Causal inference with data subject to covariate-dependent observation times: An application to a cohort of new users of antidepressants

Janie Coulombe
janie.coulombe@umontreal.ca
Department of Mathematics and Statistics
Université de Montréal

Joint work with Dr. Erica E.M. Moodie, Dr. Susan M. Shortreed, and Dr. Christel Renoux

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Context

- Cohort of new users of citalopram or fluoxetine (31120 patients) from the *Clinical Practice Research Datalink* (CPRD)
- Adverse effects include changes in weight and appetite

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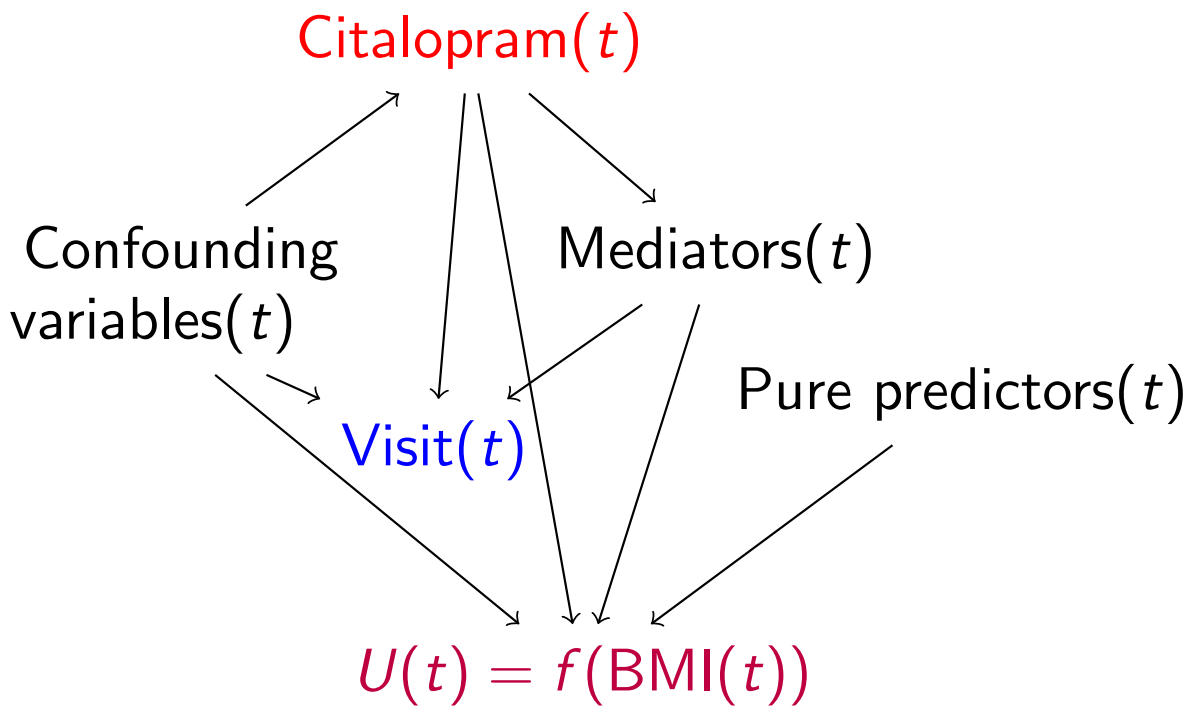
- Adverse effects include changes in weight and appetite
- We aim to develop an individualized treatment rule of the type

  "**Treat with citalopram if detrimental changes in weight are minimized under citalopram, treat with fluoxetine otherwise**"

- Repeated measures of a utility function $U(t)$, a function of $\text{BMI}(t)$

The causal diagram that is postulated at each time t:



with $\text{Visit}(t) = 1$ corresponding to the observation of $U(t) = f(\text{BMI})$.

The individualized treatment rule will depend on treatment effect estimates.

