Generalization of the Risk Difference, Risk Ratio, OR, etc... from one trial to a target population.

Ahmed Boughdiri (INRIA, Premedical Team)

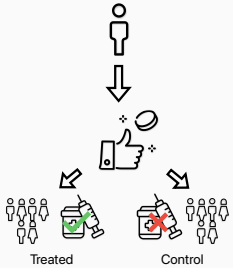
A Unified Framework for the Transportability of Population-Level Causal Measures

NEURAL INFORMATION PROCESSING SYSTEMS

Clément Berenfeld (INRIA, Montpellier), Julie Josse (INRIA, Montpellier) and Erwan Scornet (Sorbonne, Paris)

Introduction to Generalization

Randomized Controlled Trials:



+ direct causal association
− selective population, small sample, not always feasible

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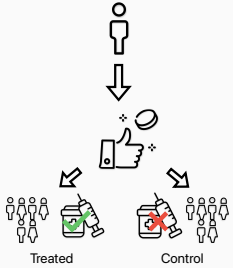

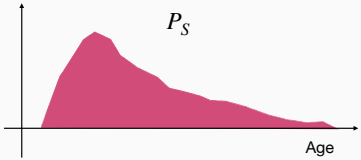

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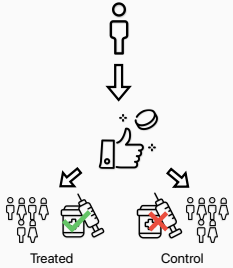

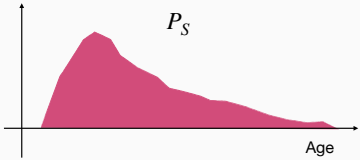

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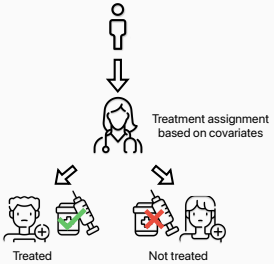

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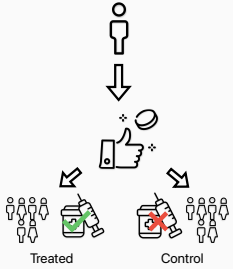

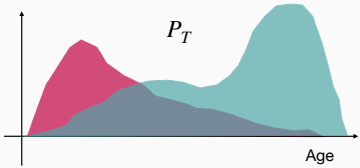

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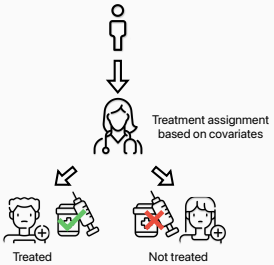

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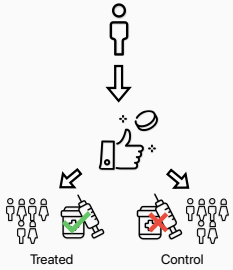

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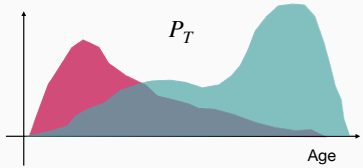

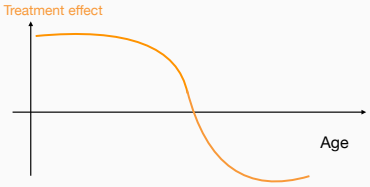

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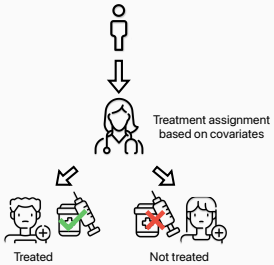

+ abundant, representative population
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$$p_S(x) \neq p_T(x) \Rightarrow \underbrace{\text{ATE in the RCT}}_{>0} \neq \underbrace{\text{Target ATE}}_{<0}$$

Problem setting: Generalization from one RCT to a Target pop.

Goal: estimate the treatment effect on the target population.

Source	Obs.	Covariates			Treatment	Outcomes	Potential Outcomes	
S	i	X^1	X^2	X^3	A	Y	$Y^{(1)}$	$Y^{(0)}$
0	1	37	2.0	F	0	1.7	??	1.7
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
0	m	52	1.7	M	1	2.4	2.4	??

IPW, G-formula, AIPW under $Y(1), Y(0) \perp A \mid X \implies$ Strong assumption !

Problem setting: Generalization from one RCT to a Target pop.

