Sense and sensitivity when estimating causal effects in clinical trials

Mid-Atlantic Causal Inference

joint work with Stijn Vansteelandt and many others

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Outline

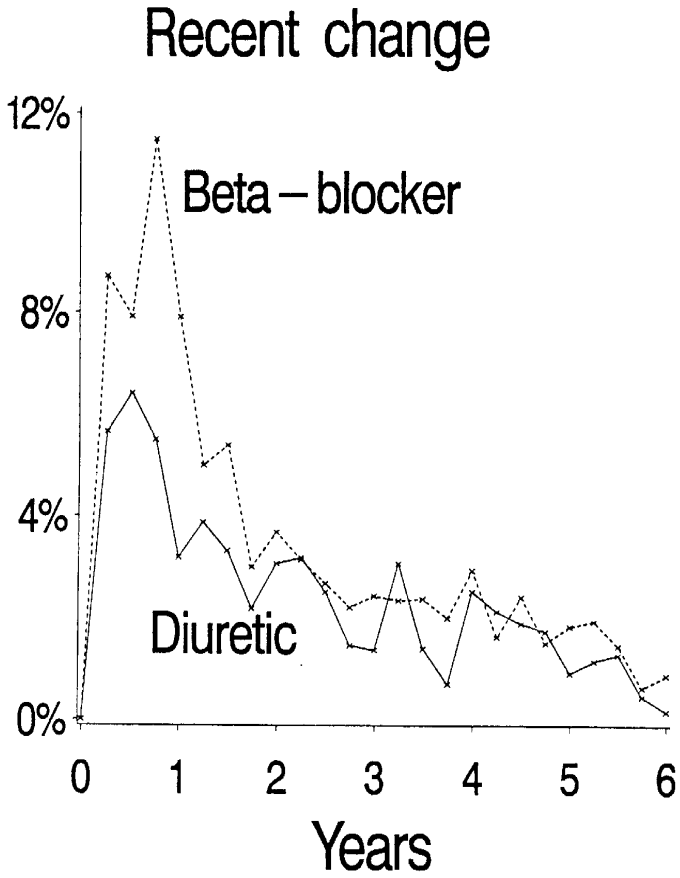
- Randomized trials and causal inference for observed exposure
  Why complicate matters when you have randomization?
- Several types of sensitivity analysis in the causal analysis framework - what is feasible - what is necessary ?
  1. Measurement error problem (IV):
     Putting varying bounds on expected measurement error
  2. Causal model for exposure:
     Allowing unidentified parameters to the causal model,
     condition on a sensitivity parameter and use
     HEIRs: Honestly Estimated Ignorance Regions and
     EUROs: Estimated Uncertainty Regions
     to summarize results
  3. Direct effect estimation:
     Comparing results from several models which make nested assumptions (DR)

Example I: treatment cross-over

White I. and Goetghebeur E. (1998) MRC elderly hypertension trial

- 4396 men and women aged 65-74 with raised systolic blood pressure randomized to diuretic, beta-blocker or placebo
- 3-monthly clinic visits for a mean of 5-8 years.
- ITT: significant reduction in risk of cardiac events in combined active arms, but not in beta-blocker arm
- 30% risk reduction on diuretic compared to beta-blocker, p = 0.03
- side effects and lack of blood pressure control lead to prescribed treatment changes, first to rival drug, then to other treatments

Can ITT be explained by treatment changes?


Recent change
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Beta – blocker
Diuretic
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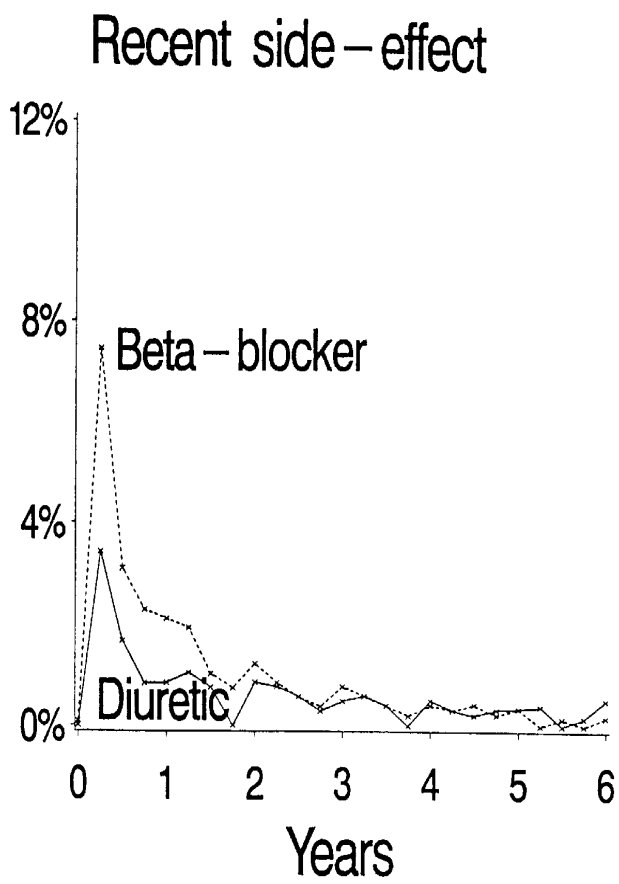
Years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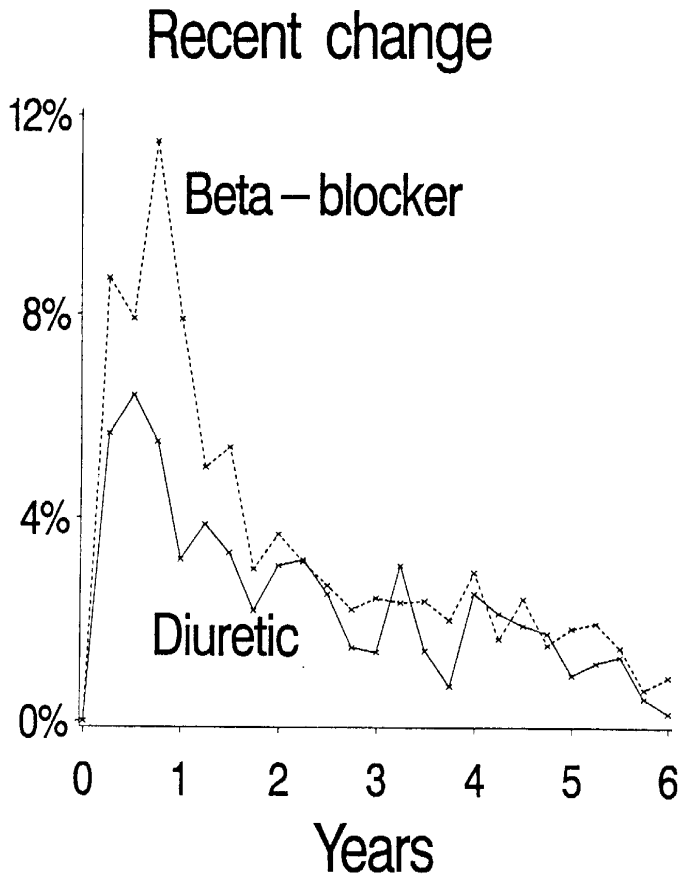

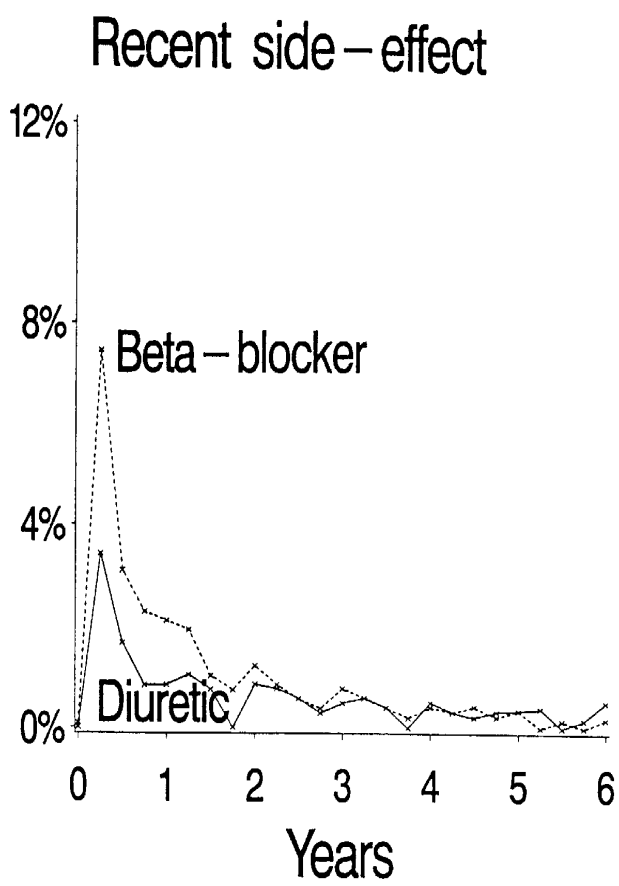

Robins, J. M. and Greenland, S. (1994)