Informative observation in causal inference

- Outcomes are observed at irregular times. **Confounding** or **collider stratification** bias? (Greenland, 2003)

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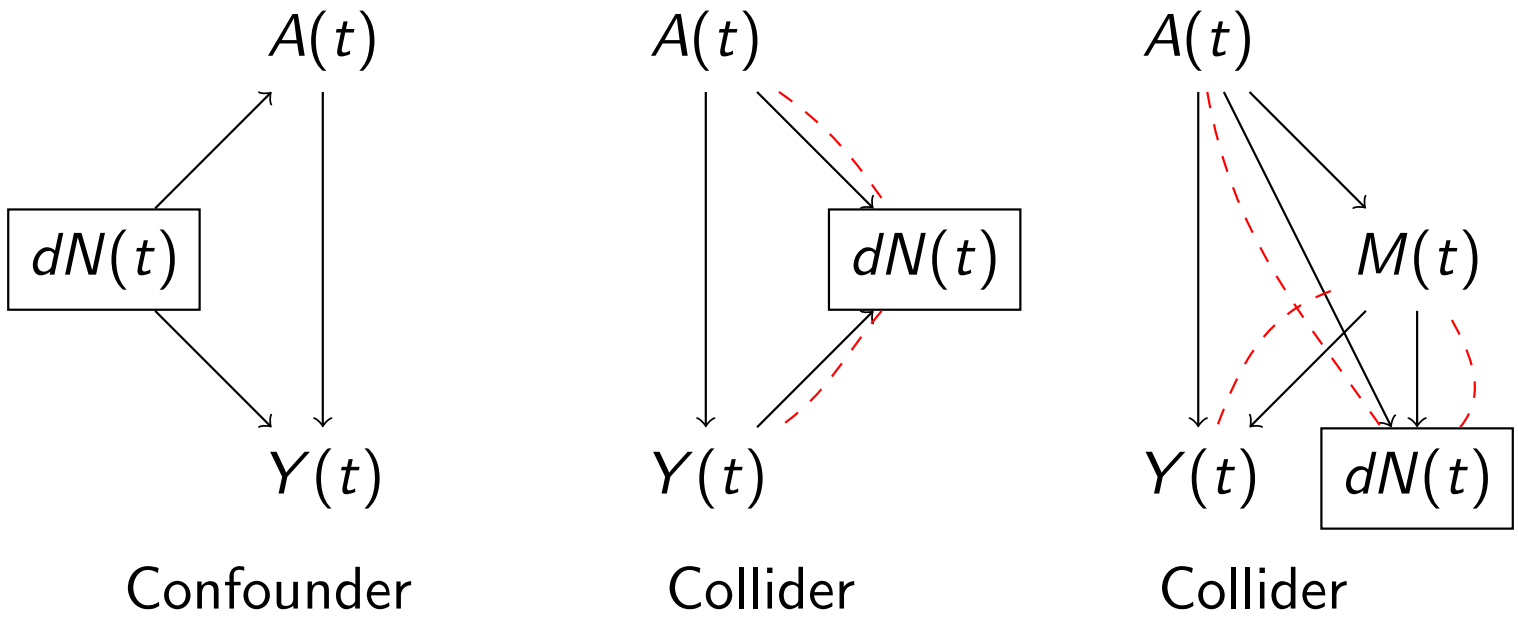
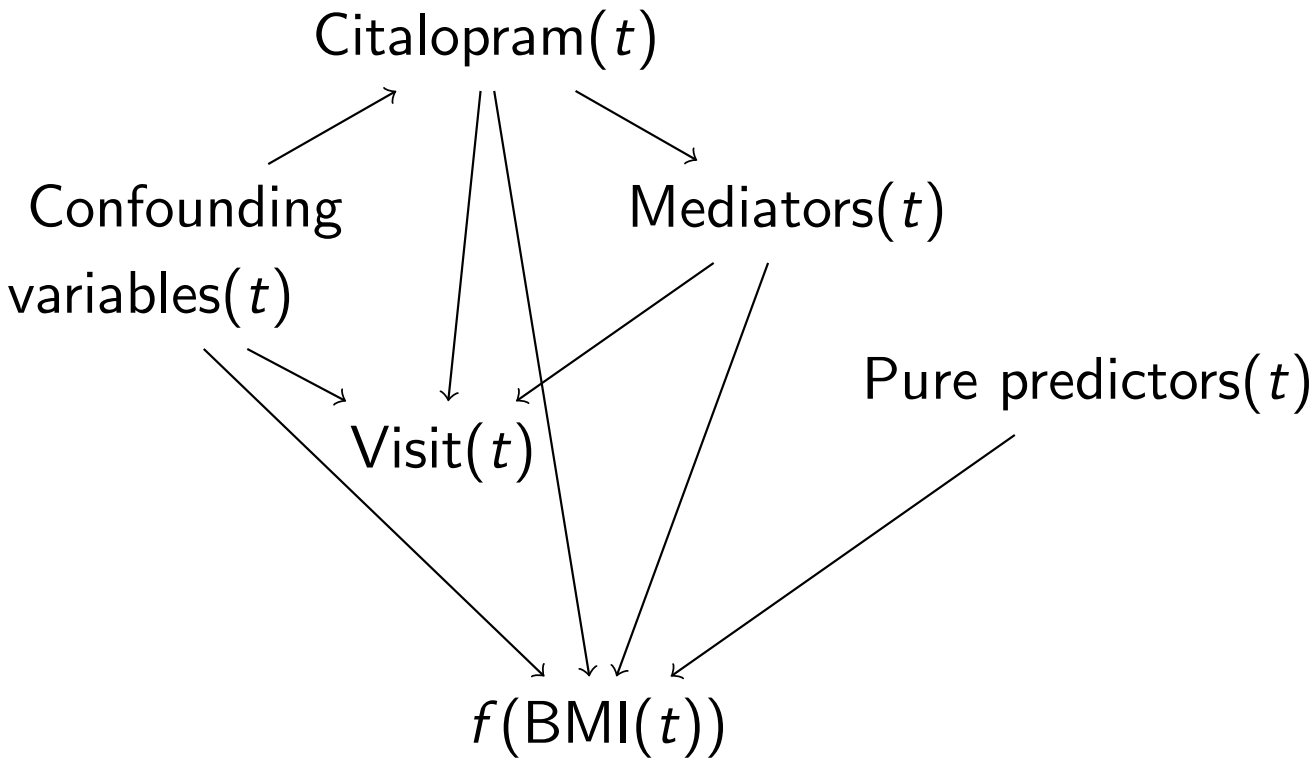
E.g., if $dN(t)$ is a visit indicator, $A(t)$ a treatment, $M(t)$ a mediator of the treatment effect and $Y(t)$ an outcome at time t:



Confounder Collider Collider

Motivation: Choice of antidepressant

Causal diagram at time t:



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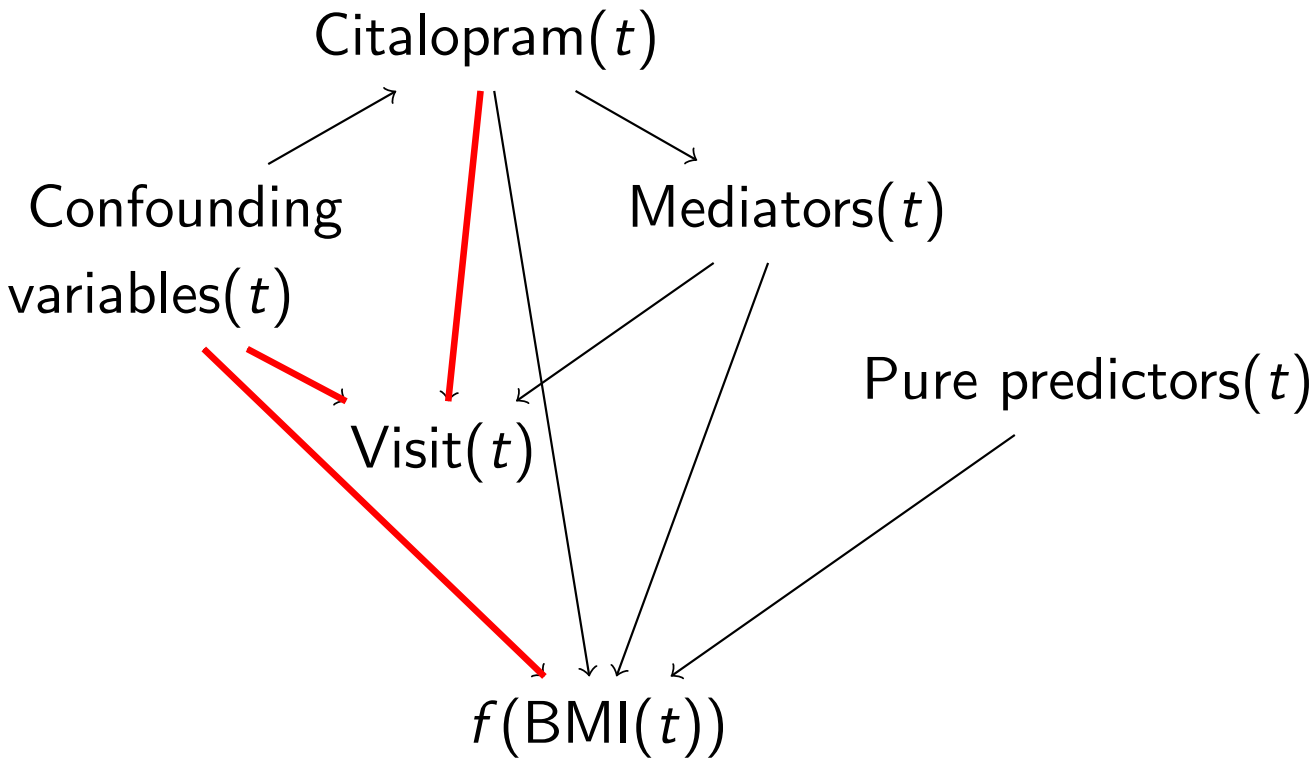

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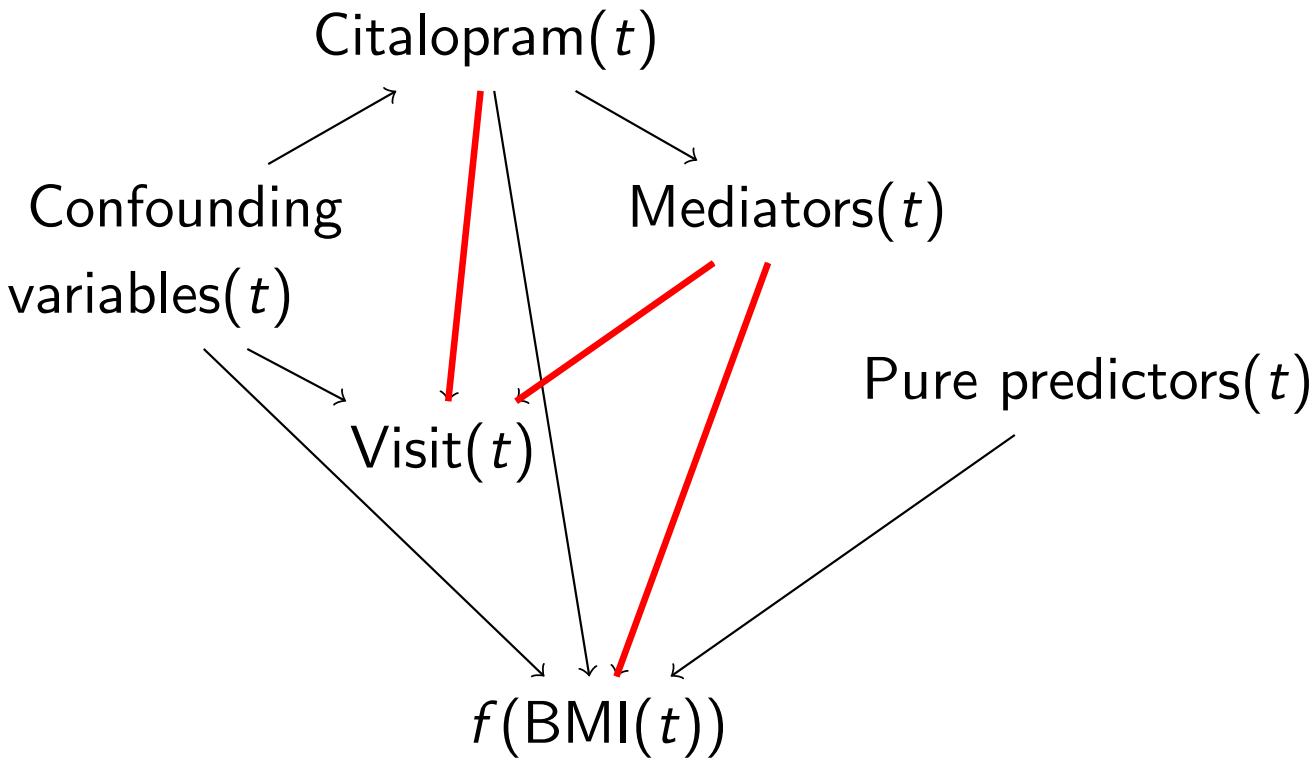

