

Assumption-Lean Analysis of Cluster Randomized Trials in Infectious Diseases for
Intent-to-Treat Effects and Network Effects

Chan Park (Joint work with Dr. Hyunseung Kang)

University of Wisconsin-Madison

EuroCIM2021

CRTs with interference and noncompliance

- In many CRTs of infectious diseases, both interference and noncompliance are present ([Miguel and Kremer \(2004\)](#)), [Cowling et al. \(2009\)](#) (**Hong Kong**), [Devoto et al. \(2012\)](#), [Duflo et al. \(2015\)](#)).

CRTs with interference and noncompliance

- In many CRTs of infectious diseases, both interference and noncompliance are present ([Miguel and Kremer \(2004\)](#), [Cowling et al. \(2009\)](#) (**Hong Kong**), [Devoto et al. \(2012\)](#), [Duflo et al. \(2015\)](#)).
- Example: 2009 Hong Kong Influenza Study
 - Goal: the effect of using face masks and hand sanitizer on the secondary attack rate of influenza.

CRTs with interference and noncompliance

- In many CRTs of infectious diseases, both interference and noncompliance are present ([Miguel and Kremer \(2004\)](#), [Cowling et al. \(2009\)](#) (**Hong Kong**), [Devoto et al. \(2012\)](#), [Duflo et al. \(2015\)](#)).
- Example: 2009 Hong Kong Influenza Study
 - Goal: the effect of using face masks and hand sanitizer on the secondary attack rate of influenza.
 - Households with one infected individual were recruited. Each household was randomly assigned to receive, among other things, free face masks (i.e. treated) or none (i.e. control)

CRTs with interference and noncompliance

- In many CRTs of infectious diseases, both interference and noncompliance are present ([Miguel and Kremer \(2004\)](#), [Cowling et al. \(2009\)](#) (**Hong Kong**), [Devoto et al. \(2012\)](#), [Duflo et al. \(2015\)](#)).
- Example: 2009 Hong Kong Influenza Study
 - Goal: the effect of using face masks and hand sanitizer on the secondary attack rate of influenza.
 - Households with one infected individual were recruited. Each household was randomly assigned to receive, among other things, free face masks (i.e. treated) or none (i.e. control)
 - Some individuals in treated households did not use face masks (i.e. **noncompliance**).

CRTs with interference and noncompliance

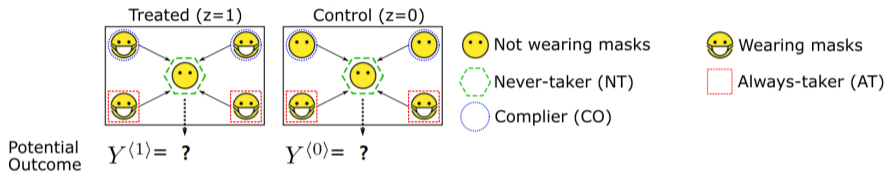
- In many CRTs of infectious diseases, both interference and noncompliance are present (Miguel and Kremer (2004), Cowling et al. (2009) (**Hong Kong**), Devoto et al. (2012), Duflo et al. (2015)).
- Example: 2009 Hong Kong Influenza Study
 - Goal: the effect of using face masks and hand sanitizer on the secondary attack rate of influenza.
 - Households with one infected individual were recruited. Each household was randomly assigned to receive, among other things, free face masks (i.e. treated) or none (i.e. control)
 - Some individuals in treated households did not use face masks (i.e. **noncompliance**).
 - Interference is present mainly among household members (i.e. **partial interference**) because using face masks likely prevents spread of influenza to others.

CRTs with interference and noncompliance

- In many CRTs of infectious diseases, both interference and noncompliance are present (Miguel and Kremer (2004), Cowling et al. (2009) (**Hong Kong**), Devoto et al. (2012), Duflo et al. (2015)).
- Example: 2009 Hong Kong Influenza Study
 - Goal: the effect of using face masks and hand sanitizer on the secondary attack rate of influenza.
 - Households with one infected individual were recruited. Each household was randomly assigned to receive, among other things, free face masks (i.e. treated) or none (i.e. control)
 - Some individuals in treated households did not use face masks (i.e. **noncompliance**).
 - Interference is present mainly among household members (i.e. **partial interference**) because using face masks likely prevents spread of influenza to others.
- **Today's Talk:** Do individuals not using face masks and hand sanitizer (i.e. never-takers) benefit from peers' using them (i.e. spillover effect among NTs)?

