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SCIENCE MEDICINES HEALTH

g-estimation for the hypothetical strategy with an application to Alzheimer's Disease and COVID-19-related intercurrent events

BBS & EFSPI virtual event

Presented by Dr. Florian Lasch on 15 December 2022

Meet the Speaker

Dr. Florian Lasch

Data Analytics and Methods Task Force

Organisation: EMA

Biostatistics Specialist providing scientific support to development and evaluation throughout all stages of marketing authorisation assessments of medicinal products submitted to the EMA

Leading the Raw Data Pilot execution

Disclaimer

The views expressed in this presentation and in the following panel discussion are the personal opinion of the author and should not be understood as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties.

Outline

1. Implementation of ICH E9(R1) by the regulatory network
2. g-estimation for the hypothetical strategy
   - In Alzheimer's Disease
   - For Covid-19 related Intercurrent Events
3. General learnings

Lasch et al. (2022)

Clinical evidence 2030: vision

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- Evidence generation is planned and guided by data, knowledge and expertise
- Research question drives evidence choice: embraces spectrum of data and methods
- Clinical trials remain core but are bigger, better and faster
- Real world evidence is enabled and value is established
- The patient voice guides every step of the way
- Healthcare systems are supported in their choices
- High levels of transparency underpin societal trust

"At the core of a successful MA dossier is excellent clinical evidence"

Accelerating Clinical Trials in the EU (ACT EU)

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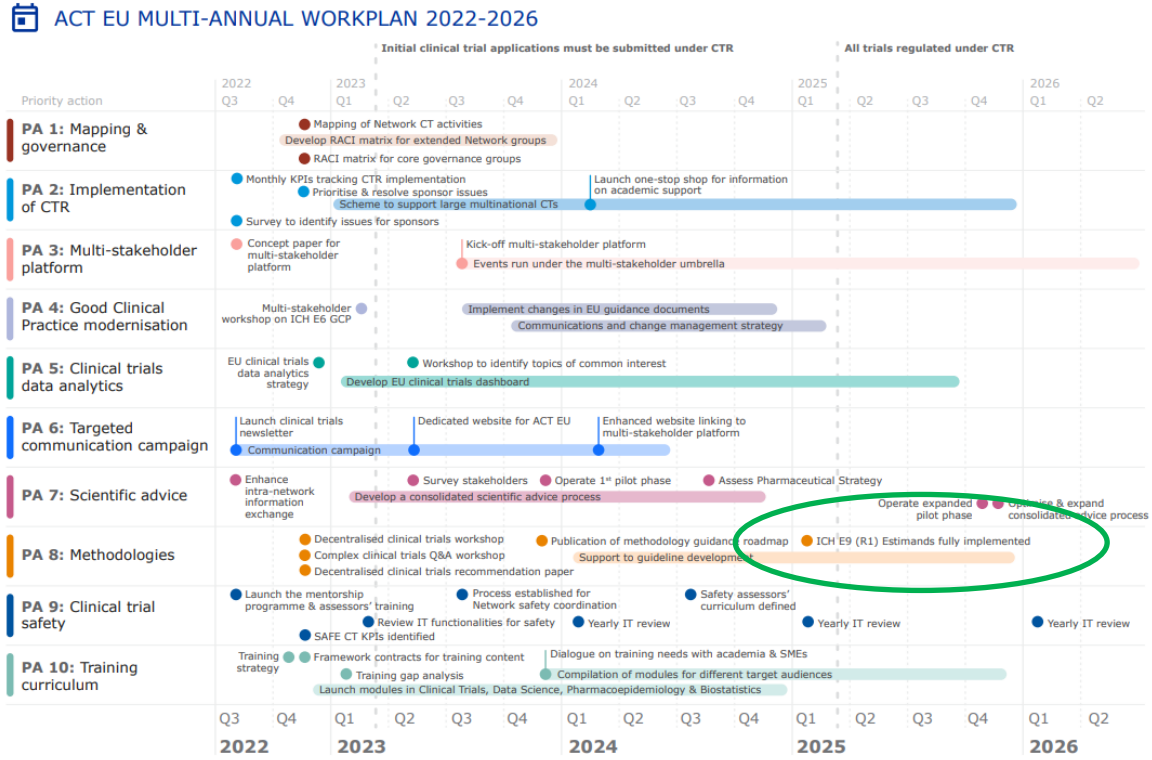
ACT EU is an initiative to **transform the EU clinical research environment** in support of medical innovation and better patient outcomes.

- **Builds on the momentum** of the Clinical Trials Regulation and CTIS
- **Driven by** the Network Strategy to 2025 and the EU Pharmaceutical Strategy
- Launched 13 January 2022
- Read the press release and paper
- Read the multiannual workplan

ACT EU PA8 workplan - estimand implementation



ACT EU multi-annual [Workplan](#) 2022-2026

g-estimation for the hypothetical strategy

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Example 1

Symptomatic treatment in trials for Alzheimer's Disease*

*: Lasch et al. (2022): A Simulation Study on the Estimation of the Effect in the Hypothetical Scenario of No Use of Symptomatic Treatment in Trials for Disease-Modifying Agents for Alzheimer's Disease

Symptomatic treatment in Alzheimer's Disease trials

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Estimand

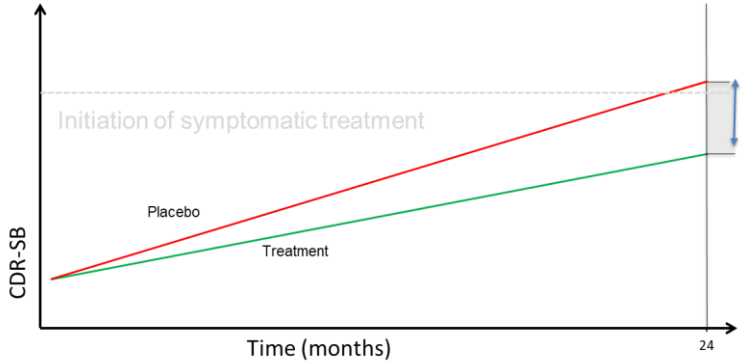
Population: Patients with prodromal AD

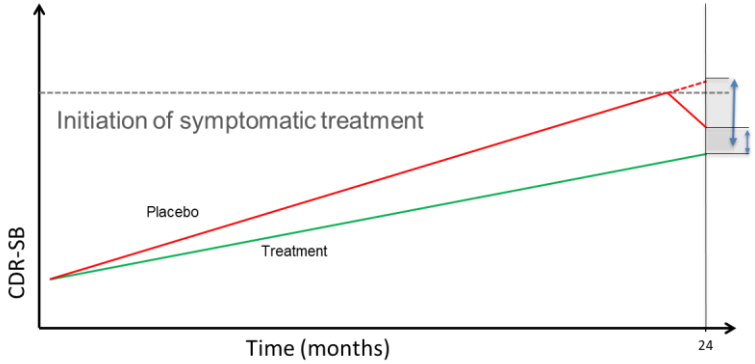
Treatment: Disease modifying treatment vs Placebo

