Estimating Treatment Effects in Cluster Randomized Trials by Calibrating Covariate Imbalances between Clusters

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Individualizing Health

Source: http://www.diabetesdaily.com/voices/2014/07/why-one-size-fits-all-doesnt-work-in-diabetes

Evaluation of individualized intervention

1. **Scientific question:** To what extent has the individualized rule improved health outcomes for the entire population? (Policy makers may care more than clinicians)
2. **Statistical question:** How to estimate the overall effect *consistently* and *efficiently*?

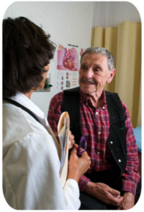
Wu, Frangakis, Louis, Scharfstein (2014). Estimating Treatment Effects in Cluster Randomized Trials by Calibrating Covariate Imbalances between Clusters. *Biometrics*. doi: 10.1111/biom.12214.

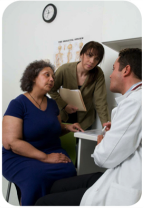
R package: http://github.com/zhenkewu/mpcr

Example: Guided Care study

Background: specially trained nurses to help deliver patient-centered care

Online course and certificate for specially trained nurses





Study website: http://www.guidedcare.org/
Nurse training courses: https://www.ijhn-education.org/content/guided-care-nursing

How data is collected?

Matched-pair cluster randomized (MPCR) design–rationale

1. Sometimes, investigators are only able to intervene on clusters of individuals, e.g., a nurse for each clinical practice

1. Cornfield J (1978)
2. Gail et al. (1992)
3. Moulton L (2004)
4. Imai K, King G, and Nall C (2009)

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2. To recoup the resulting efficiency loss[1], some studies pair similar clusters and randomize treatments within pairs[2,3]

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2. To recoup the resulting efficiency loss[1], some studies pair similar clusters and randomize treatments within pairs[2,3]
3. The use of pre-treatment variables that affect the outcome can improve estimation efficiency[4]

1. Cornfield J (1978)
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Matched-pair cluster randomized (MPCR) design

One pair

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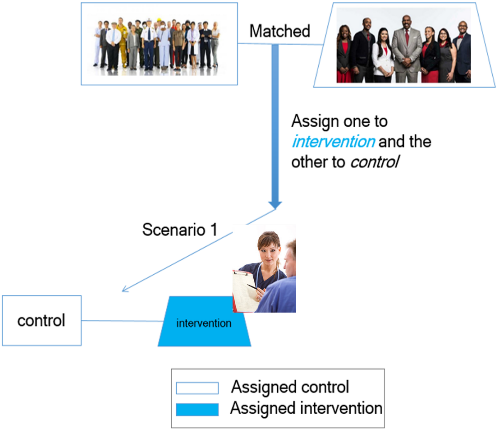

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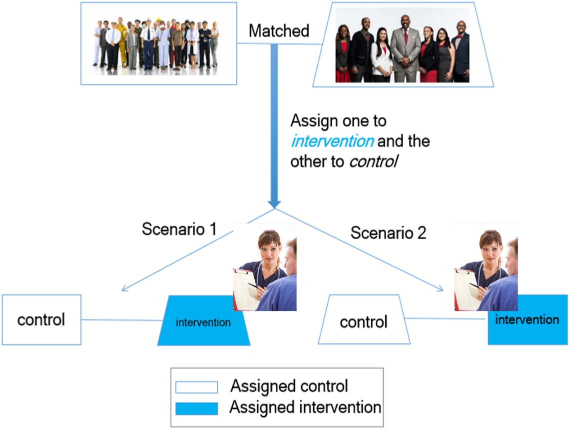
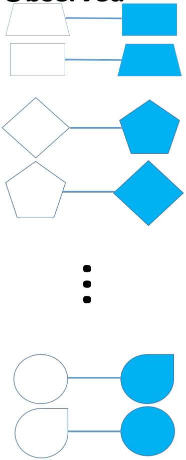