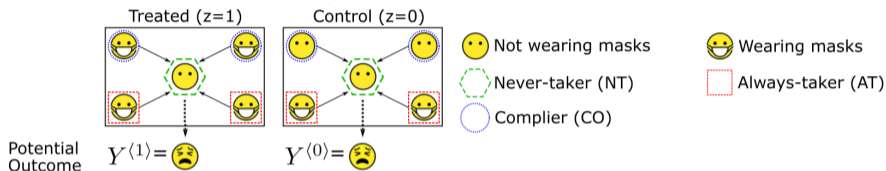
Spillover Effect Among Never-Takers τ_{NT}

- Graphical illustration of τ_{NT} : Consider a household having 5 members:



Spillover Effect Among Never-Takers τ_{NT}

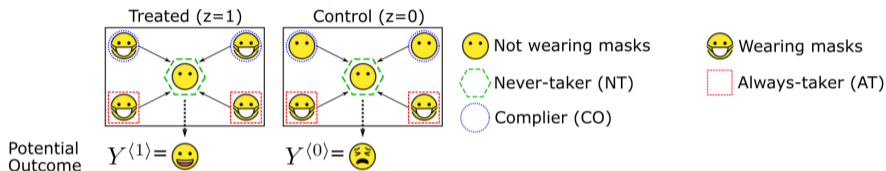
- Graphical illustration of τ_{NT} : Consider a household having 5 members:



- If $Y^{(1)} = Y^{(0)}$, peers using face masks do not benefit a NT

Spillover Effect Among Never-Takers τ_{NT}

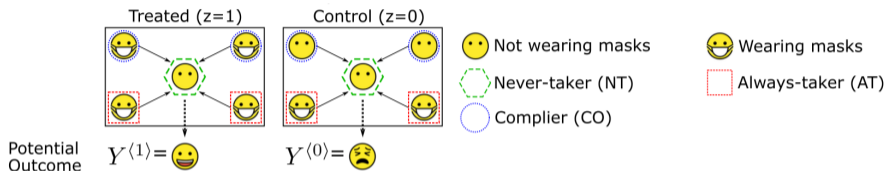
- Graphical illustration of τ_{NT} : Consider a household having 5 members:



- If $Y^{(1)} = Y^{(0)}$, peers using face masks do not benefit a NT
- If $Y^{(1)} > Y^{(0)}$, peers using face masks do benefit a NT

Spillover Effect Among Never-Takers τ_{NT}

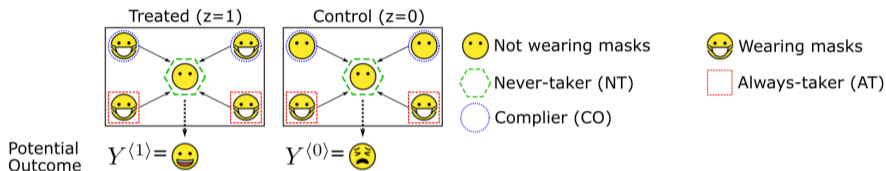
- Graphical illustration of τ_{NT} : Consider a household having 5 members:



- If $Y^{(1)} = Y^{(0)}$, peers using face masks do not benefit a NT
- If $Y^{(1)} > Y^{(0)}$, peers using face masks do benefit a NT $\Rightarrow \tau_{NT} > 0$