Postulate or Estimate the effect of changing treatment and evaluate the remaining treatment difference

Example II: a third 'treatment'

Differential condom use in HIV prevention trial padian et al (2007) Rosenblum, Jewell et al. (2007):

- 5045 women randomized to diaphragm+gel use or not for the prevention of HIV; all receive active condom counselling
- 3-monthly clinic visits, asked about diaphragm and condom use atlast sex act.
- Observed 'exposures':
  - 75% adherence to diaphragm+gel use

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- 3-monthly clinic visits, asked about diaphragm and condom use atlast sex act.
- Observed 'exposures':
  - 75% adherence to diaphragm+gel use
  - reported condom use:
    53.5% in the diaphragm arm versus 85.1% in the control arm
- ITT effect relative risk of 1.05 (95% CI: [0.84, 1.30])

Has the diaphragm compensated for the lack of condom use?

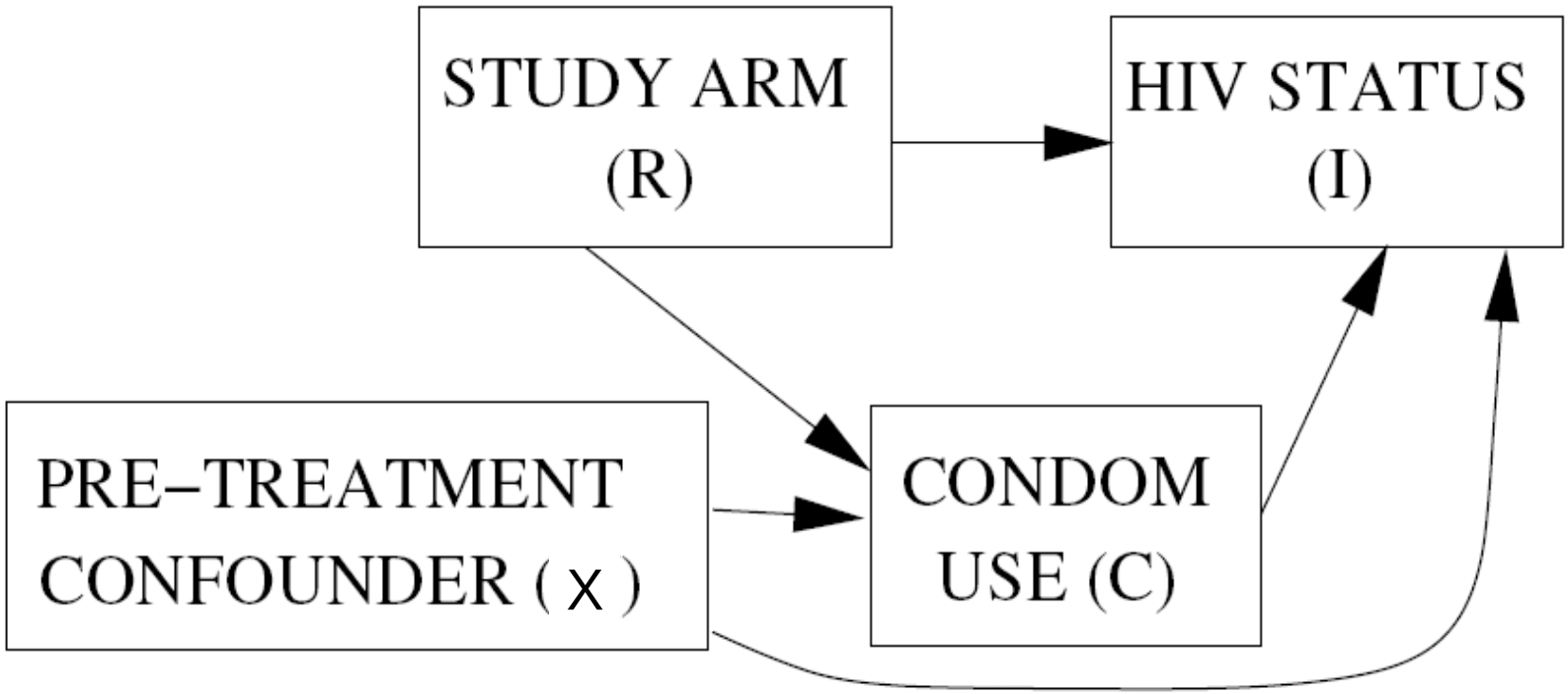


Figure 2: Direct Effects Causal Diagram
with Pre–Treatment Confounder X

Direct effect of diaphragm use

The Direct effect of diaphragm assignment/use
= controlling for level of condom use
I_{rc} incidence when all are randomized to r at fixed condom level c.
Assume:

- no unmeasured confounders for condom use C

Assumption:

$$C \coprod I_{rc} | X, R$$

i.e.

$$f(I_{rc}|C, X, R) = f(I_{rc}|X, R)$$

$\Rightarrow$ inverse weighting by the probability of condom use (IPTW)
allows to infer

the marginal direct effect $I_{r1} - I_{r0}$
HIV risk if all were possibly
randomized to 'r' and using condom level as in fixed 'c'

Estimated marginal direct effect -IPW

$$\sum_{i=1^n} \frac{1}{P(R|X)P(C|X,R,D)} (I - m(R,C|\beta))$$

with X baseline caovariates $m(R,C|\beta)$ a saturated model for the unknown probability $P(I_{rc} = 1)$

No unmeasured confounders for condom use

$$f(I_{rc}|C=1,X,R) = f(I_{rc}|C=0,X,R)$$

implication:

- Condom users and non-condom users
  - would be at equal risk if they were not protected by either the condoms nor the diaphragm (I_{00})
  - experience equal impact of a condom
    i.e. no compliance by treatment effect interaction
- Both of the above may fail:
  - condom users may generally demonstrate less risky behavior: hence less risk
  - Even if this is true for I_{00}, the way in which 'natural condom users' apply the condom may differ and lead to a differential impact of the condom (different $I_{r1} - I_{r0}$)

Results possibly sensitive to several assumptions:

1. there are unmeasured confounders (e.g. characteristics of male partners associated with their condom use and HIV status);
2. there is measurement error in reported condom use (for example, due to social desirability bias, or if quarterly reported condom use at last sex is not sufficiently informative about overall condom use) or measurement error in confounders;
3. the models for condom use (or hazard of HIV infection) are not correctly specified;
4. missing data values are very different from observed values;
5. the experimental treatment assignment assumption is violated
6. the consistency assumption or time-ordering assumption is violated.

The first two are the most important here

Deviations from these assumptions can be modelled and a sensitivity analysis can be conducted - but is not done

Direct effect of assigning diaphragm+gel

Under the (time-varying version of the) proposed model they find:

- For condom use set to zero:
  relative risk of HIV infection by visit 8: 0.59 95% CI [0.26 - 4.56]
- For condom use set to one:
  relative risk of HIV infection by visit 8: 0.96 95% CI [0.59 - 1.45]

Authors' Conclusion: insufficient information about the direct effect and no further need for sensitivity analysis.