MPCR design

Example: Guided Care study[5]

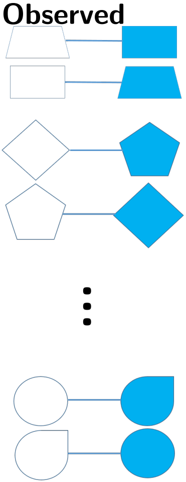
Observed



5. Boult C. et al. (2013)

MPCR design

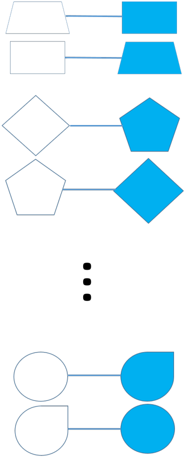
Example: Guided Care study[5]



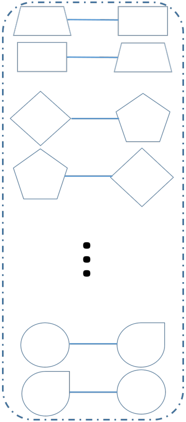
- Intervention: assignment of specially trained nurses to coordinate patient-centered care
- 14 teams of clinical practices matched into 7 pairs
- Covariates: hierarchical condition category (hcc), age, race, gender, education, livesalone, etc.
- Primary outcome: physical component summary in Short-Form 36 (SF-36) Version 2

5. Boult C. et al. (2013)

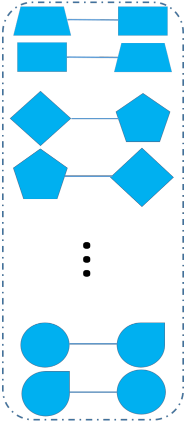
Observed



If all are assigned control



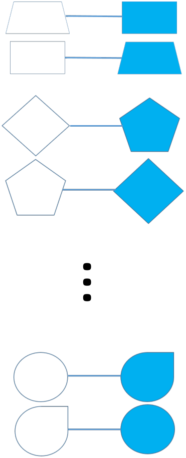
if all are assigned intervention



MPCR design

Goal

Observed

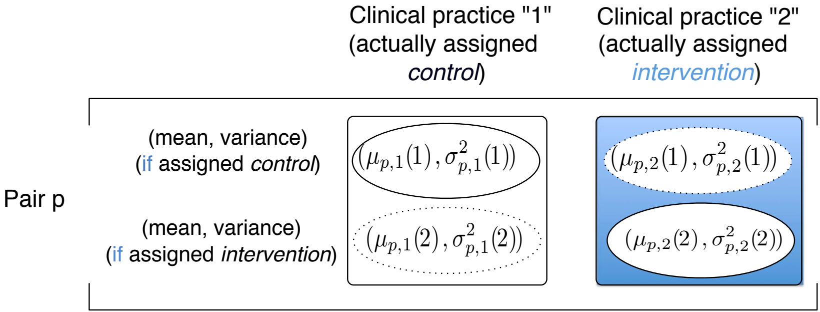


Goal: To estimate the average outcome if all clusters in all pairs are assigned control (1) versus if all clusters in all pairs are assigned to intervention (2):