Spillover Effect Among Never-Takers τ_{NT}

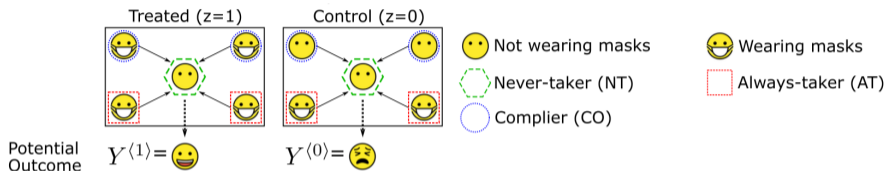
- Graphical illustration of τ_{NT} : Consider a household having 5 members:



- If $Y^{(1)} = Y^{(0)}$, peers using face masks do not benefit a NT
- If $Y^{(1)} > Y^{(0)}$, peers using face masks do benefit a NT $\Rightarrow \tau_{NT} > 0$
- τ_{NT} is not point-identifiable (Kang and Keele, 2018) unless strong assumptions and/or particular experimental designs are used (Jo and Stuart, 2009; Kilpatrick et al., 2020).

Spillover Effect Among Never-Takers τ_{NT}

- Graphical illustration of τ_{NT} : Consider a household having 5 members:



- If $Y^{(1)} = Y^{(0)}$, peers using face masks do not benefit a NT
- If $Y^{(1)} > Y^{(0)}$, peers using face masks do benefit a NT $\Rightarrow \tau_{NT} > 0$
- τ_{NT} is not point-identifiable (Kang and Keele, 2018) unless strong assumptions and/or particular experimental designs are used (Jo and Stuart, 2009; Kilpatrick et al., 2020).
- Our “Assumption-Lean” Approach:** Make only “standard” assumptions in CRTs and obtain sharp bound of network effects using machine learning (ML) and linear programming (LP).

Our Procedure

- **Step 1:** Construct (potentially imperfect) classifier for each compliance type (e.g. NT/AT/CO) using machine learning (ML).

Our Procedure

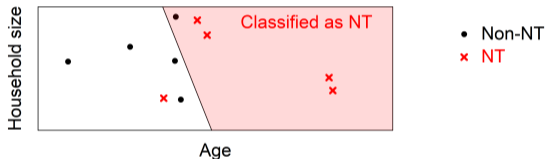
- **Step 1:** Construct (potentially imperfect) classifier for each compliance type (e.g. NT/AT/CO) using machine learning (ML).
 - Classifiers are based on constrained empirical risk minimization.

Our Procedure

- **Step 1:** Construct (potentially imperfect) classifier for each compliance type (e.g. NT/AT/CO) using machine learning (ML).
 - Classifiers are based on constrained empirical risk minimization.
 - Any classifiers works (even random classifiers), but good classifiers shorten bounds.

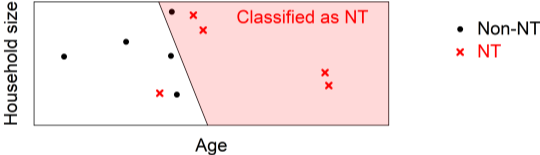
Our Procedure

- **Step 1:** Construct (potentially imperfect) classifier for each compliance type (e.g. NT/AT/CO) using machine learning (ML).
 - Classifiers are based on constrained empirical risk minimization.
 - Any classifiers works (even random classifiers), but good classifiers shorten bounds.



Our Procedure

- **Step 1:** Construct (potentially imperfect) classifier for each compliance type (e.g. NT/AT/CO) using machine learning (ML).
 - Classifiers are based on constrained empirical risk minimization.
 - Any classifiers works (even random classifiers), but good classifiers shorten bounds.



- **Step 2:** Use classifiers from **Step 1** + Assumptions from CRT's design to construct bounds for τ_{NT} .

Our Procedure

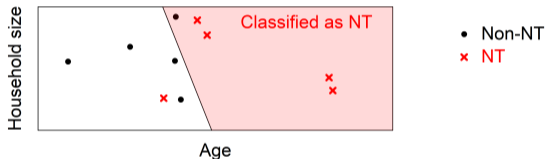
- **Step 1:** Construct (potentially imperfect) classifier for each compliance type (e.g. NT/AT/CO) using machine learning (ML).
 - Classifiers are based on constrained empirical risk minimization.
 - Any classifiers works (even random classifiers), but good classifiers shorten bounds.