Endpoint: Change in CDR-SB (24 months – baseline)

Summary measure: Difference in mean change in CDR-SB between treatment arms

Intercurrent event: Initiation of symptomatic treatment





Symptomatic treatment in Alzheimer's Disease trials

EMA Guideline on Clinical investigation of medicines for the treatment of Alzheimer's disease (2018):

"Patients can be expected to initiate new medication or to modify the dose of concomitant symptomatic treatments, with or without discontinuing assigned treatment. The impact of those medication changes complicates the evaluation of the effect of the test product compared to placebo or active control. Therefore, providing that reliable methods of estimation can be identified, an appropriate target of estimation could be based on a **hypothetical scenario** in which the new concomitant medication or modifications in the dose of concomitant medications had not been introduced."

→ **What is a reliable method of estimation?**

Common practice:

(i) set values after the initiation of symptomatic treatment as missing

(ii) apply missing data approaches using mixed models for repeated measures, Inverse probability weighting, etc.

Alzheimer's Disease - Causal structure

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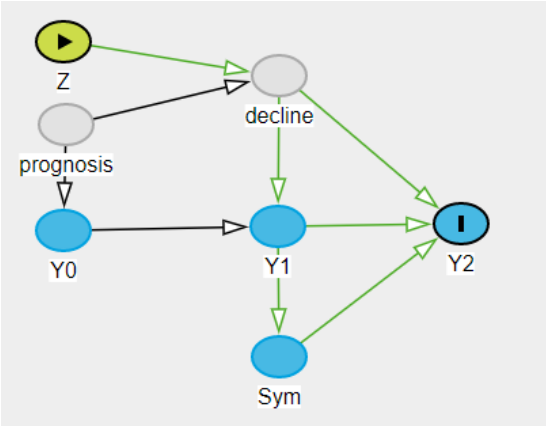
Observation

- Sym is a mediator of the effect of Z on Y_2
- The Estimand of interest is the controlled direct effect of Z on Y_2 controlling Sym at $Sym = 0$:

  $E[\,Y_2(Z = 1, Sym = 0)] - E[\,Y_2(Z = 0, Sym = 0)]$

- de-mediation approaches like g-estimation can be applied for the estimation



Z: randomized treatment

Sym: Initiation of symptomatic treatment

Y_t: observed CDR-SB at time t

Alzheimer's Disease – g-estimation

G-estimation*

1. Estimate the effect of the mediator Sym on Y_2

   Predict the probability of Sym: $P(Sym = 1) \sim Y_1 + Y_0 + Z$

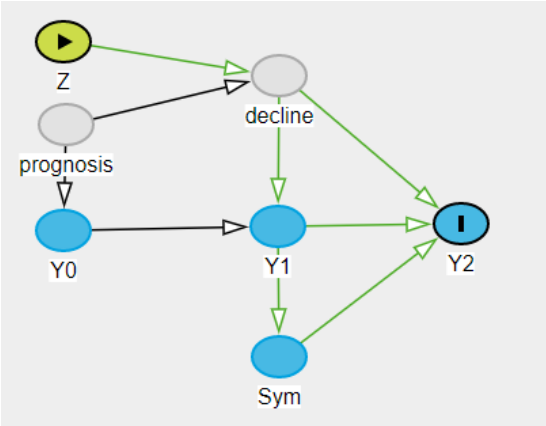
   Estimate the effect of Sym: $Y_2 \sim Z + Y_0 + Y_1 + p_{sym} + Sym$

2. De-mediate the effect of Sym from Y_2

   $R_2 = Y_2 - Sym * \beta_{sym}$

3. Estimate the effect of Z on the de-mediated values

   $R_2 \sim Z + Y_0$



Z: randomized treatment

Sym: Initiation of symptomatic treatment

Y_t: observed CDR-SB at time t

*: Loh et al.: Estimation of Controlled Direct Effects in Longitudinal Mediation Analyses with Latent Variables in Randomized Studies

Alzheimer's Disease - Simulation study

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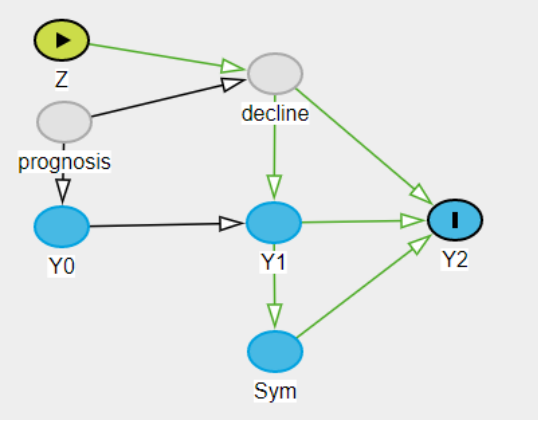
Objectives:

- Quantify the performance of commonly used estimators (bias, T1E / power)
- Compare the performance to de-mediation via g-estimation



Data generating mechanism

Disease progression model: beta regression model with Richard's logistic link function g

$$\frac{Y^*_{t,i}}{18} \sim \beta(a,b), \quad g(x) = \left(\frac{x^\beta}{1-x^\beta}\right)^{\frac{1}{\beta}}$$

für $\tilde{t} > t$: $g(\overline{Y^*_{\tilde{t},i}}) = g(Y^*_{t,i}) + \alpha_i * \frac{\tilde{t}-t}{52} * (E_{DM})^{treat_i} * (E_C)^{confound_i}$

