogeneity across IPD studies. • Sensitivity analysis to assess the robustness of PAIC findings should be considered.

Recommendations on PAIC (Truong et al, 2023)

Reporting and discussion	• Provide a clear description of the PAIC protocol, for example, what method is used for: ▫ Variable selection ▫ Bias and heterogeneity assessment ▫ Handing missing data ▫ Population adjustment (e.g., whether MAIC, STC, or any other method is used) ▫ Sensitivity analyses • Report the results of every step in the implemented PAIC, including: ▫ Which covariates are adjusted for in the analysis ▫ Covariate distribution in each study before adjustment ▫ Bias and heterogeneity assessment results ▫ Results of the outcome model estimation when using STC and ML-NMR; effective sample size, distribution of weights, percentage of extreme weights, distribution of covariates after adjustment by MAIC (or by any other weighting-based methods). ▫ Treatment effect estimates and corresponding uncertainty measures. ▫ Results of sensitivity analyses. • Discuss the clinical relevance of the obtained PAIC results by, for instance, comparing treatment effect estimates before versus after population adjustment.[3] • Discuss the limitations of the PAIC analysis, for example, whether there are important covariates that cannot be adjusted for (due to the unavailability of such covariates in some or all studies). Mention explicitly the unmeasured covariates and explain their potential impact on the validity of the findings.

Abbreviations: AgD, aggregate data; IPD, individual patient data; MAIC, matching-adjusted indirect comparison; NIH, National Institutes of Health; PAIC, population-adjusted indirect comparison; RoB-2, version 2 of the Cochrane risk-of-bias tool for randomized trials; ROBINS-I, risk of bias in non-randomized studies—of interventions; STC, simulated treatment comparison.

References

1. Truong, B., Tran, L.A.T., Le, T.A., Pham, T.T. and Vo, T.T., 2023. Population adjusted-indirect comparisons in health technology assessment: A methodological systematic review. Research Synthesis Methods, 14(5), pp.660-670.
2. Vuong, M.L., Tu, P.H.T., Duong, K.L. and Vo, T.T., 2024. Development of minimum reporting sets of patient characteristics in epidemiological research: a methodological systematic review. Research Methods in Medicine & Health Sciences, 5(2), pp.49-62.
3. Vo, T.T., 2023. A cautionary note on the use of G-computation in population adjustment. Research Synthesis Methods, 14(3), pp.338-341.
4. Vo, T.T., Porcher, R., Chaimani, A. and Vansteelandt, S., 2019. A novel approach for identifying and addressing case-mix heterogeneity in individual participant data meta-analysis. Research synthesis methods, 10(4), pp.582-596.
5. Vo, T.T., Porcher, R. and Vansteelandt, S., 2021. Assessing the impact of case-mix heterogeneity in individual participant data meta-analysis: novel use of I2 statistic and prediction interval. Research Methods in Medicine & Health Sciences, 2(1), pp.12-30.