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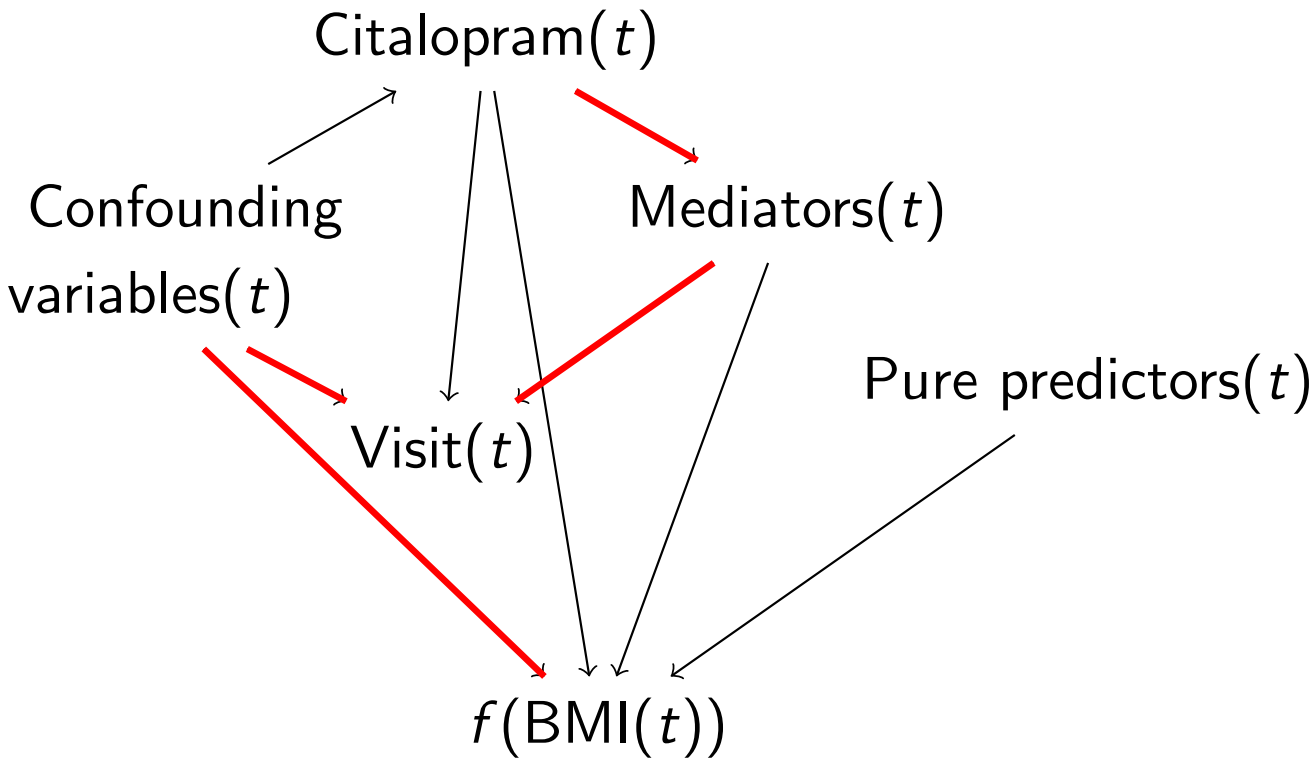