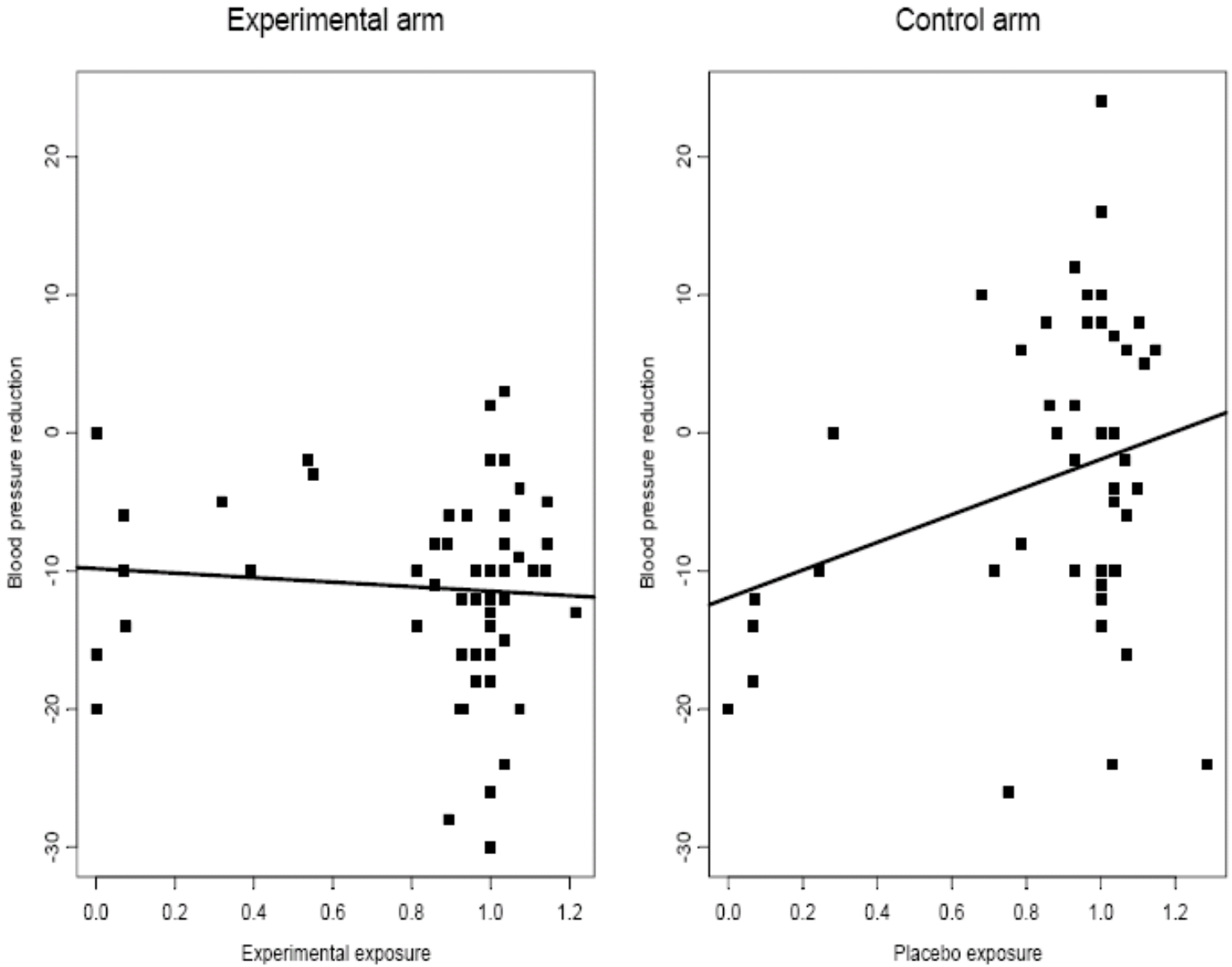
No doubly robust analyses was attempted based on the fact that the authors found it easier to model $P(C = c|past)$
than $P(X = x|past)$ or $P(I = 1|past)$.
This could however narrow the bounds.
van der Laan M. and Robins (2003)

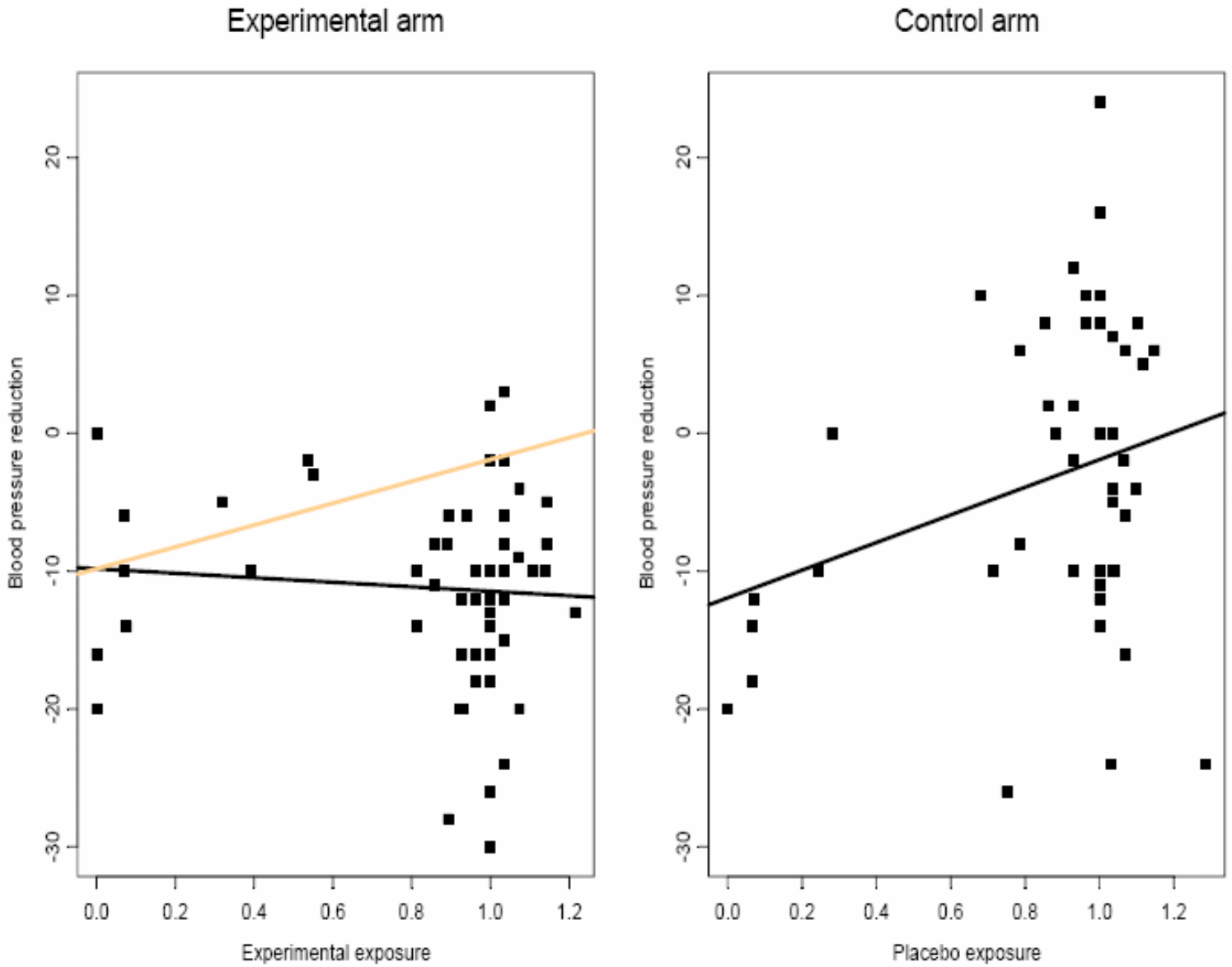
Blood pressure reduction trial

A placebo-controlled randomized hypertension trial enrolled some 300 hypertensive patients. 1 daily pill prescribed over 8 weeks (with run-in).

- 105 patients randomized to A or placebo, with MEMS measures over the active period
- Y_i diastolic blood pressure reduction over active period
  D_i average daily number of pills taken , and
  X_i age of patient i.

- ITT: extra 7.5 mmHg (95% CI [4.0; 11.0]) DBP-reduction on trt arm
- Randomization based estimated effect for treatment arm full compliers:
  estimated reduction would have been
  9.6 mmHg (95% CI [3.5; 11.8]) smaller
  had those who took one pill a day, not taken their active drug.