α_i: random decline rate

Simulation results – Null hypothesis

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Estimator	Bias (SE*)	Coverage (SE*)	sqrMSE (MSE (SE*))	CI length (SE*)*	empirical type-I-error (95% CI*)
reference estimator – linear model using Y_2^*	-0.001 (0.003)	95.3 (0.952)	0.269 (0.113 (0.002))	1.329 (0.001)	**0.022 (0.019, 0.025)**
Observed Value	-0.001 (0.003)	95.18 (0.951)	0.261 (0.106 (0.002))	1.287 (0.001)	**0.022 (0.019, 0.025)**
Mixed Effects Model with observed values	-0.001 (0.004)	94.68 (0.945)	0.298 (0.138 (0.002))	1.461 (0.001)	**0.026 (0.023, 0.03)**
Observed Values - adjusted	0 (0.003)	95.14 (0.95)	0.247 (0.095 (0.001))	1.218 (0.001)	**0.023 (0.02, 0.026)**
Loh's g-estimation, model-based SE	-0.001 (0.003)	95.19 (0.951)	0.268 (0.113 (0.002))	1.325 (0.001)	**0.022 (0.019, 0.025)**
Loh's g-estimation, Bootstrap based SE	-0.001 (0.003)	95.21 (0.951)	0.268 (0.113 (0.002))	1.322 (0.001)	**0.022 (0.019, 0.025)**
Linear Sequential g-Estimation	-0.001 (0.003)	95.06 (0.949)	0.266 (0.111 (0.002))	1.308 (0.001)	**0.023 (0.02, 0.026)**
Predictive Mean Matching (PMM)	0 (0.003)	95.64 (0.955)	0.248 (0.097 (0.001))	1.271 (0.001)	**0.02 (0.017, 0.023)**
PMM worsening adjustment 0.5	0 (0.003)	95.65 (0.956)	0.256 (0.103 (0.001))	1.308 (0.001)	**0.02 (0.017, 0.023)**
PMM worsening adjustment 2	0 (0.004)	95.73 (0.956)	0.286 (0.129 (0.002))	1.453 (0.001)	**0.02 (0.018, 0.023)**
PMM worsening adjustment 3	-0.001 (0.004)	95.66 (0.956)	0.311 (0.152 (0.002))	1.573 (0.001)	**0.02 (0.017, 0.023)**
Inverse Probability WeightingWeighting	0 (0.005)	93.74 (0.935)	0.397 (0.253 (0.004))	1.882 (0.005)	**0.032 (0.029, 0.035)**
doubly robust Inverse Probability Weighting	-0.001 (0.004)	94.77 (0.946)	0.287 (0.129 (0.002))	1.39 (0.001)	**0.026 (0.023, 0.029)**
Mixed Effects Model	0 (0.004)	94.75 (0.946)	0.297 (0.139 (0.002))	1.462 (0.001)	**0.028 (0.024, 0.031)**

*: Monte Carlo estimates of the standard errors, Performance parameter are rounded to three digits.

Simulation results – Alternative hypothesis

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Estimator	Bias (SE*)	Coverage (SE*)	sqrMSE (MSE (SE*))	CI length (SE*)*	empirical power (95% CI*)
reference estimator – linear model using Y_2^*	0.004 (0.003)	94.61 (0.945)	0.235 (0.088 (0.001))	1.167 (0.001)	**0.896 (0.89, 0.902)**
Observed Value	0.035 (0.003)	94.24 (0.941)	0.229 (0.084 (0.001))	1.13 (0.001)	**0.895 (0.889, 0.901)**
Mixed Effects Model with observed values	0.037 (0.003)	94.79 (0.946)	0.261 (0.108 (0.002))	1.281 (0.001)	**0.804 (0.796, 0.812)**
Observed Values - adjusted	0.122 (0.003)	92.73 (0.924)	0.24 (0.091 (0.001))	1.088 (0.001)	**0.855 (0.848, 0.862)**
Loh's g-estimation, model-based SE	0.007 (0.003)	94.45 (0.943)	0.235 (0.088 (0.001))	1.163 (0.001)	**0.897 (0.891, 0.903)**
Loh's g-estimation, Bootstrap based SE	0.007 (0.003)	94.38 (0.942)	0.235 (0.088 (0.001))	1.162 (0.001)	**0.893 (0.887, 0.899)**
Linear Sequential g-Estimation	0.014 (0.003)	94.27 (0.941)	0.233 (0.087 (0.001))	1.148 (0.001)	**0.897 (0.891, 0.903)**
Predictive Mean Matching (PMM)	0.152 (0.003)	90.41 (0.899)	0.264 (0.107 (0.001))	1.121 (0.001)	**0.8 (0.793, 0.808)**
PMM worsening adjustment 0.5	0.127 (0.003)	91.85 (0.915)	0.26 (0.105 (0.001))	1.154 (0.001)	**0.805 (0.797, 0.813)**
PMM worsening adjustment 2	0.051 (0.003)	94.12 (0.939)	0.266 (0.112 (0.002))	1.288 (0.001)	**0.783 (0.775, 0.791)**
PMM worsening adjustment 3	0 (0.004)	94.57 (0.944)	0.285 (0.129 (0.002))	1.402 (0.001)	**0.756 (0.748, 0.765)**
Inverse Probability WeightingWeighting	0.118 (0.004)	91.57 (0.912)	0.332 (0.175 (0.003))	1.532 (0.004)	**0.593 (0.583, 0.603)**
doubly robust Inverse Probability Weighting	0.028 (0.003)	94.06 (0.939)	0.252 (0.101 (0.001))	1.217 (0.001)	**0.855 (0.848, 0.862)**
Mixed Effects Model	0.107 (0.003)	93.08 (0.928)	0.275 (0.119 (0.002))	1.27 (0.001)	**0.746 (0.738, 0.755)**

*: Monte Carlo estimates of the standard errors, Performance parameter are rounded to three digits.