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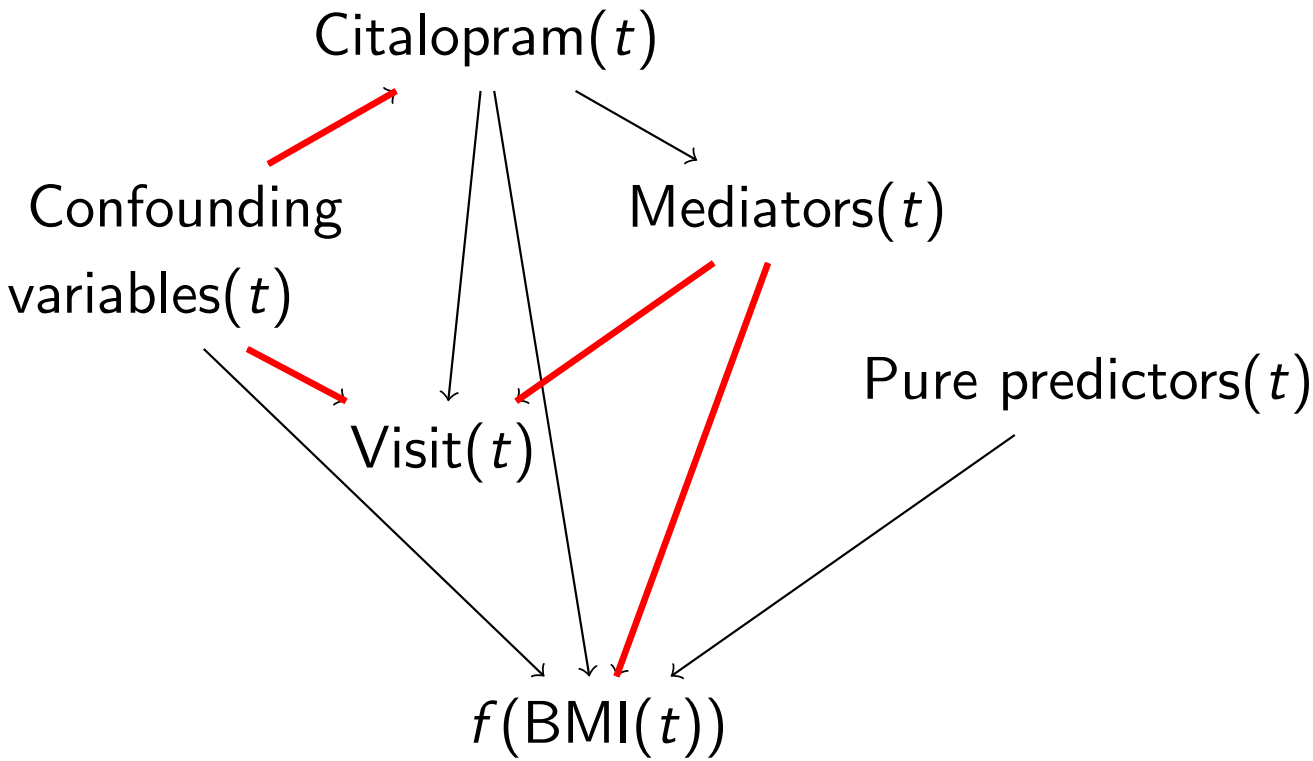