Experimental arm
Control arm
Blood pressure reduction
Experimental exposure
Placebo exposure
20
10
0
-10
-20
-30
0.0
0.2
0.4
0.6
0.8
1.0
1.2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0.6
0.8
1.0
1.2

More formally

Consider for independent subjects $i = 1, \ldots, n$:

- D_i true 'Dose' or any summary of Experimental Exposure
- Y_i Outcome
- X_i set of baseline/ pre-exposure covariates

We wish to estimate

$$E(Y_i - Y_{i0} | D_i, \mathbf{X}_i),$$

with Y_{i0} a potential dose-free outcome

Assumptions

Assumption A1: an instrumental variable IV R_i exists for the causal effect :

- within strata of baseline covariates $\mathbf{X}_i$,

$$E(Y_{i0}|\mathbf{X}_i, R_i) = E(Y_{i0}|\mathbf{X}_i)$$

.

Assumption A2 (Consistency assumption):

- $Y_i = Y_{i0}$ for subjects with $D_i = 0$ on either arm.

Implies as such the Exclusion restriction (AIR, 1996):
R_i has no direct effect on outcome

Assumptions

Assumption A3 (Model assumption): the causal effect obeys the linear structural mean model (Robins, 1994)

$$E(Y_i - Y_{i0}|D_i, \mathbf{X}_i, R_i) = \gamma(\mathbf{X}_i, R_i; \psi^*)D_i$$

$\gamma(\mathbf{X}_i, R_i; \psi)$ is a known function smooth in ψ, with $\gamma(\mathbf{X}_i, R_i; \mathbf{0}) = 0$

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$\gamma(\mathbf{X}_i, R_i; \psi)$ is a known function smooth in ψ, with $\gamma(\mathbf{X}_i, R_i; \mathbf{0}) = 0$

For instance, in placebo-controlled randomized experiments with $R_i = 1$ for experimental arm and $R_i = 0$ for control,

$$E(Y_i - Y_{i0}|D_i, \mathbf{X}_i, R_i) = \psi D_i R_i$$

$$E(Y_i - Y_{i0}|D_i, \mathbf{X}_i, R_i) = (\psi_1 + \psi_2' \mathbf{X}_i) D_i R_i.$$

Estimation basis

Randomization is exploited as an instrumental variable:

$$Y_{i0} \coprod R_i | X_i$$

and a causal model is proposed for the effect of observed exposure:

$$Y_i - \psi R_i D_i \coprod R_i | X_i$$

$Y_i - \psi R_i D_i \sim Y_{i0} | X_i, R_i$ up to some random error

$$E\left[Y_i - \psi R_i D_i | \mathbf{X}_i, R_i\right] = E\left[Y_i - \psi R_i D_i | \mathbf{X}_i\right].$$

Measurement Error

Consider for independent subjects $i = 1, \ldots, n$:

- D_i true 'Dose' or any summary of Exposure
- Y_i Outcome
- X_i set of baseline/ pre-exposure covariates

We wish to estimate

$$E(Y_i - Y_{i0}|D_i, \mathbf{X}_i),$$

with Y_{i0} a potential exposure-free outcome

However: D_i is imprecisely measured

$$\Downarrow$$

M_i measured exposure level with error 'added' to actual exposure level D_i (unobserved)

Basis for estimation

Let $\delta(\mathbf{X}_i, R_i) \equiv E(M_i - D_i|\mathbf{X}_i, R_i)$ be the average measurement error , then:

$$\begin{aligned} &E\left[Y_i - \psi R_i \left\{M_i - \delta(\mathbf{X}_i, R_i)\right\} | \mathbf{X}_i, R_i\right] \\ &\quad = E\left[Y_i - \psi R_i \left\{M_i - \delta(\mathbf{X}_i, R_i)\right\} | \mathbf{X}_i\right]. \end{aligned}$$

Option 1: estimate the causal parameter ψ for different values of δ
Option 2: joint estimation of the causal parameter ψ and the expected measurement error δ [under extra assumptions]

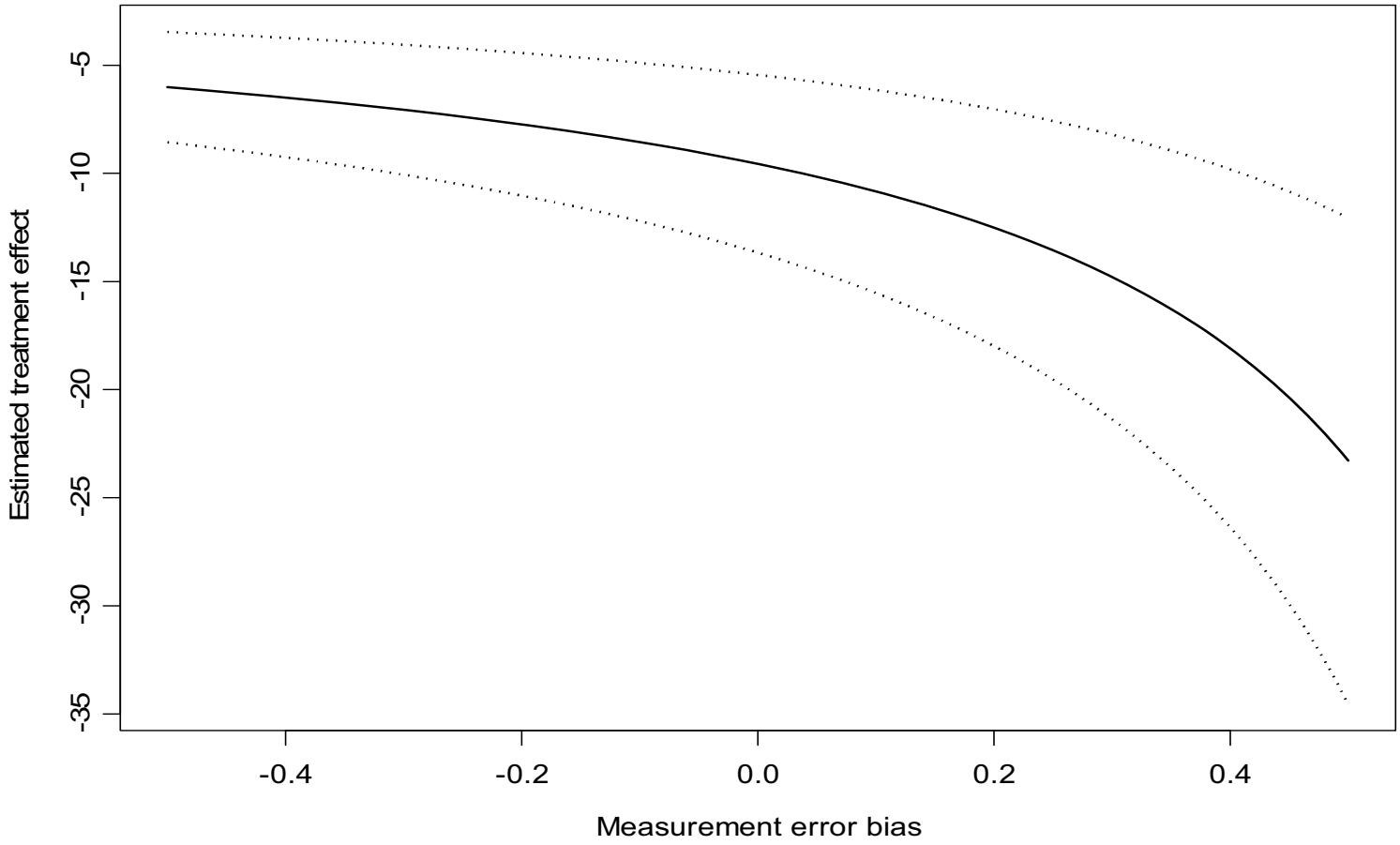


Fig. 1. Estimated average causal effect ψ with 95% confidence interval in function of δ.

Assumptions

A4: Measurement error assumptions:

$\exists$ **M**easurement error **I**nstrumental **V**ariable $\mathbf{T}_i \subseteq \mathbf{X}_i$ (MIV).