Generalization: estimate the treatment effect on the target population using the RCT

Source	Obs.	Covariates			Treatment	Outcomes	Potential Outcomes	
S	i	X^1	X^2	X^3	A	Y	$Y^{(1)}$	$Y^{(0)}$
1	1	23	1.5	M	1	3.2	3.2	??
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
1	n	17	2.9	M	0	1.5	??	1.5
0	1	37	2.0	F	??	??	??	??
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
0	m	52	1.7	M	??	??	??	??

Note that here we do not need the treatment and the outcome in the target population.

The age-old question of how to report treatment effects

Count the dead

$$\tau_{RR} = \frac{\mathbb{E}\left[Y^{(1)}\right]}{\mathbb{E}\left[Y^{(0)}\right]}$$

Count the living

$$\tau_{SR} = \frac{1 - \mathbb{E}\left[Y^{(1)}\right]}{1 - \mathbb{E}\left[Y^{(0)}\right]}$$

$$\tau_{RD} = \mathbb{E}\left[Y^{(1)}\right] - \mathbb{E}\left[Y^{(0)}\right]$$

Risk Difference

$$\tau_{NNT} = \tau_{RD}^{-1}$$

Number Needed to Treat

Odds Ratio

$$\tau_{OR} = \frac{\mathbb{E}[Y^{(1)}]}{1 - \mathbb{E}[Y^{(1)}]} \left(\frac{\mathbb{E}[Y^{(0)}]}{1 - \mathbb{E}[Y^{(0)}]} \right)^{-1}$$

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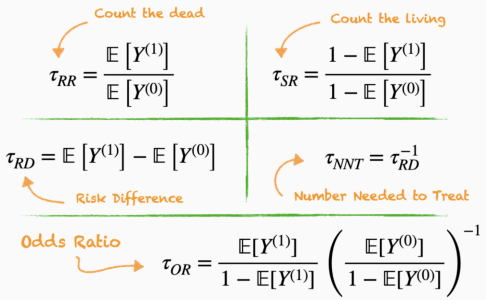

Risk Ratio, odds ratio, risk difference...
Which causal measure is easier to generalize?

Bénédicte Colnet *Julie Josse* *Gaël Varoquaux* *Erwan Scornet*

Measure	Dir. collapsible	Collapsible	Logic-respecting
RD	Yes	Yes	Yes
NNT	No	No	Yes
RR	No	Yes	Yes
SR	No	Yes	Yes
OR	No	No	No

e.g. Huitfeldt et al., 2021; Lapointe-Shaw et al., 2022; Liu et al., 2022; Colnet, et al. J.J. 2022; Colnet, J.J et al. 2023; Boughdiri, J.J et al 2025; Dumas, E., Stensrud (2025) ...

• CONSORT guidelines recommend to report all of them •

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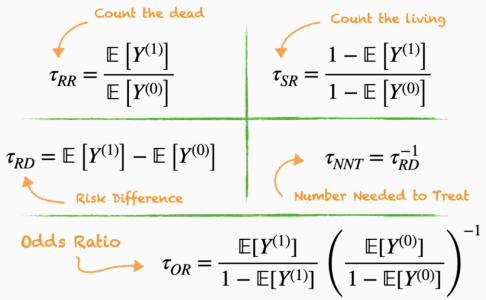

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Existing studies have generalized the RD but not other causal measures. Here, we propose

A Unified Framework for the Transportability of Population-Level Causal Measures

First moment population-level measure

- τ^P a 1st moment population-level[1] measure if $\exists\ \Phi : D_\Phi \to \mathbb{R}$, $D_\Phi \subset \mathbb{R}^2$

$$\tau^P_\Phi = \Phi\left(\mathbb{E}_P[Y(1)], \mathbb{E}_P[Y(0)]\right)$$

Note that a 1st moment population-level measure depends on a population P: $\tau^S_\Phi \neq \tau^T_\Phi$

[1] Fay & Li. (2024). Causal interpretation of the hazard ratio in RCTs. *Clinical Trials*.

[2] Even, **J.J.** (2025). Rethinking the win ratio: causal framework for hierarchical outcome Analysis.