$$\delta^{\text{effect}} = \mu(1) - \mu(2)$$

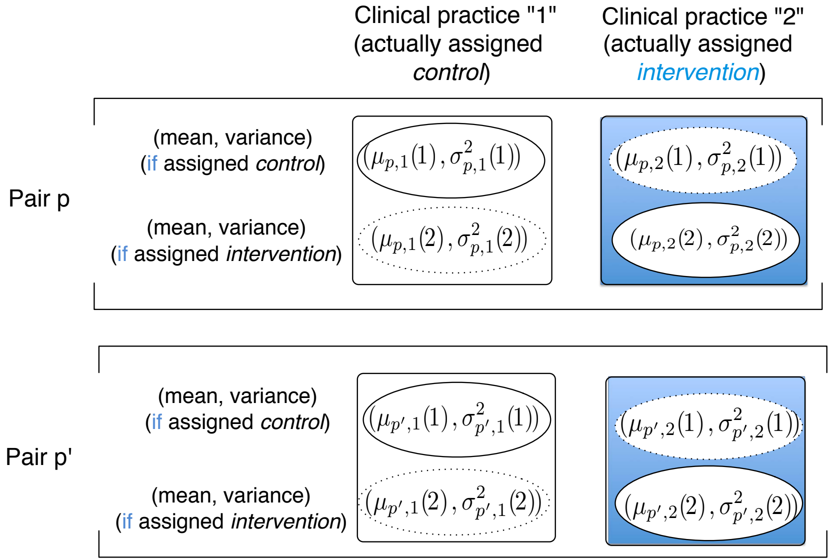
Understanding the observed data from MPCR design

Type 1



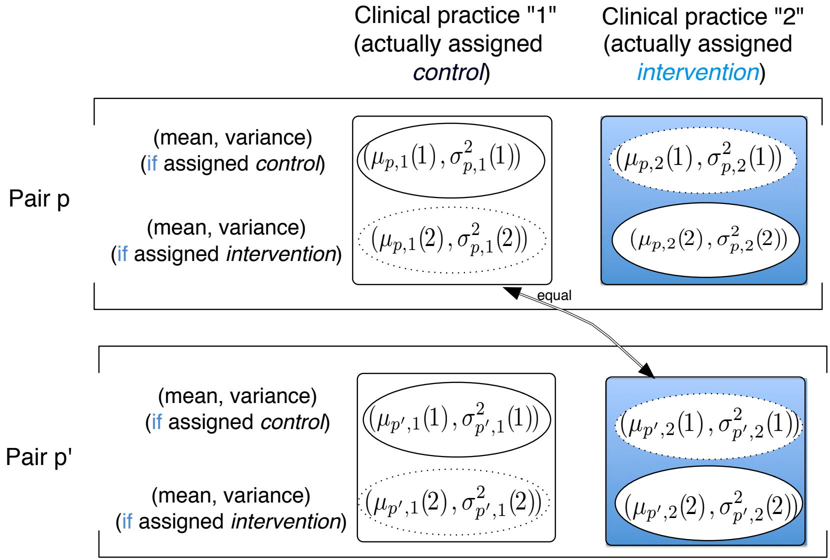
Understanding the observed data from MPCR design

Type 1 and Type 2



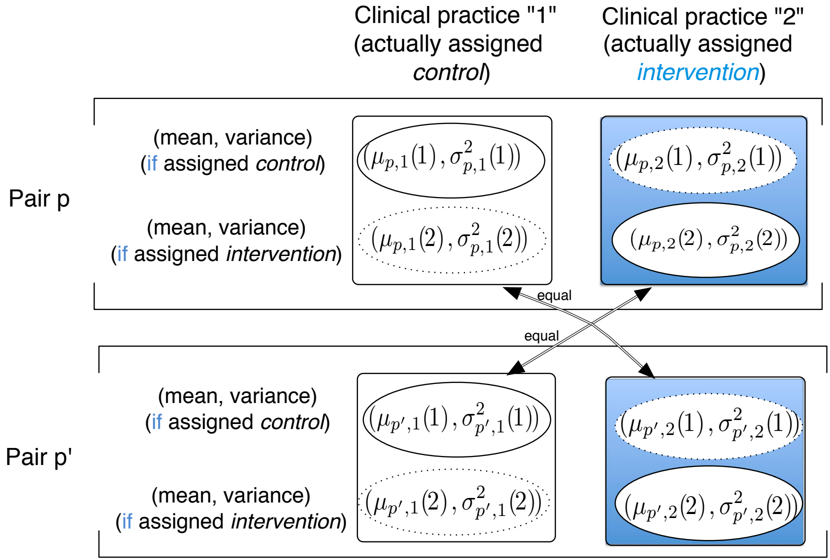
Understanding the observed data from MPCR design