- **Step 2:** Use classifiers from **Step 1** + Assumptions from CRT's design to construct bounds for τ_{NT} .
 - The bounds are based on using linear programming (LP).

Our Procedure

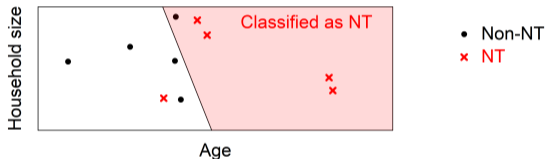
- **Step 1:** Construct (potentially imperfect) classifier for each compliance type (e.g. NT/AT/CO) using machine learning (ML).
 - Classifiers are based on constrained empirical risk minimization.
 - Any classifiers works (even random classifiers), but good classifiers shorten bounds.



- **Step 2:** Use classifiers from **Step 1** + Assumptions from CRT's design to construct bounds for τ_{NT} .
 - The bounds are based on using linear programming (LP).
 - The restrictions in LP are from $\| \text{Population quantities} - \text{Classifier-based quantities} \| \leq \text{Mis-classification rate}$.

Our Procedure

- **Step 1:** Construct (potentially imperfect) classifier for each compliance type (e.g. NT/AT/CO) using machine learning (ML).
 - Classifiers are based on constrained empirical risk minimization.
 - Any classifiers works (even random classifiers), but good classifiers shorten bounds.



- **Step 2:** Use classifiers from **Step 1** + Assumptions from CRT's design to construct bounds for τ_{NT} .
 - The bounds are based on using linear programming (LP).
 - The restrictions in LP are from $\| \text{Population quantities} - \text{Classifier-based quantities} \| \leq \text{Mis-classification rate}$.
 - Our approach is similar (in spirit) to [Balke and Pearl \(1997\)](#)'s LP bounds in IV settings, but our approach (i) targets subgroup network effects and (ii) uses covariates adjusted via ML to further sharpen bounds.

Key Properties of Our Method

- **Property 1:** Regardless of quality of classifiers, our bounds will always cover τ_{NT} .

Key Properties of Our Method

- **Property 1:** Regardless of quality of classifiers, our bounds will always cover τ_{NT} .
- **Property 2:** Given classifiers, our bounds are sharp
(i.e. the narrowest possible given these particular classifiers).

Key Properties of Our Method

- **Property 1:** Regardless of quality of classifiers, our bounds will always cover τ_{NT} .
- **Property 2:** Given classifiers, our bounds are sharp
(i.e. the narrowest possible given these particular classifiers).
- **Property 3:** If the classifier has a lower mis-classification rate, our bounds are narrower.

Key Properties of Our Method

- **Property 1:** Regardless of quality of classifiers, our bounds will always cover τ_{NT} .
- **Property 2:** Given classifiers, our bounds are sharp (i.e. the narrowest possible given these particular classifiers).
- **Property 3:** If the classifier has a lower mis-classification rate, our bounds are narrower.
If the classifier has zero mis-classification rate (i.e. perfect classifier), our bounds shrink to a point τ_{NT} .

Key Properties of Our Method

- **Property 1:** Regardless of quality of classifiers, our bounds will always cover τ_{NT} .
- **Property 2:** Given classifiers, our bounds are sharp (i.e. the narrowest possible given these particular classifiers).
- **Property 3:** If the classifier has a lower mis-classification rate, our bounds are narrower.
If the classifier has zero mis-classification rate (i.e. perfect classifier), our bounds shrink to a point τ_{NT} .
- **Property 4:** Under some mild conditions on classifiers (e.g. smoothness of loss function), our bounds can be consistently estimated.