Handling symptomatic treatment in AD - learnings

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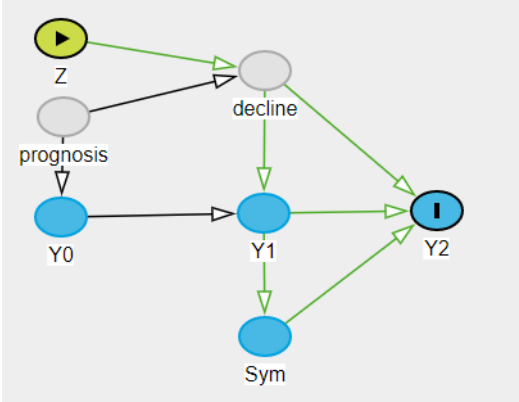
- For estimating the controlled direct effect:
  - Using the observed values leads to a small bias proportional to the imbalance in patients starting symptomatic medication between the treatment arms, and underestimation of the variability

    (= estimating the total effect of Z on Y_2)
  - Adjusting for Sym leads to bias

    (= conditioning on the descendent of Y_1 results in conditioning on the collider Y_1, which opens another path from Z to Y_2, and blocks the path Z -> $decline$ -> Y_1 -> Y_2)



  - Setting observations post-IE to missing and using missing data approaches leads to bias and loss of power

    (Donor sparseness for patients with high values for Y_1 & violation of the linearity assumption leads to underestimation of the decline)

  - **Best performing method** is Loh's g-estimation* showing no bias and minimal loss of power

*: Loh et al.: Estimation of Controlled Direct Effects in Longitudinal Mediation Analyses with Latent Variables in Randomized Studies

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Example 2

Covid-19 related intercurrent events*

*: Lasch & Guizzaro (2022): Estimators for handling COVID-19-related intercurrent events with a hypothetical strategy

Covid-19 impact on clinical trials

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Estimand

Population: adult patients with chronic tic disorders

Treatment: treatment with Nabiximols vs placebo

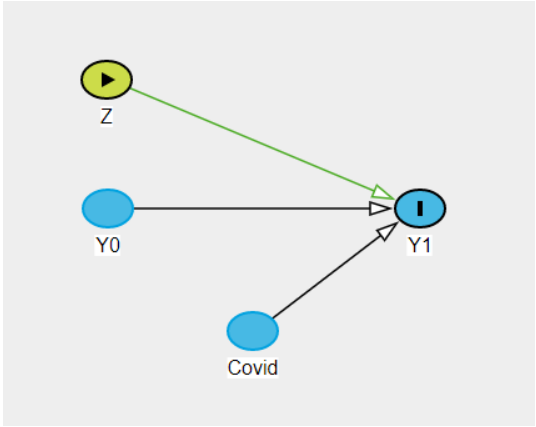
Endpoint: relative change in the Total Tic Score (TTS) of the Yale Global Tic Severity Scale (YGTSS) 13 weeks after treatment initiation as compared to baseline

Summary measure: Mean difference in relative change between treatment arms

Intercurrent events:

- Implementation of social distancing measures
- Change in measurement technique from in-person to remote

→ A **hypothetical strategy** is of interest for both of these IEs



Z: randomized treatment

Covid: occurrence of Covid-19 related IE

Y_t: observed YGTSS-TTS at time t

Covid-19 impact – causal structure

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Observation

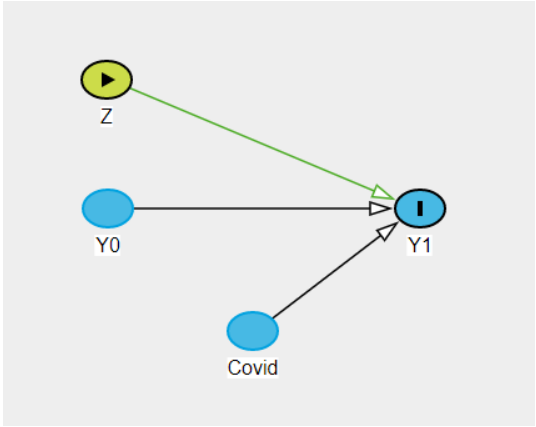
- The Estimand of interest is the controlled direct effect of Z on Y_1 controlling $Covid$ at $Covid = 0$:

  $E[\,Y_1(Z = 1, Covid = 0)] - E[\,Y_1(Z = 0, Covid = 0)]$

- $Covid$ is <u>not</u> a mediator of the effect of Z on Y_1
- de-mediation approaches are not needed. Could they still be useful?
- Commonly used approaches:

(i) set values after the initiation of symptomatic treatment as missing

(ii) apply missing data approaches (MI, IPW, PMM, complete case analysis)



Covid-19 impact – causal structure

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G-estimation

1. Estimate the effect of $Covid$ on Y_1

   Predict the probability of $Covid$: $P(Covid = 1) \sim Y_0 + Z$

   Estimate the effect of $Covid$

   a) Additive: $Y_1 \sim Z + Y_0 + p_{covid} + Covid$

   b) Multiplicative: $\log(Y_1) \sim Z + Y_0 + p_{covid} + Covid$

   c) Adaptive: either a) or b) depending on the R^2 of the respective models

2. De-mediate the effect of $Covid$ from Y_1

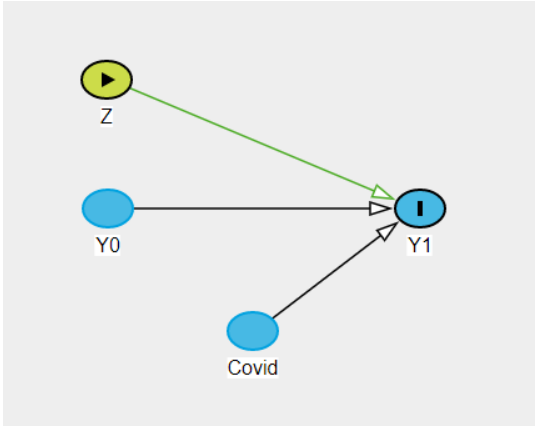
   a) $R_1 = Y_1 - Covid * \beta_{covid}$

   b) $R_1 = \exp(\log(Y_1) - Covid * \beta_{covid})$

   c) either a) or b) depending on the R^2 of the respective models

3. Estimate the effect of Z on the de-mediated values

   $R_1 \sim Z + Y_0$



Covid-19 impact - simulation study

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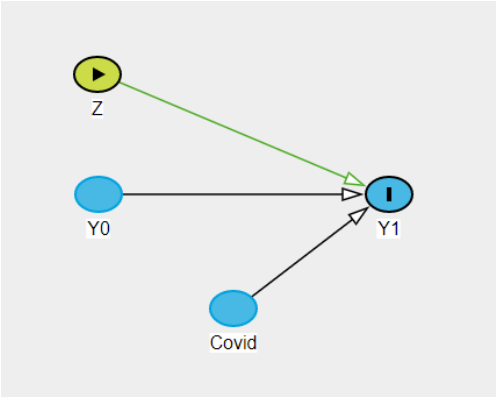
Objectives:

- Quantify the performance of commonly used estimators (bias, T1E / power) depending on the proportions of patients with an IE



Data generating mechanism

$Y_0 \sim N(25, 6.5)\big|_{[14,50]}$

$change_{underlying}|_{Z=1} \sim N(-0.234, 0.12)$ and $change_{underlying}|_{Z=0} \sim N(-0.122, 0.12)$

Impact of Covid:

a) Additive $Y_1 = (Y_0 + Y_0 * change_{underlying}) + C * C_{effect}$ with $C_{effect} \sim N(2, 1)$

b) Multiplicative $Y_1 = (Y_0 + Y_0 * change_{underlying}) * C_{effect}\hat{}C$ with $C_{effect} \sim N(1.5, 0.1)$

$$change_{obs} = \frac{Y_1 - Y_0}{Y_0}$$

Covid-19 impact – simulation results

Null hypothesis

- No bias for the investigated estimators
- No type I error rate inflation
    - Exception: IPW for large proportions of affected patients ($\geq 70\%$).

Simulation results – alternative hypothesis - bias

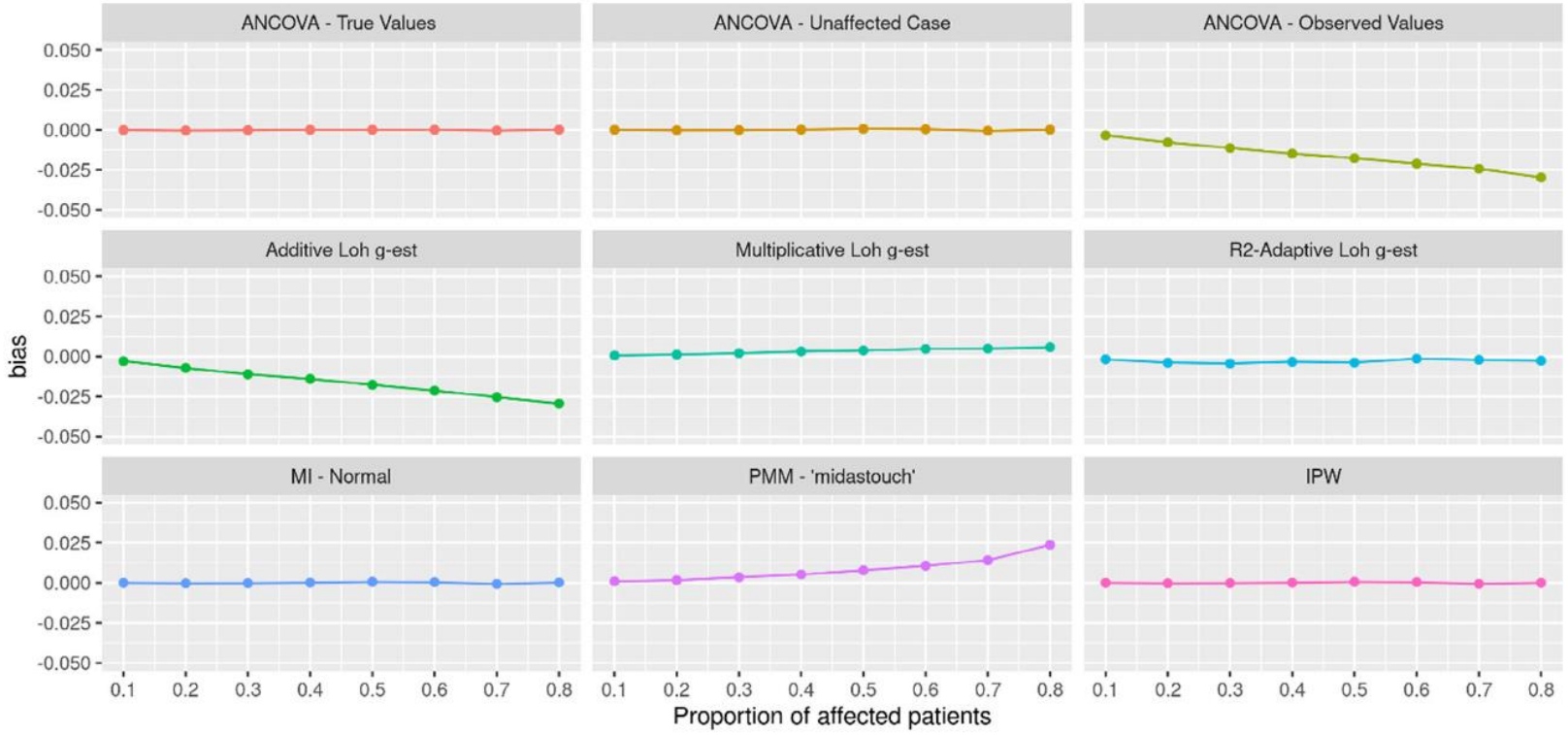


FIGURE 5 Bias of the candidate estimators for the continuous estimand under the alternative hypothesis, multiplicative IE impact