Two types share the same characteristics

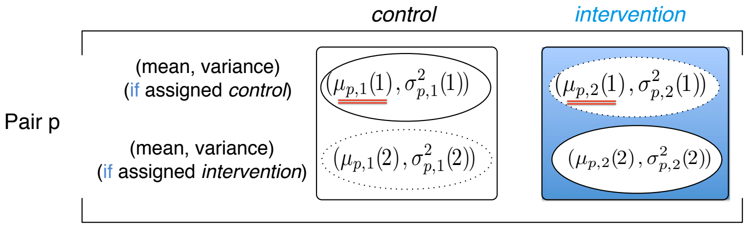


Understanding the observed data from MPCR design

Each type is sampled with probability $\frac{1}{2}$ (design-based)



The right target

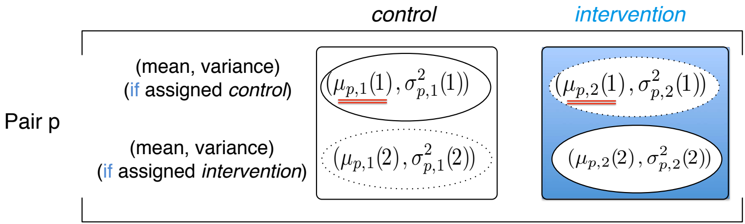


- If all patients are assigned with intervention t,

$$\mu_p(t) = \mu_{p,1}(t)\pi_{p,1} + \mu_{p,2}(t)\pi_{p,2},$$

where $\pi_{p,1}$ is the fraction of patients served by the first clinic; $\pi_{p,2} = 1 - \pi_{p,1}$.

The right target



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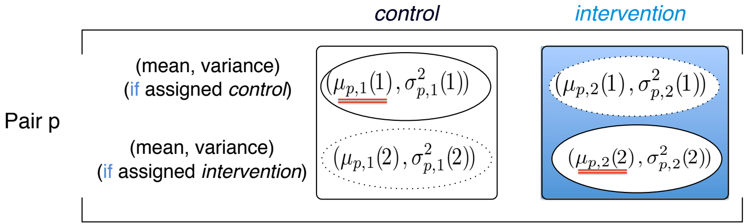
  where $\pi_{p,1}$ is the fraction of patients served by the first clinic; $\pi_{p,2} = 1 - \pi_{p,1}$.
- Averaging over a population of pairs, $\mu(1) = \mathbb{E}\{\mu_p(1)\}$, $\mu(2) = \mathbb{E}\{\mu_p(2)\}$, $\boxed{\delta^{\text{effect}} = \mu(1) - \mu(2)}$.

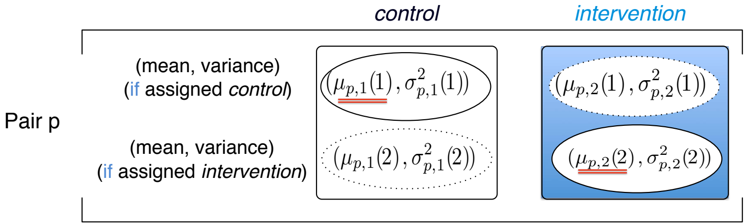
Directly estimable contrasts



- Direct difference between observed means

$$\hat{\delta}_p^{\text{crude}} = \hat{\mu}_{p,1}(1) - \hat{\mu}_{p,2}(2),$$

Directly estimable contrasts



- Direct difference between observed means

$$\hat{\delta}_p^{\text{crude}} = \hat{\mu}_{p,1}(1) - \hat{\mu}_{p,2}(2),$$

with $[\hat{\delta}_p^{\text{crude}} \mid \delta_p^{\text{crude}}, v_p^{2,\text{crude}}]$ approximately normal

Methods for effect estimation under MPCR design

First-level only

Only based on the following equality

$$\underline{\mathbb{E}\left(\delta_p^{\text{crude}}\right) = \delta^{\text{effect}}},$$

without assumptions on $[\delta_p^{\text{crude}}, v_p^{2,\text{crude}}]$.