- Surrogate for observed exposure:

$$T_i \not\perp\!\!\!\perp M_i | \{S_i, R_i\}$$

  where $\mathbf{X}_i \equiv (\mathbf{S}_i, \mathbf{T}_i)$, measured prior to exposure and
- does not modify the causal effect of received exposure on the outcome, i.e. such that

$$E(Y_i - Y_{i0} | D_i, \mathbf{X}_i, R_i) = E(Y_i - Y_{i0} | D_i, \mathbf{S}_i, R_i)$$

  Hence $\gamma((\mathbf{S}_i, \mathbf{T}_i), R_i; \psi) = \gamma(\mathbf{S}_i, R_i; \psi)$

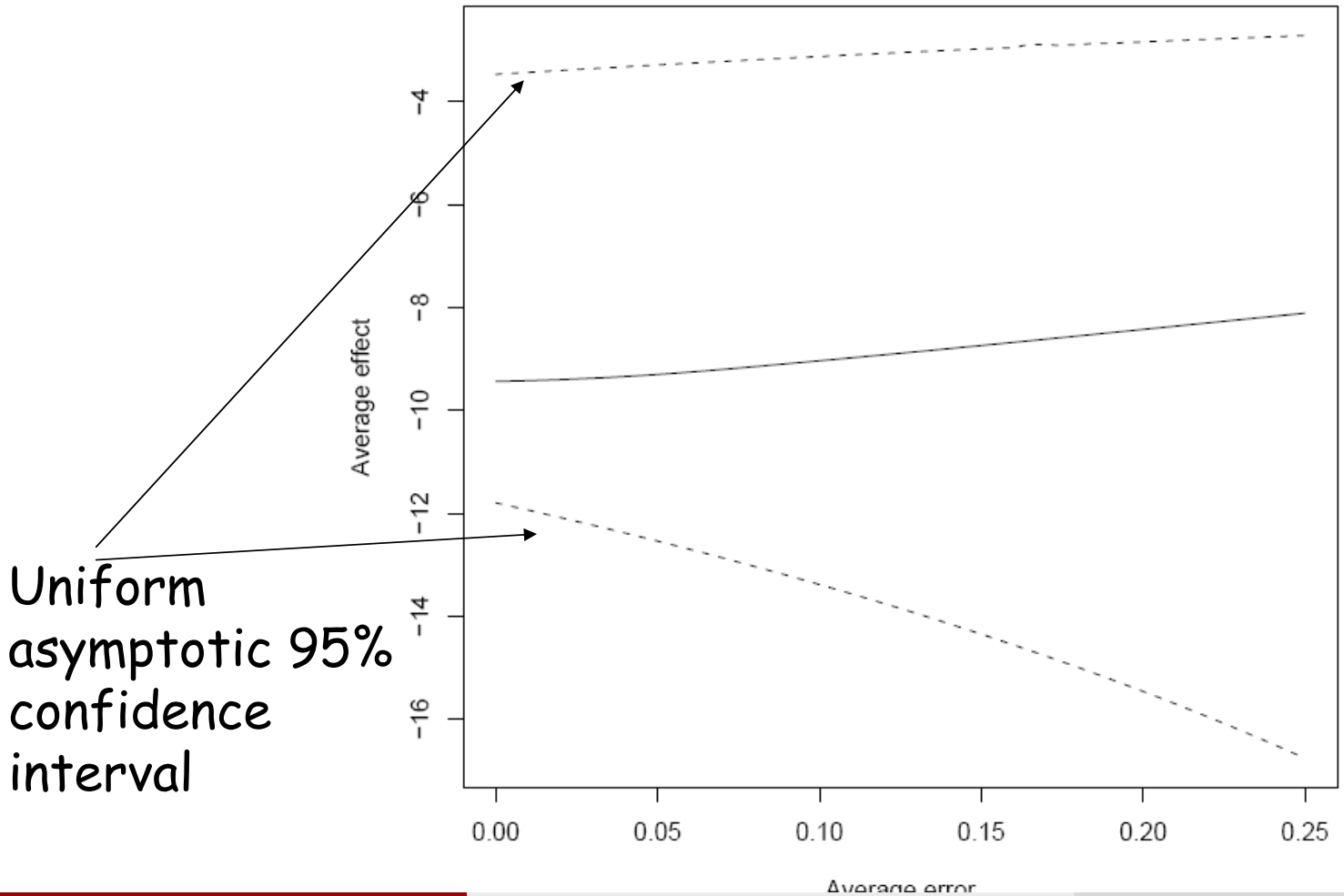
- Assuming perfectly measured compliance:
  estimated reduction would have been 9.6 mmHg [3.5 ; 11.8]
  had those who took one pill a day, not taken their active drug.
- Instrumental variable T for measurement error:
  Not considered at the design stage
  - Age is available:
    effect modification through age not foreseen in these middle-aged subjects (5th, 95th percentiles: 41 and 69 years).
  - Placebo compliance during the run-in period was not recorded here should be a considered at the design stage

Measurement error adjusted average causal effect

- Straight forward error-adjusted estimator: estimates a much larger treatment effect of 27.0 mmHg (95% CI -91.2; 145.2)
- Assume the average error δ is smaller than 0.25
  - the observed % of assigned dose taken is 85% on average.
  - $\Delta = [-0.25, 0.25]$ thus allows for 30% of the observed average exposure to be due to systematic error.
- results in slightly smaller effect of 9.0 mmHg (95% CI [4.4; 17.4]) as compared to the standard analysis.
- still significantly different from 0 at the 5% significance level.
- The uniform asymptotic 95% confidence interval [2.7; 16.8] has a more guaranteed performance in finite samples (Robins, 2005).

Improved error-adjusted estimator in function of Δ_U

Figure 2: Improved error adjusted estimate in function of Δ_U with $\Delta = [-\Delta_U, \Delta_U]$



- Consider targeted blood pressure 'success' ($Y_i = 1$):
  - baseline DBP of at least 95 mmHG drops to below 90 mm HG or
  - 10% reduction in DBP from baseline.
- ITT: Odds of succes is 3.44 times higher on trt arm
- The logistic association model

$$\text{logit}\{\text{pr}(Y_{iD_i} = 1 | D_i, R_i = 1)\} = \beta_1 + \beta_2 D_i$$

$\exp \hat{\beta}_2 = 1.09[.21; 5.66]$ and

- the structural (causal) model

$$\text{logit}\left\{\text{pr}(Y_{iD_i} = 1 | D_i, R_i = 1)\right\} - \text{logit}\left\{\text{pr}(Y_{i0} = 1 | D_i, R_i = 1)\right\} = \psi D_i,$$

  - Effect of full treatment among the fully treated, Conditional causal OR : $\exp \hat{\psi} = 4.44$ [1.58; 12.49]
  - Effect of full treatment for the whole population assuming no current treatment interaction, Marginal causal OR estimate: 4.14 [1.69; 10.17]

The double logistic structural mean model

Association model:

$$\text{logit}\{\text{pr}(Y_{i\mathbf{D}_i} = 1 | \mathbf{D}_i, \mathbf{X}_i, R_i = 1)\} = \eta_a(\mathbf{D}_i, \mathbf{X}_i)$$

Causal model:

$$\text{logit}\{\text{pr}(Y_{i\mathbf{D}_i} = 1 | \mathbf{D}_i, \mathbf{X}_i, R_i = 1)\} - \text{logit}\{\text{pr}(Y_{i\mathbf{0}} = 1 | \mathbf{D}_i, \mathbf{X}_i, R_i = 1)\}$$

$$= D_{i1}\eta_{s1}(\mathbf{X}_i) + \eta_{s2}(\mathbf{D}_i, \mathbf{X}_i)$$

- Any $\eta_{s2}(\mathbf{D}_i, \mathbf{X}_i)$ compatible with any observed data law.
- Thus $\eta_{s2}(\mathbf{D}_i, \mathbf{X}_i)$ cannot be identified from observed data
- The natural choice, $\eta_{s2}(\mathbf{D}_i, \mathbf{X}_i) = 0$, assumes that
  - the conditional causal odds ratio is loglinear in $\mathbf{D_{i1}}$;
  - no further untestable assumptions under all-or-nothing compliance,
  - yields 1st order approximations of conditional causal log OR.