Simulation results – alternative hypothesis - power

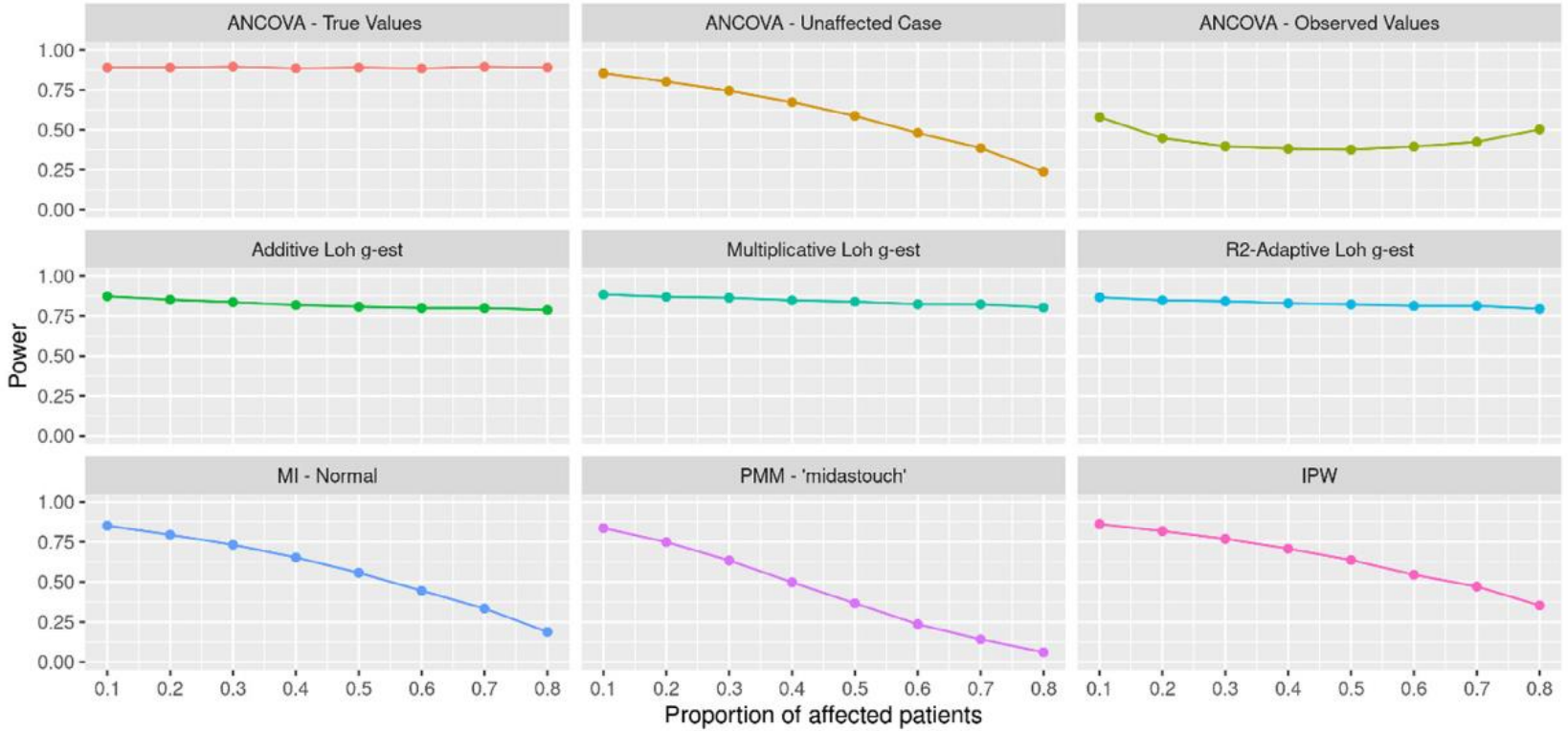


FIGURE 7 Power of the candidate estimators for the continuous estimand under the alternative hypothesis, multiplicative IE impact

Learnings

- The biasedness of estimators depends on the causal structure and the (true data generating mechanism (including of the occurrence / effect of IEs)
- At least in some scenarios, the affected values carry valuable information that can be used for estimation
- g-estimation is suitable for IEs that are mediators, but also works if the IE is independent from other study variables (other than the outcome)
- For data collection: It is important to capture values after the occurrence of IEs, even if a hypothetical strategy is used

Next questions

- Is g-estimation always better than missing data techniques?
- How to best quantify the relative amount of information in the affected values?
- How can scenarios with high / low relative information be predicted / distinguished in practice?

Any questions?

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Telephone +31 (0)88 781 6000
Send us a question Go to www.ema.europa.eu/contact