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Measure	**Effect Measure**	**Domain D_Φ**
Risk Difference (RD)	$\Phi(x, y) = x - y$	$\mathbb{R}^2$
Risk Ratio (RR)	$\Phi(x, y) = \frac{x}{y}$	$\mathbb{R} \times \mathbb{R}^*$
Odds Ratio (OR)	$\Phi(x, y) = \frac{x}{1-x} \cdot \frac{1-y}{y}$	$\mathbb{R}/\{1\} \times \mathbb{R}^*$
NNT	$\Phi(x, y) = \frac{1}{x-y}$	$\{(x, y) \in \mathbb{R}^2 \mid x - y \neq 0\}$

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- In contrast an individual-level measure depends on the joint distribution. Most are non identifiable but workarounds exist[2]. Ex: $\mathbb{E}\left[\frac{Y_i(1)}{Y_i(0)}\right] \neq \frac{\mathbb{E}[Y_i(1)]}{\mathbb{E}[Y_i(0)]}$ or $\mathbb{P}[Y(1) > Y(0)]$

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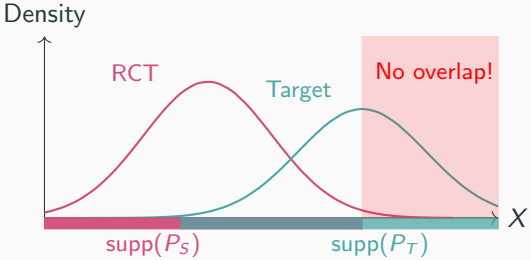
Assumptions for ATE identifiability in generalization

Overlap

$\forall x \in \mathbb{X}, p_S(x) > 0$ and

$$\text{supp}(P_T(X)) \subset \text{supp}(P_S(X))$$



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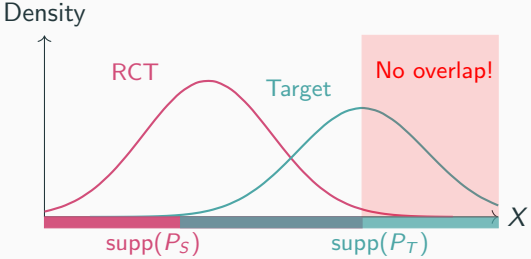


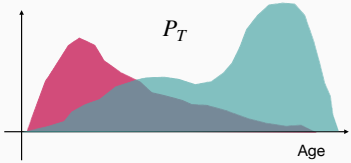
Intuition: Every covariate profile in the target population must be represented in the RCT. We cannot generalize on people not represented in S

Exchangeability in mean

$\forall a \in \{0, 1\}$,

$$\mathbb{E}_S[Y(a) \mid X] = \mathbb{E}_T[Y(a) \mid X]$$

In general $\mathbb{E}_S[Y(a)] \neq \mathbb{E}_T[Y(a)]$ since:



- what about: $\mathbb{E}_S[Y(a)|age] = \mathbb{E}_T[Y(a)|age]$?
- what if we have $p_s(weight) \neq p_T(weight)$?

Intuition: X must contain all shifted and prognostic covariates.

Reweighting the RCT: reweight Horvitz-Thomson

Reweighted Horvitz-Thomson

$$\hat{\tau}_{\Phi,\text{wHT}} = \Phi\left(\frac{1}{n}\sum_{S_i=1}\hat{r}(X_i)\frac{A_i Y_i}{\pi}, \frac{1}{n}\sum_{S_i=1}\hat{r}(X_i)\frac{(1-A_i)Y_i}{1-\pi}\right)$$

Estimate the **ratio of densities** with a logistic regression

$$r(X) := \frac{p_T(X)}{p_S(X)} = \frac{\mathbb{P}(X = x|S = 0)}{\mathbb{P}(X = x|S = 1)}$$

$$\overset{\text{Bayes}}{=} \frac{\mathbb{P}(S = 1)\,\mathbb{P}(S = 0|X = x)}{\mathbb{P}(S = 0)\,\mathbb{P}(S = 1|X = x)}$$

$$\frac{\mathbb{P}(S = 0|X = x)}{\mathbb{P}(S = 1|X = x)} = \exp(x^\top \beta)$$

Transport the RCT: G-formula

Fit models on RCT data
$\hat{\mu}_a^S(X) = \mathbb{E}_S[Y|A = a, X]$

↓

Predict on the target data
$Y(a) = \hat{\mu}_a^S(X)$ where $X \sim P_T(X)$

↓

Average over the target
$\hat{\tau}_{\Phi,tG} = \Phi\left(\frac{1}{m}\sum_i \hat{\mu}_1^S(X_i), \frac{1}{m}\sum_i \hat{\mu}_0^S(X_i)\right)$