Ignorance regions

Considering:

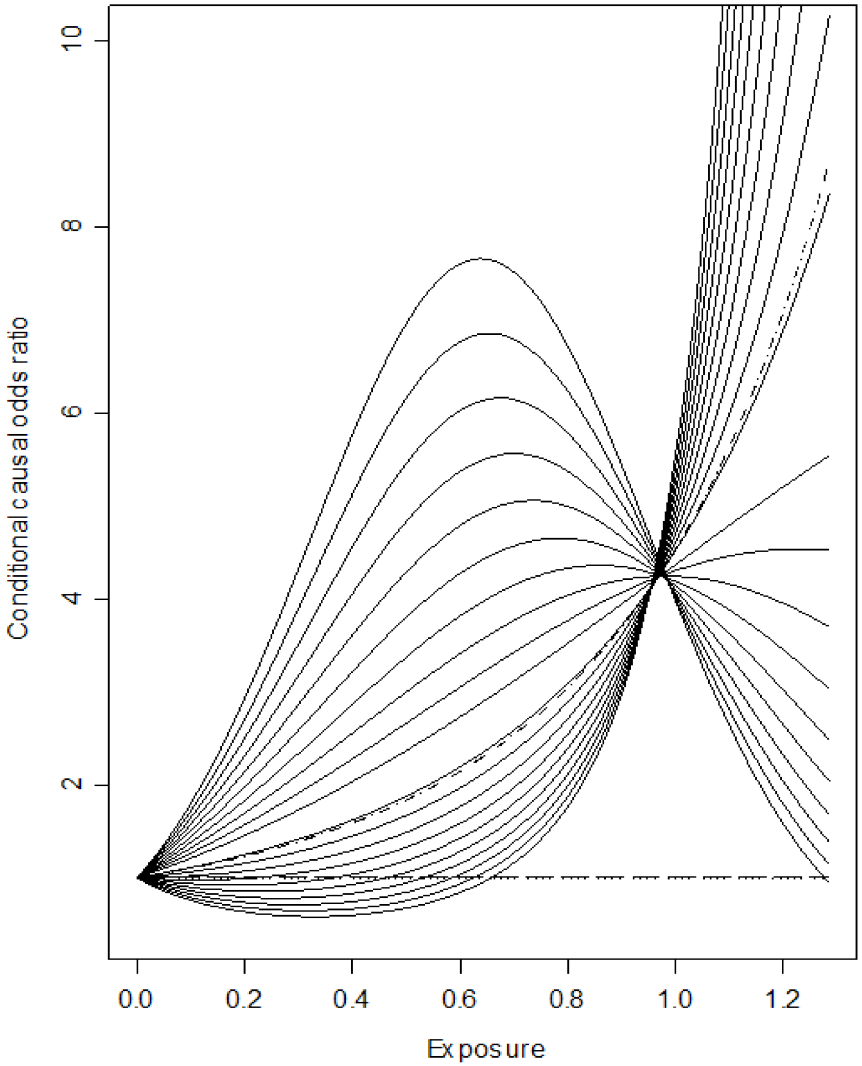
$$\log\left(\frac{\text{odds}(Y_{i\mathbf{D}_i}=1|\mathbf{D}_i,\mathbf{X}_i,R_i=1)}{\text{odds}(Y_{i\mathbf{0}}=1|\mathbf{D}_i,\mathbf{X}_i,R_i=1)}\right)=D_i\psi-\gamma D^2$$

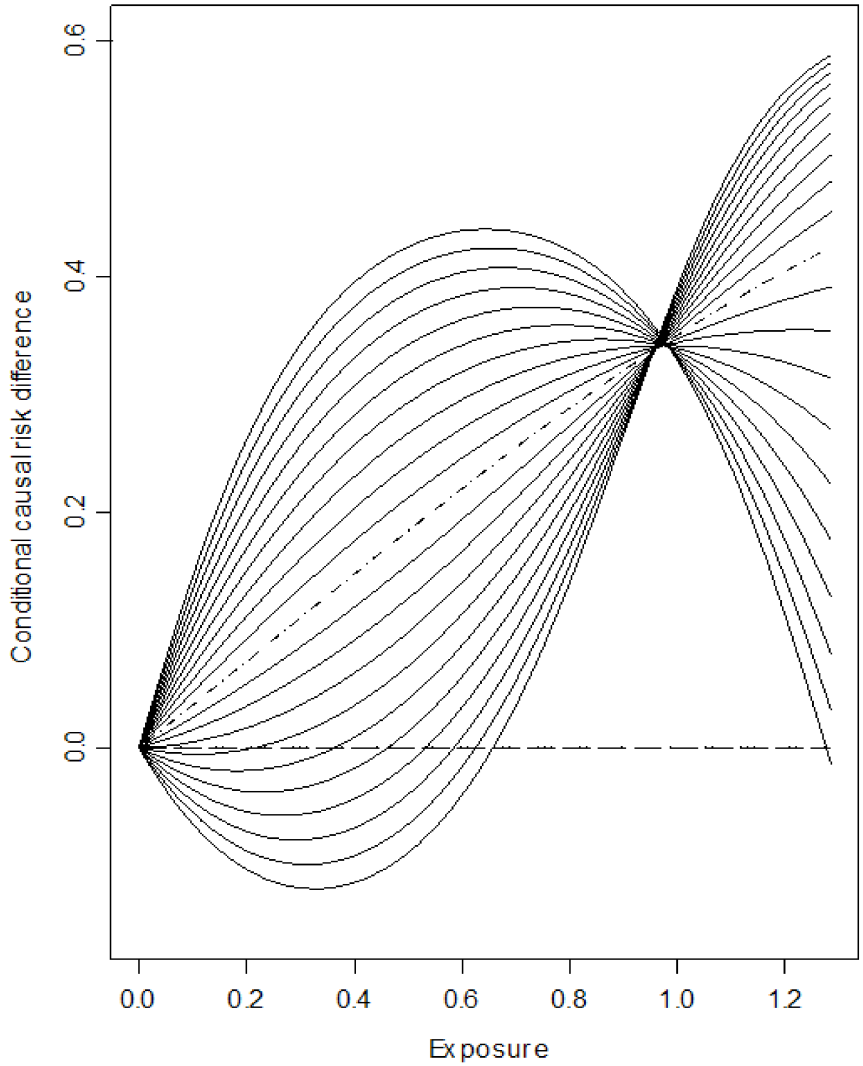
with $\eta_{s2}(\mathbf{D}_i,\mathbf{X}_i)=\gamma D_i^2$ and $\Gamma_\gamma=[-5,5]$, we estimate

- the conditional causal odds ratio $\exp\{D_i\psi+\gamma D_i^2\}$
- the conditional causal risk difference $E(Y_{iD_i}-Y_{i0}|D_i,R_i=1)$
  $=\text{expit}(\beta_1+D_i\beta_2)-\text{expit}\{\beta_1+D_i(\beta_2-\psi)-D_i^2\gamma\}$

for each possible value of γ.

HEIRs for OR and RD





Uncertainty regions

A summary could give the extreme estimates:

Honestly Estimated Ignorance Regions (HEIRs)

Uncertainty regions

A summary could give the extreme estimates:

Honestly Estimated Ignorance Regions (HEIRs)

- HEIRs: express structural model uncertainty
- EUROs - Estimated Uncertainty RegiOns: in addition acknowledge finite-sample imprecision.