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Example: Average of $\hat{\delta}_p^{\text{crude}}$ or other weighted extensions[4]

Methods for effect estimation under MPCR design

With a hierarchical second-level (meta-analysis)

- Directly models observed outcomes, using two-level model[6]

$$\hat{\delta}_p^{\text{crude}} \mid \delta_p^{\text{crude}}, v_p^{2,\text{crude}} \quad \sim \quad \text{Normal}\left(\delta_p^{\text{crude}}, v_p^{2,\text{crude}}\right),$$

6. Thompson et al., (1997)

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$$
\begin{aligned}
\hat{\delta}_p^{\text{crude}} \mid \delta_p^{\text{crude}}, v_p^{2,\text{crude}} &\sim \text{Normal}\left(\delta_p^{\text{crude}}, v_p^{2,\text{crude}}\right), \\
\delta_p^{\text{crude}} \mid \tau^2 &\sim \text{Normal}\left(\delta^{\text{effect}}, \tau^2\right)
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- **Question:** an implicit assumption in the second level ?

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$$\delta_p^{\text{crude}} \perp\!\!\!\perp v_p^{2,\text{crude}} \mid \tau^2$$

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- Can lead to inconsistent effect estimator if not true!

Example of inconsistent estimation

6. Thompson et al., (1997)

Another practical problem: covariate imbalance despite matching

Data from the Guided Care study

	pair						
	1	2	3	4	5	6	7
age at interview[a]	0.3	-0.3	0.1	0.6	0.0	0.1	-0.1
Chronic Illness Burden[a]	0.5	-0.6	0.0	0.0	-1.1	0.1	0.6
SF36 Mental[a]	-0.3	0.1	0.3	0.2	0.3	-0.6	-0.5
SF36 Physical[a]	-0.1	-0.4	0.1	0.5	0.4	-0.6	-0.3

Standardized differences of several continuous covariates between two clusters within each of 7 pairs.

Proposed method: covariate calibration

- **Bias consideration:** If a hierarchical second level is used, to make the following more plausible:

$$\delta_p^{\text{crude}} \perp\!\!\!\perp v_p^{2,\text{crude}} \mid X, \tau^2$$

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- **Efficiency consideration:** To decrease residual variance by conditional on important covariates that affect outcomes

Methods to handle covariate imbalance

Existing approaches

1. Interpretation of treatment effect conditional on covariates[6]
2. Normal assumption on individual level: does not necessarily hold; interpretation of treatment effect conditional on cluster-specific random effects, thus treatment effect require a model to be estimable[7,8]

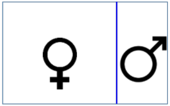
7. Feng et al. (2001)
8. Hill J. and Scott M. (2009)

Covariate-calibrated estimation

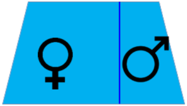
1 Combine covariate distribution, and 2 re-weight outcome regression

1. Stratify the average outcome by covariate

75% Female, n=100



85% Female, n=200



Combined covariate distribution P(x=F)

$$75\%\frac{1}{3} + 85\%\frac{2}{3} = 82\%$$

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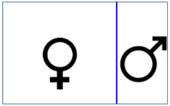

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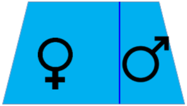

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$$75\%\frac{1}{3} + 85\%\frac{2}{3} = 82\%$$