Key Properties of Our Method

- **Property 1:** Regardless of quality of classifiers, our bounds will always cover τ_{NT} .
- **Property 2:** Given classifiers, our bounds are sharp (i.e. the narrowest possible given these particular classifiers).
- **Property 3:** If the classifier has a lower mis-classification rate, our bounds are narrower.
If the classifier has zero mis-classification rate (i.e. perfect classifier), our bounds shrink to a point τ_{NT} .
- **Property 4:** Under some mild conditions on classifiers (e.g. smoothness of loss function), our bounds can be consistently estimated.
- For inference, we use resampling approaches of [Efron and Tibshirani \(1993\)](#) and [Romano and Shaikh \(2010\)](#), modified for cluster-level resampling.

Application: Hong Kong Study

- We construct classifiers by using 13 pre-treatment covariates (e.g. age, gender, household size, vaccination history).

Application: Hong Kong Study

- We construct classifiers by using 13 pre-treatment covariates (e.g. age, gender, household size, vaccination history).
- We compare classifier-based bounds to non-ML bounds based on [Grilli and Mealli \(2008\)](#) and [Long and Hudgens \(2013\)](#) adapted to network settings (see paper for details).

Application: Hong Kong Study

- We construct classifiers by using 13 pre-treatment covariates (e.g. age, gender, household size, vaccination history).
- We compare classifier-based bounds to non-ML bounds based on [Grilli and Mealli \(2008\)](#) and [Long and Hudgens \(2013\)](#) adapted to network settings (see paper for details).

Estimand	Statistics	ML (classifier-based) Bound		Non-ML Bound	Intersection Bound
		Linear	Penalized Logistic		
τ_{NT}	Bound	[0.000, 0.173]	[0.000, 0.173]	[0.054, 0.254]	[0.054, 0.173]
	95% CI	[0.000, 0.374]	[0.000, 0.375]	[0.000, 0.395]	[0.000, 0.374]
τ_{CO}	Bound	[0.000, 0.146]	[0.000, 0.146]	[0.000, 0.186]	[0.000, 0.146]
	95% CI	[0.000, 0.299]	[0.000, 0.288]	[0.000, 0.297]	[0.000, 0.288]

Application: Hong Kong Study

- We construct classifiers by using 13 pre-treatment covariates (e.g. age, gender, household size, vaccination history).
- We compare classifier-based bounds to non-ML bounds based on [Grilli and Mealli \(2008\)](#) and [Long and Hudgens \(2013\)](#) adapted to network settings (see paper for details).

Estimand	Statistics	ML (classifier-based) Bound		Non-ML Bound	Intersection Bound
		Linear	Penalized Logistic		
τ_{NT}	Bound	[0.000, 0.173]	[0.000, 0.173]	[0.054, 0.254]	[0.054, 0.173]
	95% CI	[0.000, 0.374]	[0.000, 0.375]	[0.000, 0.395]	[0.000, 0.374]
τ_{CO}	Bound	[0.000, 0.146]	[0.000, 0.146]	[0.000, 0.186]	[0.000, 0.146]
	95% CI	[0.000, 0.299]	[0.000, 0.288]	[0.000, 0.297]	[0.000, 0.288]

- Classifier-based bounds of τ_{NT} and τ_{CO} are 13.5% and 21.5% narrower than non-ML bounds.

Application: Hong Kong Study

- We construct classifiers by using 13 pre-treatment covariates (e.g. age, gender, household size, vaccination history).
- We compare classifier-based bounds to non-ML bounds based on [Grilli and Mealli \(2008\)](#) and [Long and Hudgens \(2013\)](#) adapted to network settings (see paper for details).

Estimand	Statistics	ML (classifier-based) Bound		Non-ML Bound	Intersection Bound
		Linear	Penalized Logistic		
τ_{NT}	Bound	[0.000, 0.173]	[0.000, 0.173]	[0.054, 0.254]	[0.054, 0.173]
	95% CI	[0.000, 0.374]	[0.000, 0.375]	[0.000, 0.395]	[0.000, 0.374]
τ_{CO}	Bound	[0.000, 0.146]	[0.000, 0.146]	[0.000, 0.186]	[0.000, 0.146]
	95% CI	[0.000, 0.299]	[0.000, 0.288]	[0.000, 0.297]	[0.000, 0.288]

- Classifier-based bounds of τ_{NT} and τ_{CO} are 13.5% and 21.5% narrower than non-ML bounds.