- 95% pointwise EURO : uncertainty intervals designed to cover the true population parameter with at least 95% chance
  - we conclude equivalence when the 95% pEURO is covered by the equivalence range
  - for hypothesis tests , they act like classical confidence intervals: a conservative test of the null hypothesis that $\theta = \theta_0$ rejects when θ_0 is excluded by the 95% pEURO for θ

Alternative measures of uncertainty

Vansteelandt *et al.*, 2006. propose as alternative uncertainty measures:

- strong 95% uncertainty intervals
  designed to cover the ignorance region itself with 95% probability
- and weak uncertainty intervals
  designed to have expected 95% overlap with the ignorance region

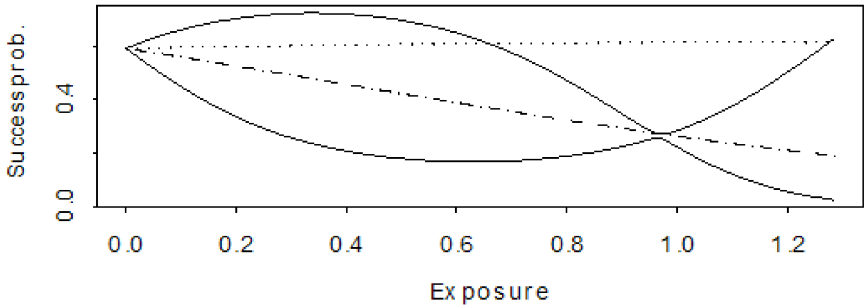
HEIRS and 95% EUROS

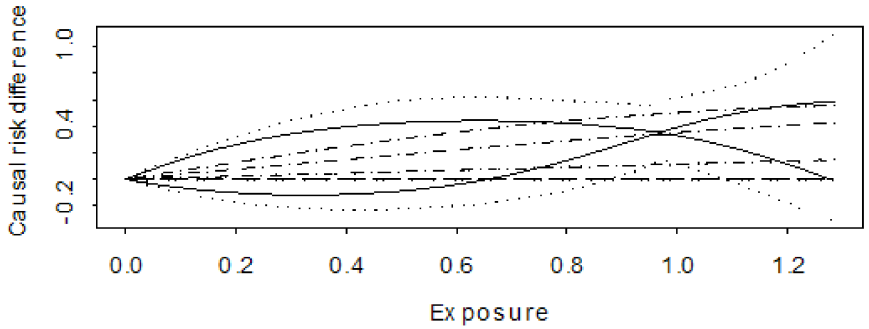
- With $\gamma \in [-8, 2]$ (causal OR between 1/15 and 15))
  - 95% pEURO for the causal RD excludes 0 for exposure levels between 0.75 and 1.04
  - 95% pEURO for causal OR for perfect compliers [1.53, 12.94]. HEIR and 95% pointwise EURO for the causal OR in perfect compliers

    $[3.92; 5.54]$ $[1.53, 12.94]$.

- With in addition monotone treatment effects
  - 95% pEURO for the causal RD excludes 0 for exposure ≥ 0.68.
  - HEIR and 95% pEURO for the causal OR in perfect compliers

    $[4.37, 4.70]$ $[1.58, 12.40]$


Success prob.
0.0
0.4
0.0
0.2
0.4
0.6
0.8
1.0
1.2
Exposure


Causal risk difference
-0.2
0.4
1.0
0.0
0.2
0.4
0.6
0.8
1.0
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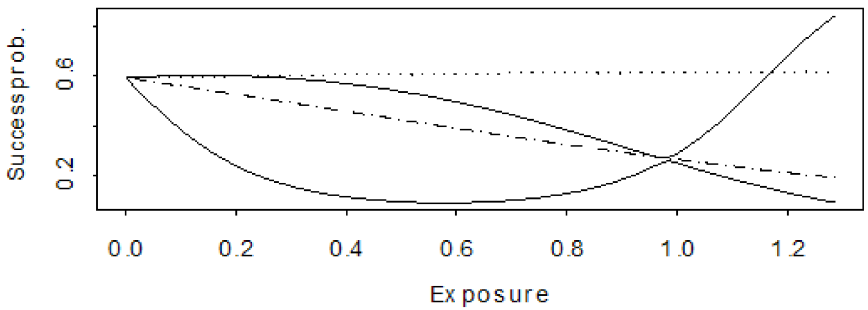
Exposure


Success prob.
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0.8
1.0
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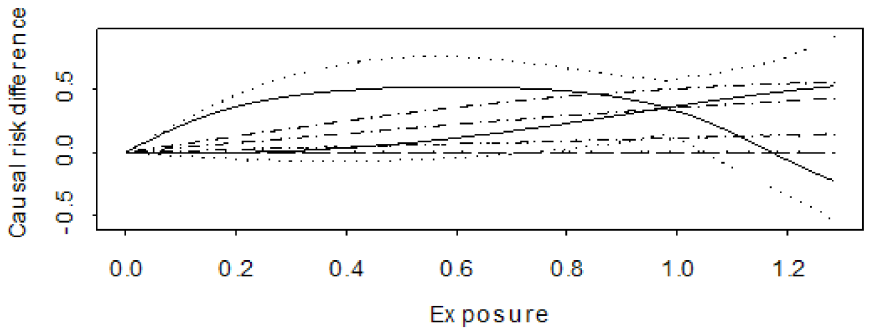
Exposure


Causal risk difference
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0.5
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0.2
0.4
0.6
0.8
1.0
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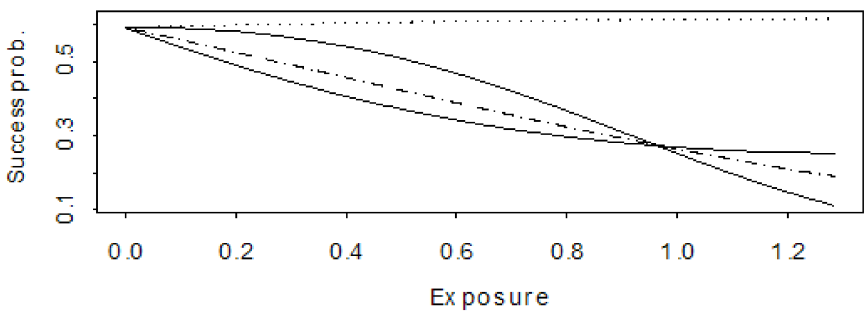
Exposure


Success prob.
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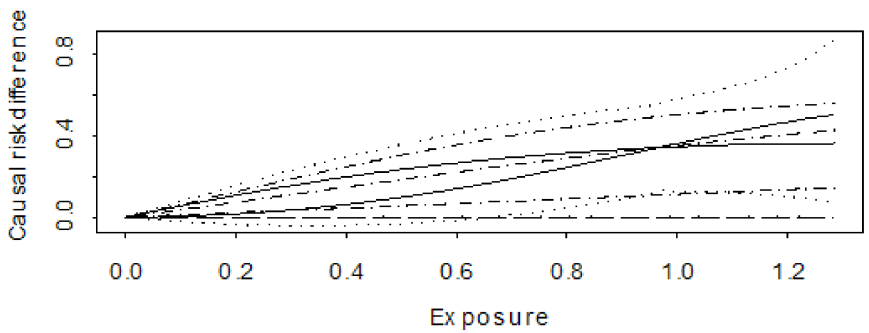
0.3
0.5
0.0
0.2
0.4
0.6
0.8
1.0
1.2
Exposure