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Back-up slides

Results – Null hypothesis

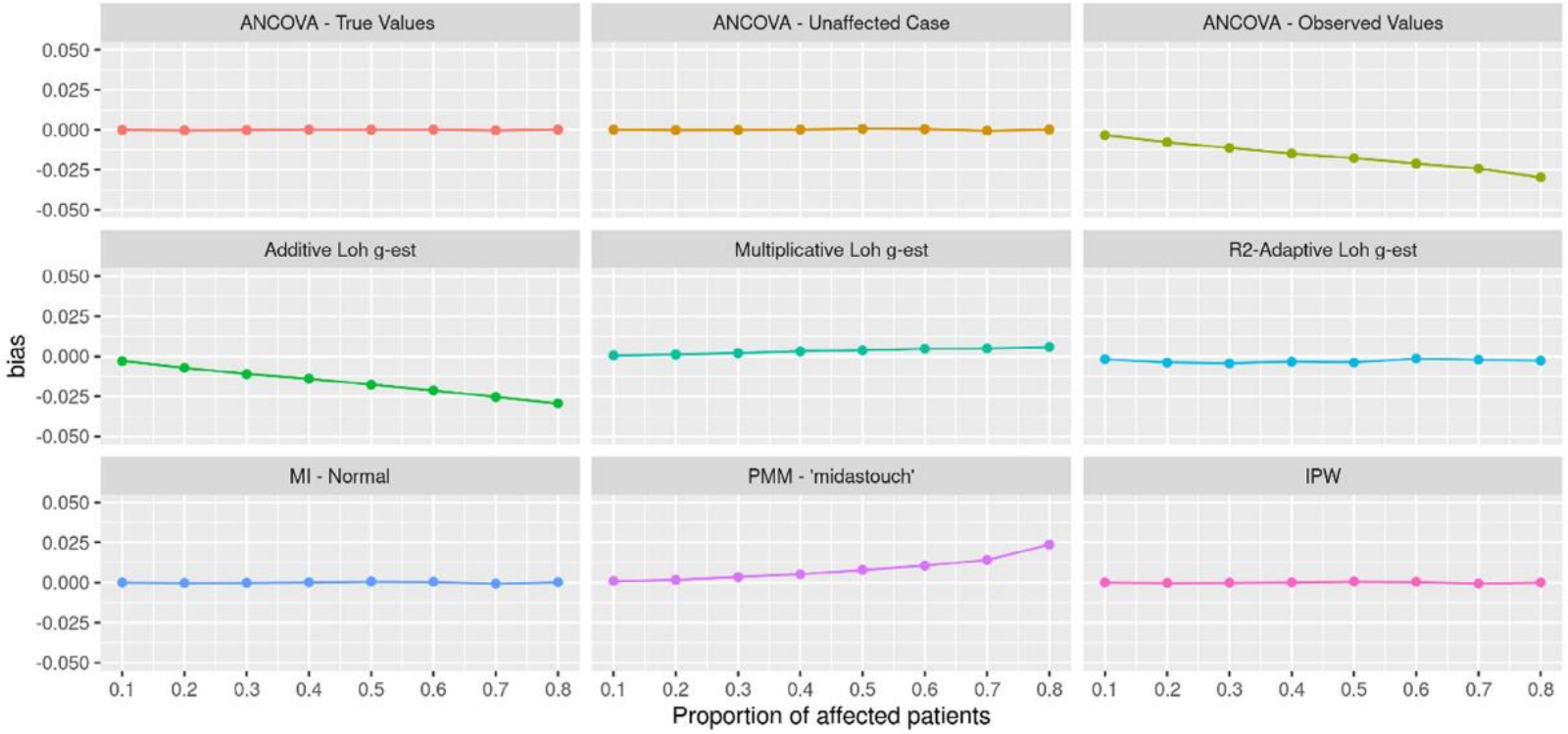

FIGURE 5 Bias of the candidate estimators for the continuous estimand under the alternative hypothesis, multiplicative IE impact

Results – Null hypothesis

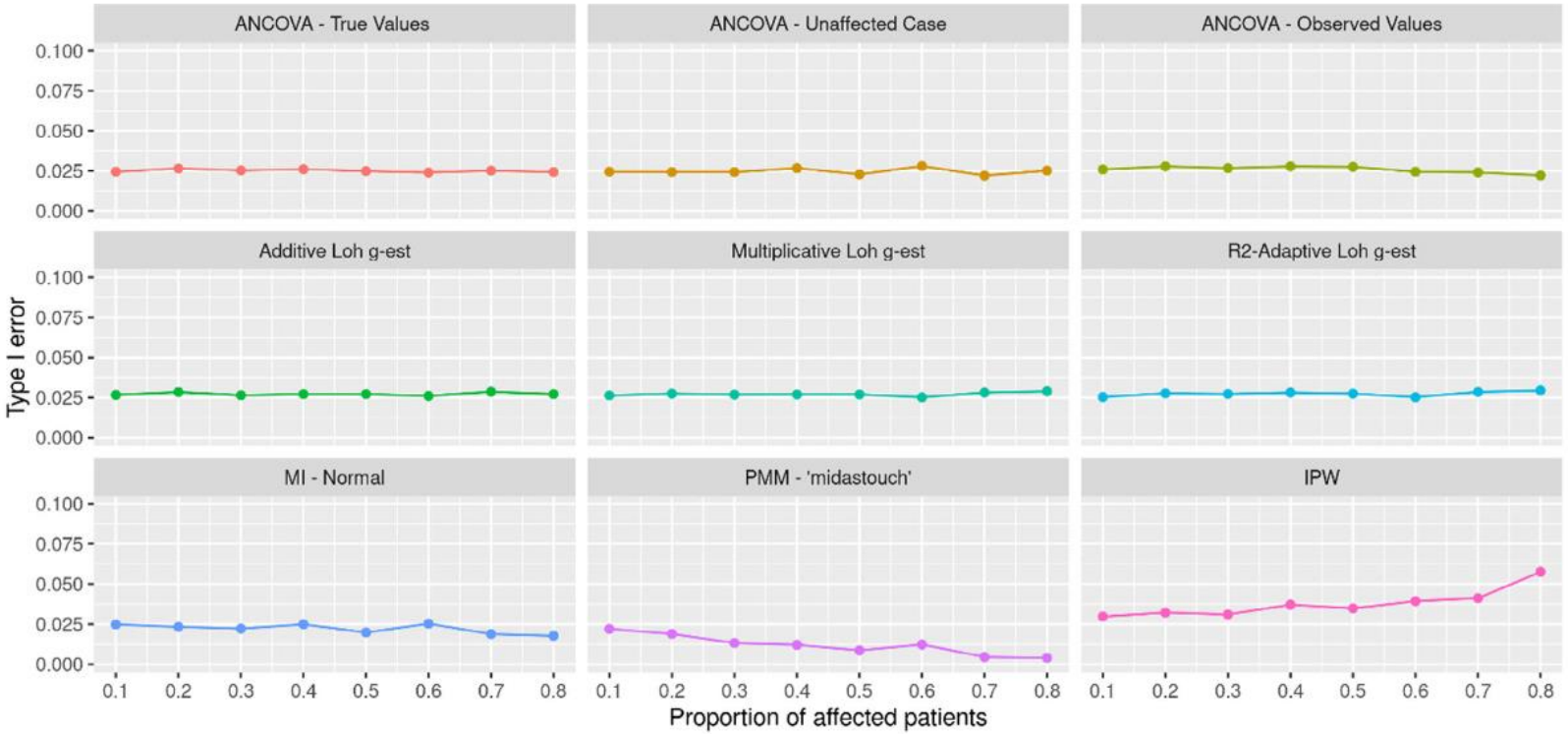

FIGURE 3 Type I error of the candidate estimators for the continuous estimand, multiplicative IE impact