Application: Hong Kong Study

- We construct classifiers by using 13 pre-treatment covariates (e.g. age, gender, household size, vaccination history).
- We compare classifier-based bounds to non-ML bounds based on [Grilli and Mealli \(2008\)](#) and [Long and Hudgens \(2013\)](#) adapted to network settings (see paper for details).

Estimand	Statistics	ML (classifier-based) Bound		Non-ML Bound	Intersection Bound
		Linear	Penalized Logistic		
τ_{NT}	Bound	[0.000, 0.173]	[0.000, 0.173]	[0.054, 0.254]	[0.054, 0.173]
	95% CI	[0.000, 0.374]	[0.000, 0.375]	[0.000, 0.395]	[0.000, 0.374]
τ_{CO}	Bound	[0.000, 0.146]	[0.000, 0.146]	[0.000, 0.186]	[0.000, 0.146]
	95% CI	[0.000, 0.299]	[0.000, 0.288]	[0.000, 0.297]	[0.000, 0.288]

- Classifier-based bounds of τ_{NT} and τ_{CO} are 13.5% and 21.5% narrower than non-ML bounds.

Application: Hong Kong Study

- We construct classifiers by using 13 pre-treatment covariates (e.g. age, gender, household size, vaccination history).
- We compare classifier-based bounds to non-ML bounds based on [Grilli and Mealli \(2008\)](#) and [Long and Hudgens \(2013\)](#) adapted to network settings (see paper for details).

Estimand	Statistics	ML (classifier-based) Bound		Non-ML Bound	Intersection Bound
		Linear	Penalized Logistic		
τ_{NT}	Bound	[0.000, 0.173]	[0.000, 0.173]	[0.054, 0.254]	[0.054, 0.173]
	95% CI	[0.000, 0.374]	[0.000, 0.375]	[0.000, 0.395]	[0.000, 0.374]
τ_{CO}	Bound	[0.000, 0.146]	[0.000, 0.146]	[0.000, 0.186]	[0.000, 0.146]
	95% CI	[0.000, 0.299]	[0.000, 0.288]	[0.000, 0.297]	[0.000, 0.288]

- Classifier-based bounds of τ_{NT} and τ_{CO} are 13.5% and 21.5% narrower than non-ML bounds.
- In paper, we show how to further sharpen bounds by combining ML-based and non-ML based bounds by **intersection**.

Application: Hong Kong Study

- We construct classifiers by using 13 pre-treatment covariates (e.g. age, gender, household size, vaccination history).
- We compare classifier-based bounds to non-ML bounds based on [Grilli and Mealli \(2008\)](#) and [Long and Hudgens \(2013\)](#) adapted to network settings (see paper for details).

Estimand	Statistics	ML (classifier-based) Bound		Non-ML Bound	Intersection Bound
		Linear	Penalized Logistic		
τ_{NT}	Bound	[0.000, 0.173]	[0.000, 0.173]	[0.054, 0.254]	[0.054, 0.173]
	95% CI	[0.000, 0.374]	[0.000, 0.375]	[0.000, 0.395]	[0.000, 0.374]
τ_{CO}	Bound	[0.000, 0.146]	[0.000, 0.146]	[0.000, 0.186]	[0.000, 0.146]
	95% CI	[0.000, 0.299]	[0.000, 0.288]	[0.000, 0.297]	[0.000, 0.288]

- Classifier-based bounds of τ_{NT} and τ_{CO} are 13.5% and 21.5% narrower than non-ML bounds.
- In paper, we show how to further sharpen bounds by combining ML-based and non-ML based bounds by intersection.
- There is no significant network effect at $\alpha = 0.05$ level.

Conclusion and Key Takeaways

- In CRTs with interference and noncompliance, network effects may exist and are generally not point-identified.

Conclusion and Key Takeaways

- In CRTs with interference and noncompliance, network effects may exist and are generally not point-identified.
- We obtain sharp bounds of network effects using machine learning (ML) and linear programming (LP).