2. Re-calibrating the stratified means with respect to the covariate distribution of the two clusters combined, for example, for the control arm $t = 1$,

$$\begin{aligned} \mu^{\text{calibr}}_{p,c=1} &= \int_{x} \mu_{p,c=1}(x; t = 1)\mathrm{d}G_p(x), \\ &= 82\% \cdot \mu_{p,c=1}(x = F; t = 1) \\ &\quad +18\% \cdot \mu_{p,c=1}(x = M; t = 1). \end{aligned}$$

Uncalibrated vs calibrated analysis

Reduced variances

	pair p						
	1	2	3	4	5	6	7
sample size							
$n_{p,c=1}$	17	16	42	23	52	23	28
$n_{p,c=2}$	38	44	43	33	42	31	43
outcome							
	uncalibrated on covariates						
$\hat{\mu}_{p,1}(1)$	36.4	36.5	39.6	39.1	39.7	33.8	39.6
$\hat{\mu}_{p,2}(2)$	37.3	36.6	39.3	35.3	35.2	36.4	40.9
$\hat{\delta}_p^{\text{crude}}$	-0.8	-0.1	0.3	3.8	4.5	-2.6	-1.3
$\left(v_p^{\text{crude}}\right)^{1/2}$	2.7	2.6	2.0	2.7	2.1	2.6	2.2
	calibrated on covariates						
$^*\hat{\mu}_{p,1}^{\text{calibr}}$	37.6	38.8	39.5	38.0	38.7	35.5	40.9
$^*\hat{\mu}_{p,2}^{\text{calibr}}$	36.7	35.8	39.4	36.0	36.4	35.1	40.0
$\hat{\delta}_p^{\text{calibr}}$	0.9	3.0	0.1	1.9	2.3	0.5	0.8
$\dagger\left(v_p^{\text{calibr}}\right)^{1/2}$	2.1	2.4	1.5	2.0	1.7	2.2	1.7

Analysis of Guided Care data

Table: Results from MLE, profile MLE, Bayes estimates and permutation test in the Guided Care study. The outcome is the physical component summary of the Short Form 36 (SF36).

		$\hat{\delta}^{\text{effect}}$	95% C.I.	s.e.($\hat{\delta}^{\text{effect}}$)	$\widehat{\text{var}}(\delta_p^*)$	p-value (two-sided)
uncalibrated on covariates	*1st level*					
	MLE	0.5	$(-1.4, 2.5)$	1.0	–	0.59
	permutation	–	–	–	–	0.61
	1st+2nd level					
	MLE	0.6	$(-1.2, 2.5)$	0.9	0.7	0.50
	pMLE	0.6	$(-1.5, 2.7)$	–	0.7	–
	Bayes	0.6	$(-1.7, 3.0)$	1.2	4.3	0.60
	permutation	–	–	–	–	0.60
calibrated on covariates	*1st level*					
	MLE	1.4	$(0.5, 2.2)$	0.4	–	<0.01
	permutation	–	–	–	–	0.02
	1st+2nd level					
	MLE	1.2	$(-0.2, 2.6)$	0.7	0.0	0.08
	pMLE	1.2	$(-0.2, 2.6)$	–	0.0	–
	Bayes	1.3	$(-0.4, 2.9)$	0.9	1.5	0.13
	permutation	–	–	–	–	0.02

*: represents δ_p^{crude} for the uncalibrated approach and δ_p^{calibr} for the calibrated approach.