X^1	X^2	X^3	$Y^{(1)}$	$Y^{(0)}$
37	2.0	F	$\hat{\mu}_0^S(X_1)$	$\hat{\mu}_1^S(X_1)$
⋮	⋮	⋮	⋮	⋮
52	1.7	M	$\hat{\mu}_0^S(X_m)$	$\hat{\mu}_1^S(X_m)$

Transported G-formula

$$\hat{\tau}_{\Phi,\mathrm{tG}} = \Phi\left(\frac{1}{m}\sum_{S_i=0} \hat{\mu}^{\mathrm{S}}_{(1)}(X_i), \frac{1}{m}\sum_{S_i=0} \hat{\mu}^{\mathrm{S}}_{(0)}(X_i)\right)$$

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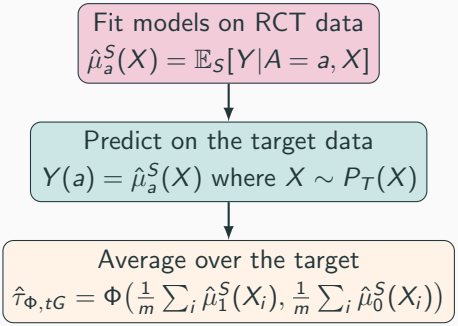

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We use data from the RCT to train $\hat{\mu}_{(1)}$ and $\hat{\mu}_{(0)}$ using

- Linear Regressions
- Random Forests

Proposition

Under a logistic $S|X$ and linear $Y(a)|X$ model for respectively the source and the outcome we have,

$$V^{\mathrm{OLS}}_{\Phi,\mathrm{tG}} \leq V_{\Phi,\mathrm{HT}},$$

Doubly robust estimator

Estimated equation estimator

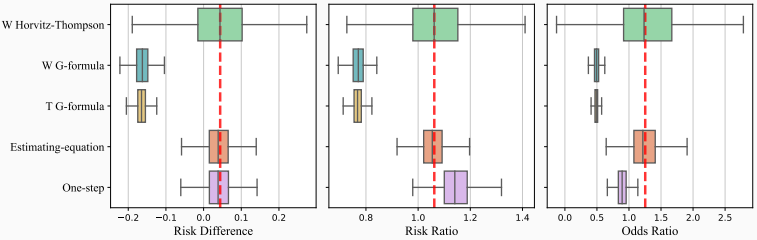
Given estimators $\hat{\mu}_{(a)}$ (resp. $\hat{r}$) of $\mu_{(a)}$ (resp. r), an estimating equation estimator $\hat{\tau}_{\Phi}^{\mathrm{EE}}$ of τ_{Φ} is given by $\hat{\tau}_{\Phi}^{\mathrm{EE}} = \Phi(\hat{\psi}_1^{\mathrm{EE}}, \hat{\psi}_0^{\mathrm{EE}})$ where for all $a \in \{0, 1\}$

$$\hat{\psi}_a^{\mathrm{EE}} := \frac{1}{m} \sum_{S_i=0} \hat{\mu}_{(a)}(X_i) + \frac{1}{n} \sum_{S_i=1} \frac{1\{A = a\}}{\mathbb{P}(A = a)} \hat{r}(X_i)(Y - \hat{\mu}_{(a)}(X_i))$$

Doubly Robust: The estimator $\hat{\tau}_{\Phi}^{\mathrm{EE}}$ is consistent as soon as either $\hat{\mu}_{(a)} = \mu$ or $\hat{r} = r$.

Robust to miss-specification :

- Logistic model on $S|X$
- Non-linear model on $Y(a)|X$



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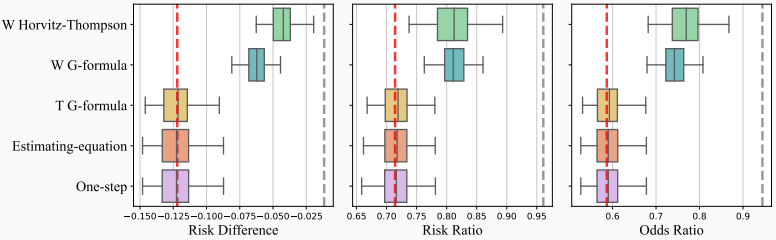
Doubly Robust: The estimator $\hat{\tau}_{\Phi}^{\mathrm{EE}}$ is consistent as soon as either $\hat{\mu}_{(a)} = \mu$ or $\hat{r} = r$.