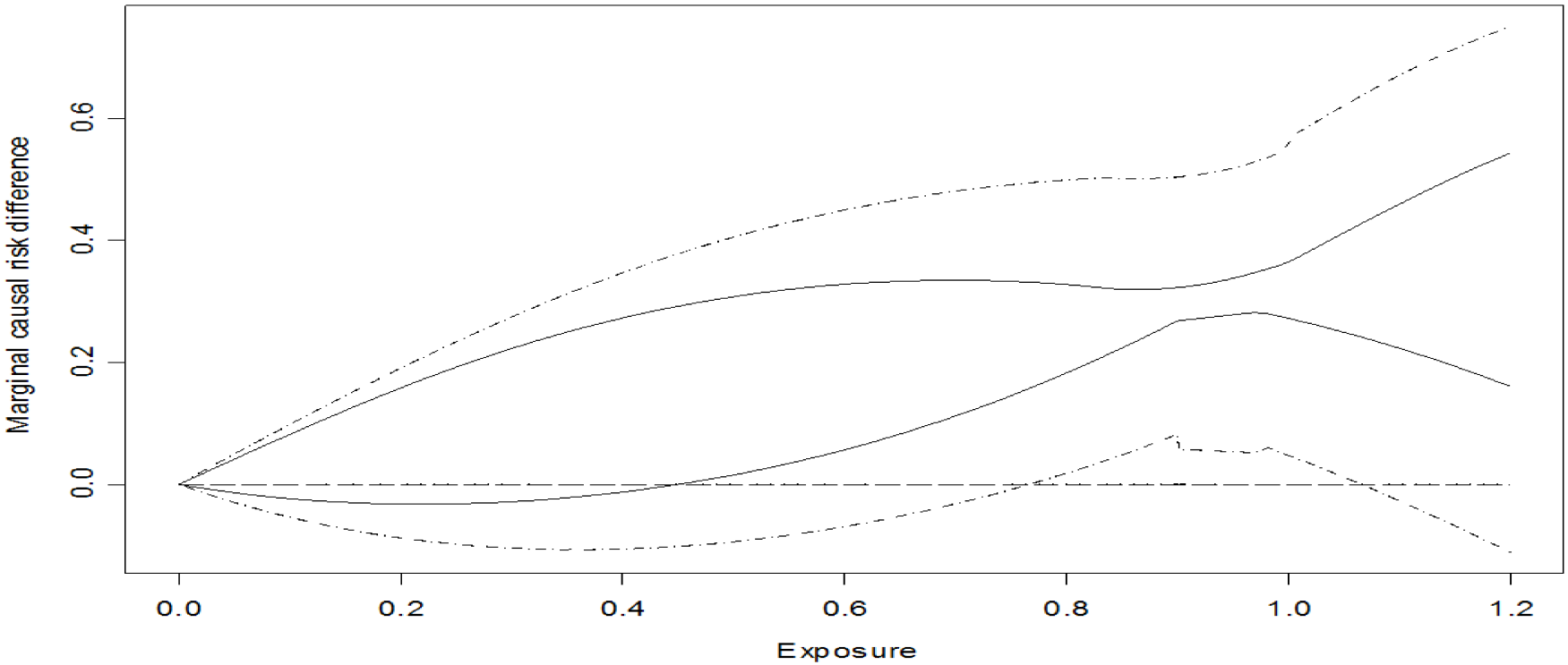

Causal risk difference
0.0
0.4
0.8
0.0
0.2
0.4
0.6
0.8
1.0
1.2
Exposure

Sensitivity analysis for marginal causal odds ratios

$$\begin{aligned}&\text{logit}\{\text{pr}(Y_{id}=1|D_i,R_i=1)\}-\text{logit}\{\text{pr}(Y_{i0}=1|D_i,R_i=1)\}\\&=\psi_0 d+\gamma d^2+\delta d(D_i-d)\end{aligned}\tag{1}$$

Shown in the next figure as δ varies over [-2,2] (γ over the monotone range)
i.e. the causal effect of unit exposure (on OR scale) can be up to $\exp(2)=7.39$ times higher/smaller for patients observed to differ one unit in exposure.
Results show:

- unit exposure uniformly applied, multiplies odds of success by a factor between 3.13 and 4.60 (95% pEURO [1.38,10.71])
- 95% pointwise EUROs suggest significant benefit for exposure levels between 0.78 and 1.08.


Marginal causal risk difference
0.0
0.2
0.4
0.6
0.0
0.2
0.4
0.6
0.8
1.0
1.2
Exposure

SET and DET and birth weight outcome (Ref. 4 below)

- De Sutter et al. (2006) estimate the effect of single versus double embryo transfer (SET versus DET) on birth weight using a survey of 557 SET and 396 DET patients who entered the subfertility program at the Ghent University hospital and who delivered a singleton child of at least 500 grams after fresh embryo transfer in a first, second or third cycle between January 2003 and May 2007. The mean gestational age (GA) of singleton babies is 273.9 days (SD 12.4). The mean birth weight (BW) is 3231.8 grams (SD 565.4).
- Birth weights are 120 grams (95% confidence interval $[44, 197]$) lower on average in babies born after double than single embryo transfer.
- Is the effect of SET/DET on birth weight is entirely mediated through gestational age?

Direct causal effect?

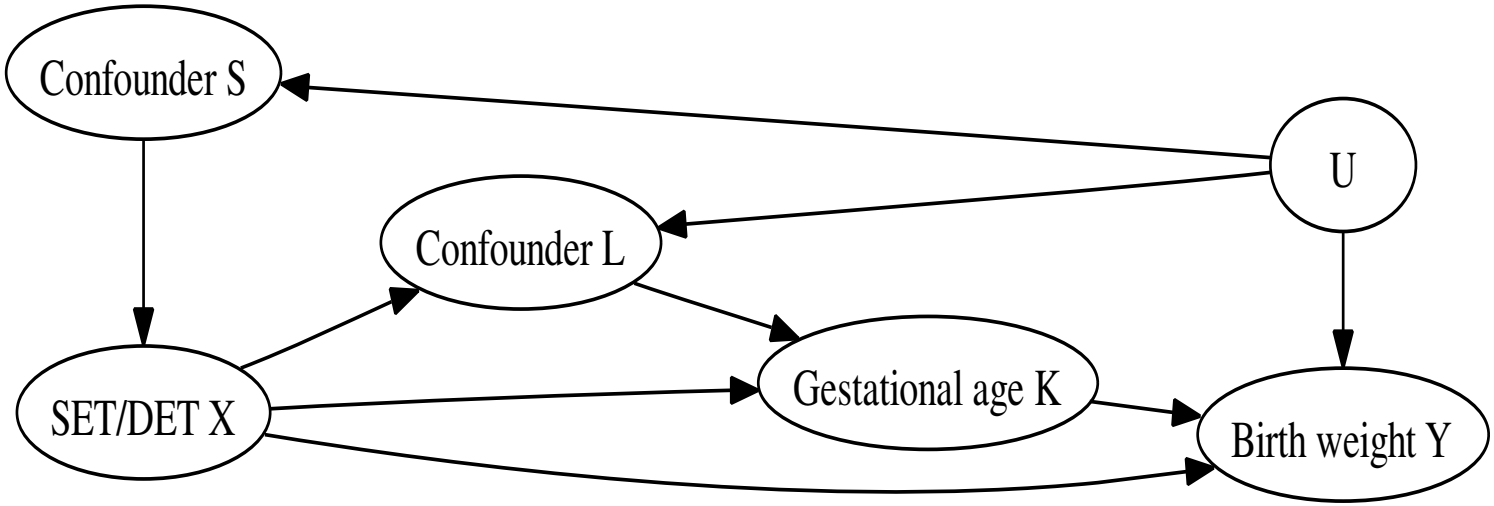


Figure 1: *Causal Diagram. Note: All edges encode the possibility of a direct causal effect; the absence of an edge between 2 variables A and B thus expresses the assumption that A does not directly affect B, and vice versa. We further assume that for any pair of variables, all common causes have been included in the diagram.*

Estimation

- Assuming a correctly specified structural nested direct-effects model with $m(X, k; \psi) = \psi X$, we estimate:
  - the Inverse Probability of Intermediate Weighting (IPIW) estimator involving a model for density of
    f(gestational age | SET/DET and time-varying confounders)

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  - the doubly-robust (DR) estimator
    or/and a model for $E(Y|$ SET/DET, confounders, gestational age)

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- Assuming a correctly specified structural nested direct-effects model with $m(X, k; \psi) = \psi X$, we estimate:
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  - the doubly-robust (DR) estimator or/and a model for $E(Y|$ SET/DET, confounders, gestational age)
  - the unweighted (UW) estimator (needs $E(Y|$ SET/DET, confounders, gestational age))
  - the stabilized doubly-robust (SDR) estimator
  - the improved doubly-robust (IDR) estimator and the stabilized
  - improved doubly-robust (SIDR) estimator

Table 4: *Data analysis results.*

	Without infertility duration			With infertility duration		
	$\hat{\psi}$	boot SE	95% CI	$\hat{\psi}$	boot SE	95% CI
IPIW	78.20	100.16	[-143.41;304.21]	91.90	144.41	[-224,78;338.44]
DR	-67.77	40.44	[-141.19;14.42]	-84.11	53.75	[-190.64;14.79]
UW	-59.64	36.70	[-136.49;13.97]	-70.76	47.92	[-156.37;14.98]
SDR	-67.69	40.38	[-141.22;14.38]	-83.82	53.54	[-189.42;15.37]
IDR	-69.52	42.46	[-154.40;18.41]	-86.07	54.87	[-181.93;15.03]
SIDR	-69.45	42.33	[-153.08;18.18]	-85.77	54.59	[-181.63;14.70]
LM	-44.59	33.49	[-115.06;28.88]	-71.14	45.18	[-148.02;6.27]

Discussion

Causal inference is demanding

1. think through the key causal question (how macro/microscopic?)
2. think through reasonable assumptions and possible study designs
3. use state of the art methods for inference
4. acknowledge key untestable assumptions or weak points for either bias or precision
5. perform and communicate results of sensitivity analysis
6. extra input may be useful at this stage, such as prior on ... the range of current treatment interactions

What is feasible - what is necessary ?

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