Conclusion and Key Takeaways

- In CRTs with interference and noncompliance, network effects may exist and are generally not point-identified.
- We obtain sharp bounds of network effects using machine learning (ML) and linear programming (LP).
 - The classifiers do not have to be perfect, but more accurate classifiers lead to shorter bounds.

Conclusion and Key Takeaways

- In CRTs with interference and noncompliance, network effects may exist and are generally not point-identified.
- We obtain sharp bounds of network effects using machine learning (ML) and linear programming (LP).
 - The classifiers do not have to be perfect, but more accurate classifiers lead to shorter bounds.
 - Given classifiers, our bounds are the sharpest possible.

Conclusion and Key Takeaways

- In CRTs with interference and noncompliance, network effects may exist and are generally not point-identified.
- We obtain sharp bounds of network effects using machine learning (ML) and linear programming (LP).
 - The classifiers do not have to be perfect, but more accurate classifiers lead to shorter bounds.
 - Given classifiers, our bounds are the sharpest possible.
- Our ML-based approach to obtaining sharp bounds for treatment effects may be applicable to other IV settings.

Conclusion and Key Takeaways

- In CRTs with interference and noncompliance, network effects may exist and are generally not point-identified.
- We obtain sharp bounds of network effects using machine learning (ML) and linear programming (LP).
 - The classifiers do not have to be perfect, but more accurate classifiers lead to shorter bounds.
 - Given classifiers, our bounds are the sharpest possible.
- Our ML-based approach to obtaining sharp bounds for treatment effects may be applicable to other IV settings.
- Thank you! Check the paper (**arXiv: 2012.13885**) for details.

References

- Balke, A. and J. Pearl (1997). Bounds on treatment effects from studies with imperfect compliance. *Journal of the American Statistical Association* 92(439), 1171–1176.
- Cowling, B. J., K.-H. Chan, V. J. Fang, C. K. Cheng, R. O. Fung, W. Wai, J. Sin, W. H. Seto, R. Yung, D. W. Chu, B. C. Chiu, P. W. Lee, M. C. Chiu, H. C. Lee, T. M. Uyeki, P. M. Houck, J. S. M. Peiris, and G. M. Leung (2009). Facemasks and hand hygiene to prevent influenza transmission in households: A cluster randomized trial. *Annals of Internal Medicine* 151(7), 437–446.
- Devoto, F., E. Duflo, P. Dupas, W. Parienté, and V. Pons (2012). Happiness on tap: Piped water adoption in urban Morocco. *American Economic Journal: Economic Policy* 4(4), 68–99.
- Duflo, E., P. Dupas, and M. Kremer (2015). Education, HIV, and early fertility: Experimental evidence from Kenya. *American Economic Review* 105(9), 2757–97.
- Efron, B. and R. J. Tibshirani (1993). *An introduction to the bootstrap*. New York: Chapman and Hall.
- Grilli, L. and F. Mealli (2008). Nonparametric bounds on the causal effect of university studies on job opportunities using principal stratification. *Journal of Educational and Behavioral Statistics* 33(1), 111–130.

References

- Jo, B. and E. A. Stuart (2009). On the use of propensity scores in principal causal effect estimation. *Statistics in Medicine* 28(23), 2857–2875.
- Kang, H. and L. Keele (2018). Spillover Effects in Cluster Randomized Trials with Noncompliance. *Preprint arXiv:1808.06418*. Department of Statistics, University of Wisconsin-Madison.
- Kilpatrick, K. W., M. G. Hudgens, and M. E. Halloran (2020). Estimands and inference in cluster-randomized vaccine trials. *Pharmaceutical Statistics* 19(5), 710–719.
- Long, D. M. and M. G. Hudgens (2013). Sharpening bounds on principal effects with covariates. *Biometrics* 69(4), 812–819.
- Miguel, E. and M. Kremer (2004). Worms: Identifying impacts on education and health in the presence of treatment externalities. *Econometrica* 72(1), 159–217.
- Romano, J. P. and A. M. Shaikh (2010). Inference for the identified set in partially identified econometric models. *Econometrica* 78(1), 169–211.