Robust to miss-specification :

- Non-Logistic model on $S|X$
- Linear model on $Y(a)|X$



Relaxing exchangeability in mean

Exchangeability in mean

$\forall a \in \{0,1\}$,

$$\mathbb{E}_S[Y(a) \mid X] = \mathbb{E}_T[Y(a) \mid X]$$

X contains shifted prognostic variables

Exchangeability in effect measure

For a given ϕ, we have

$$\tau^{\mathrm{R}}_{\Phi}(x_c) = \tau^{\mathrm{T}}_{\Phi}(x_c)$$

X_c contains all shifted effect modifiers. $X_c \subseteq X$

If $Y^{(0)}$ is known in the target population, then the target treatment effect (for a given Φ) is **identifiable:**

$$\tau^T_{\Phi} = \Phi\left(\mathbb{E}_T\left[\Gamma\left(\tau^S_{\Phi}(X_c), \mu^T_{(0)}(X_c)\right)\right], \mathbb{E}_T\left[Y^{(0)}\right]\right)$$

where Γ is the inverse of $\psi_1 \mapsto \Phi(\psi_1, \psi_0)$ It leads naturally to:

- Weighted estimators
- Regression-based estimators
- **Doubly robust** estimators combining both approaches

Estimate the treament effect on the Target pop.

	Observational studies	Gen with Conditional Outcome	Gen with Local effects
Ass.	$Y(1), Y(0) \perp A \mid X$	$\mathbb{E}_{\mathrm{R}}[Y(a) \mid X] = \mathbb{E}_{\mathrm{T}}[Y(a) \mid X]$	$\tau_{\Phi}^{\mathrm{R}}(x) = \tau_{\Phi}^{\mathrm{T}}(x)$
Var.	confounding variables	shifted prognostic covariates	shifted effect modifiers $Y(0)$ in the target population
Meas.	RD, RR[3] but can be extended	RD, RR, NNT, OR, SR, ...	only Φ

[3] Boughdiri, J.J., Scornet. Estimating Risk Ratios in Causal Inference. ICML2025

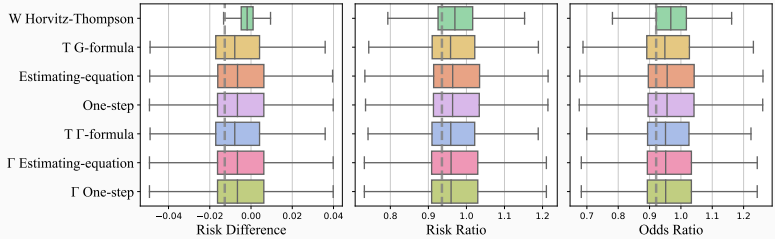
Generalizing CRASH-3 findings to the Traumabase population

CRASH-3 trial (Mostly Pakistan)

- Randomized trial ($n \approx 9{,}000$)
- Patients with TBI, GCS ≤ 12, within 3h
- Treatment: Tranexamic Acid (TXA)
- Outcome: Head injury-related death at 28 days

Traumabase cohort (France)

- Observational registry ($m \approx 8{,}200$)
- Selected CRASH-3-eligible patients
- Treatment: Tranexamic Acid (TXA)
- Deleterious/No evidence



[3] Colnet, J.J et al (2023). *Causal inference methods for combining randomized trials and observational studies: a review.*

Conclusion & Perspectives

- Identification relies on:
  - **Exchangeability in mean/effect measure:** $\mathbb{E}_S[Y(a) \mid X] = \mathbb{E}_T[Y(a) \mid X]$ or $\tau_\Phi^S(x) = \tau_\Phi^T(x)$
  - **Overlap:** $\text{supp}(P_T(X)) \subseteq \text{supp}(P_S(X))$

What we did:

- Generalized RD, RR and OR under Overlap and Exchangeability.
- Build and studied weighted, regression and doubly robust estimators.
- Applied this to **transported** the effect of TXA using CRASH-3 and Traumabase.

Perspectives:

- Relaxing **overlap**.
- Build a R and Python package.
- Meta-analysis [Berenfeld et al., 2025]

Thank you!

References i

[Berenfeld et al., 2025] Berenfeld, C., Boughdiri, A., Colnet, B., van Amsterdam, W. A., Bellet, A., Khellaf, R., Scornet, E., and Josse, J. (2025).
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