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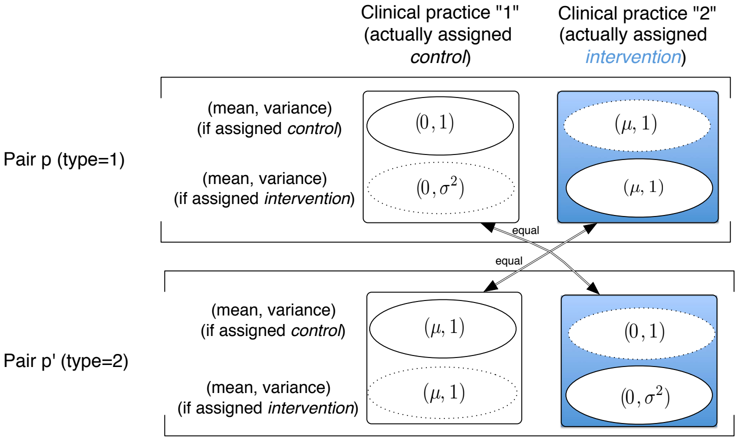
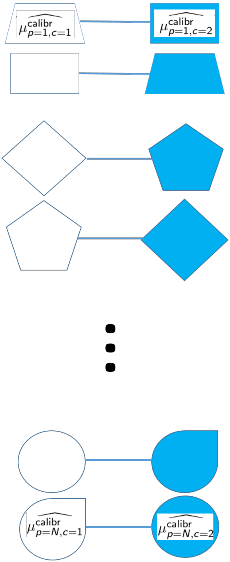
- Covariate-calibration is necessary if 2nd-level checking reveals substantial dependence
- Covariate-calibration improves estimation efficiency

Thank you!

An example of inconsistency of meta-analytic "MLE"



Matched-pair cluster randomized design



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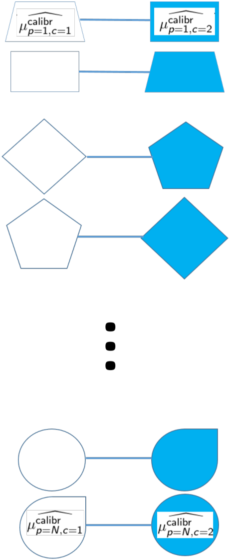

<u>level 1':</u>

$$\begin{bmatrix}\hat{\delta}_1^{\text{calibr}}\\ \vdots \\ \hat{\delta}_N^{\text{calibr}}\end{bmatrix} \Bigg| \begin{bmatrix}\delta_1^{\text{calibr}}\\ \vdots \\ \delta_N^{\text{calibr}}\end{bmatrix}, \theta, \Sigma_{\hat{\delta}^{\text{calibr}}}$$

$$\sim \mathit{Normal}\left\{\begin{bmatrix}\delta_1^{\text{calibr}}\\ \vdots \\ \delta_N^{\text{calibr}}\end{bmatrix}, \Sigma_{\hat{\delta}^{\text{calibr}}}\right\}$$

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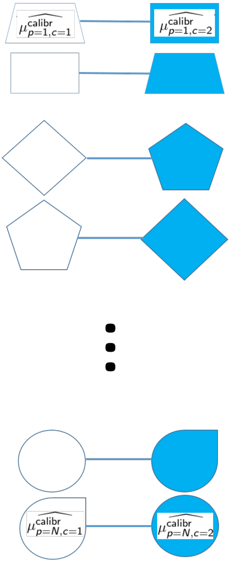

<u>level 1':</u>

$$\begin{bmatrix} \hat{\delta}_1^{\text{calibr}} \\ \vdots \\ \hat{\delta}_N^{\text{calibr}} \end{bmatrix} \Big| \begin{bmatrix} \delta_1^{\text{calibr}} \\ \vdots \\ \delta_N^{\text{calibr}} \end{bmatrix}, \theta, \Sigma_{\hat{\delta}^{\text{calibr}}}$$

$$\sim Normal \left\{ \begin{bmatrix} \delta_1^{\text{calibr}} \\ \vdots \\ \delta_N^{\text{calibr}} \end{bmatrix}, \Sigma_{\hat{\delta}^{\text{calibr}}} \right\}$$

<u>level 2':</u> $\delta_p^{\text{calibr}} \mid \delta^{\text{effect}}, \tau^2 \sim Normal(\delta^{\text{effect}}, \tau^2),$

$$p = 1, \ldots, N.$$

Checking second-level dependence