Results – Alternative hypothesis - bias

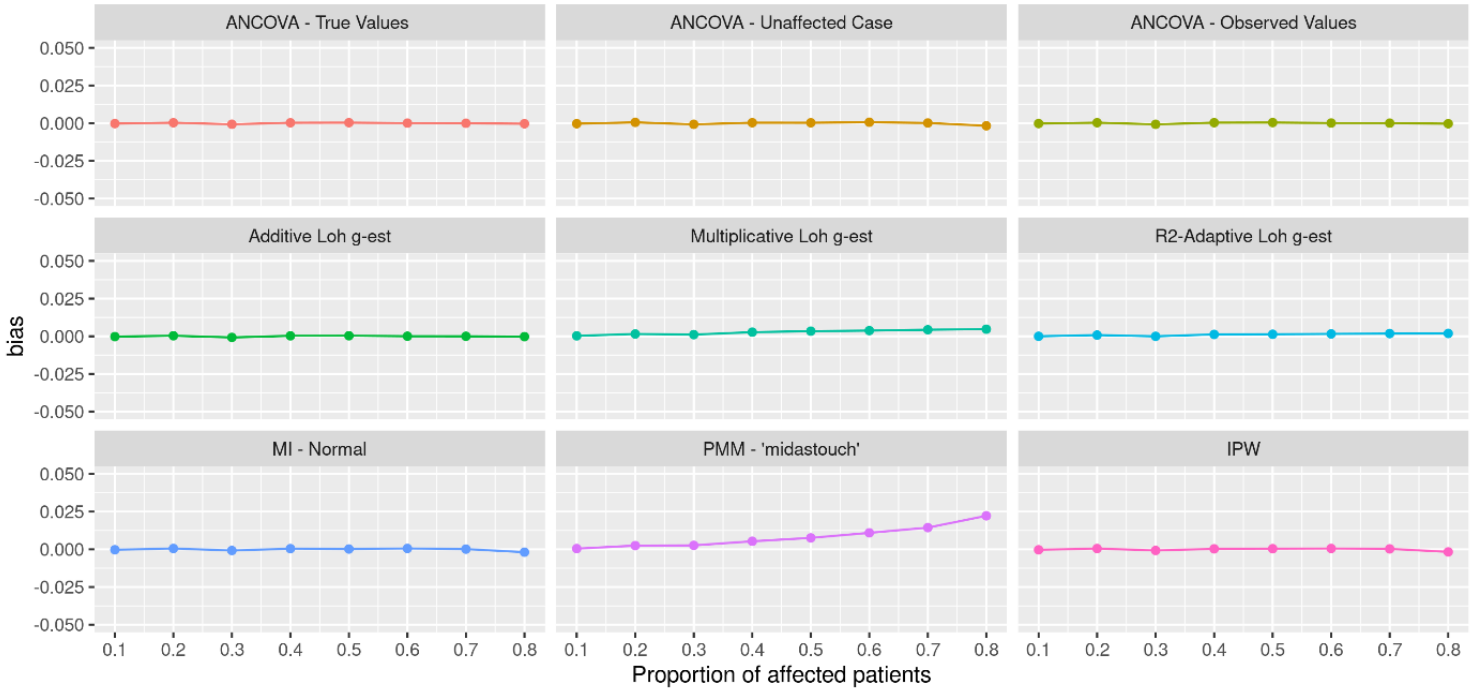

Figure S7. Bias of the candidate estimators for the continuous estimand under the alternative hypothesis, **additive IE impact.**

Results – Alternative hypothesis - power

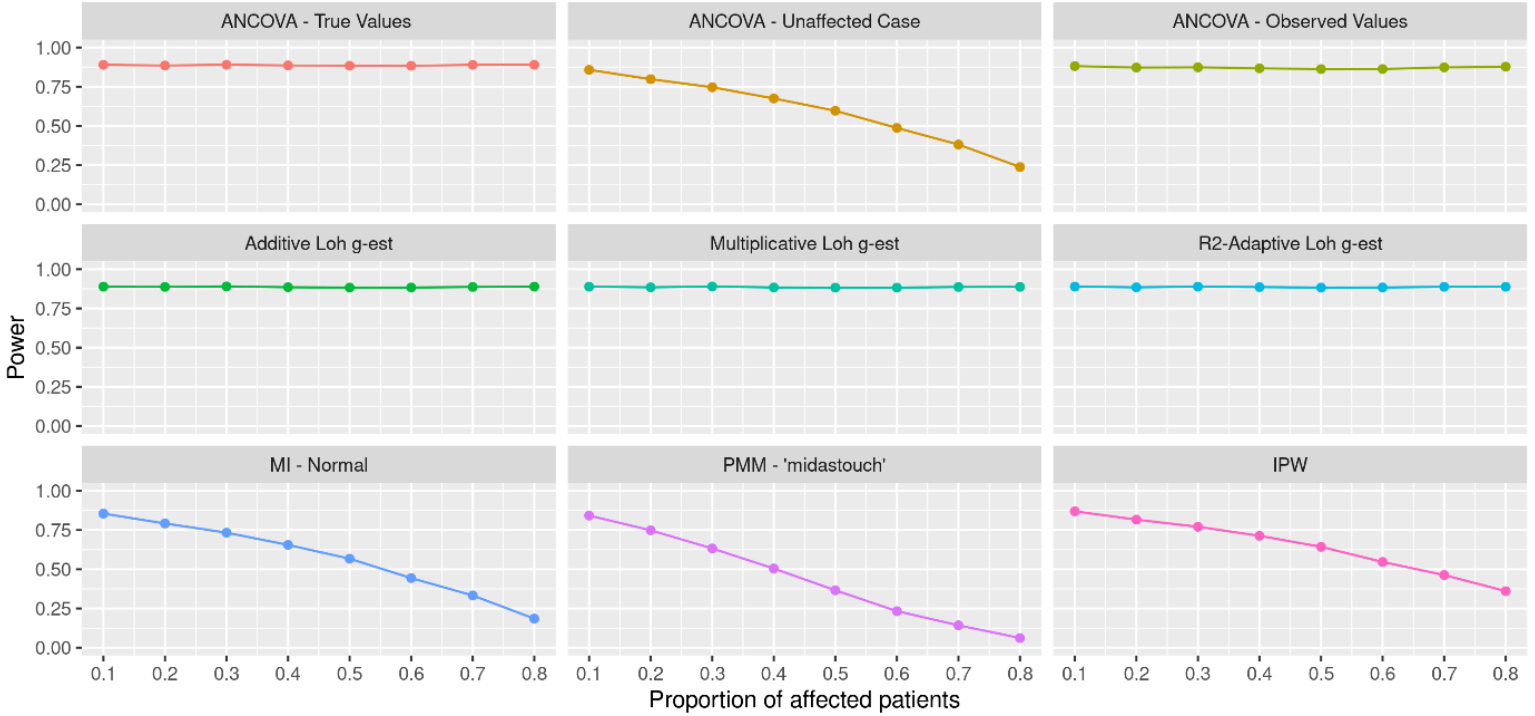

Figure S9. Power of the candidate estimators for the continuous estimand under the alternative hypothesis**, additive IE impact.**