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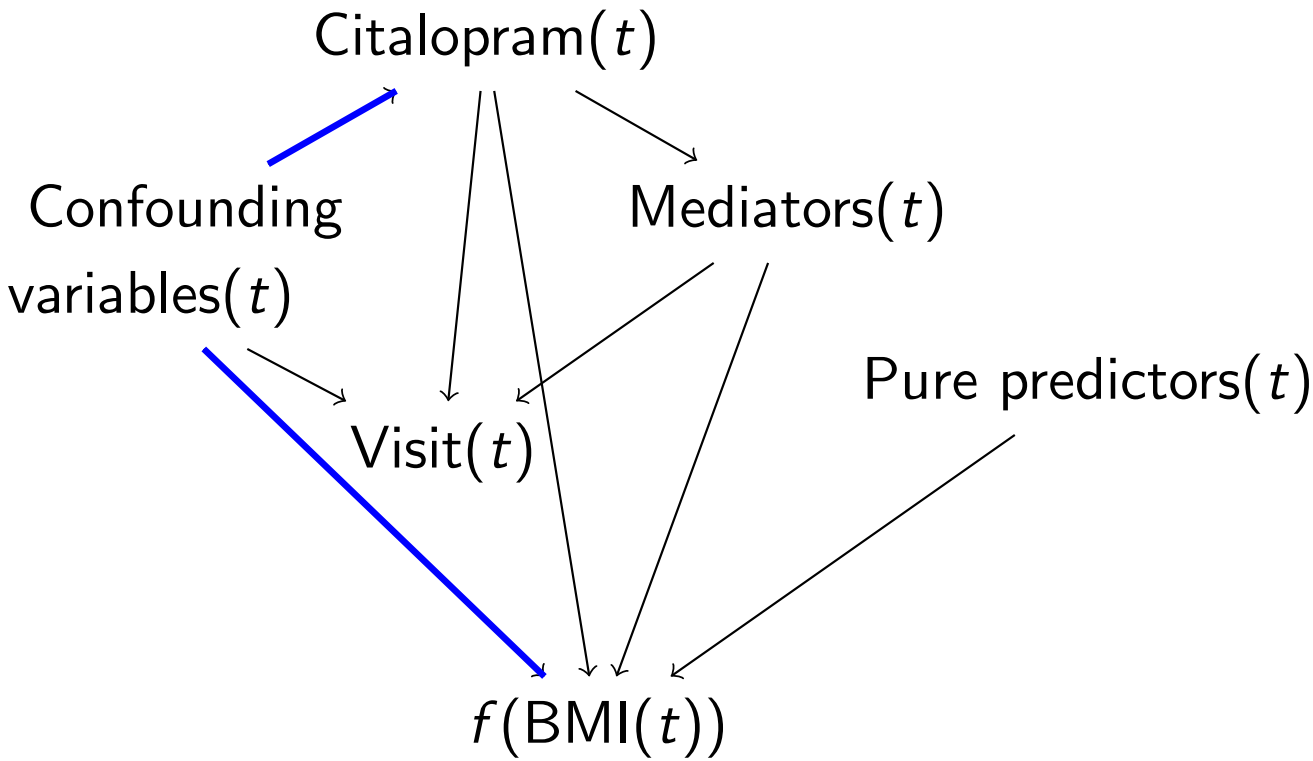

Methods

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Suppose a random sample of patients indexed by $i = 1, ..., n$. Let:

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- The effect modifiers $\mathbf{X}^{\psi}(\mathbf{t})$
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- $dN_i(t)$ the visit indicator ($=$ observation of $Y_i(t)$)
- C_i the follow-up time of patient i
- $\xi_i(t) = \mathbb{I}(C_i \geq t)$ the indicator for still being at risk

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- We assume $dN_i(t) \perp Y_i(t) | \mathbf{V_i(t)}$ a set of variables

The outcome model includes a treatment-free model and a blip:

$$\mathbb{E}[Y_i(t)|A_i(t), \mathbf{X}_i(t)] = f\left\{\mathbf{X}_i^{\beta}(t); \boldsymbol{\beta}\right\} + A_i(t)\boldsymbol{\psi}'\mathbf{X}_i^{\psi}(t).$$

The following rule:

"Treat with citalopram if the outcome expectation is optimized under citalopram, and with fluoxetine otherwise"

becomes

"Treat with citalopram if $\hat{\boldsymbol{\psi}}'\mathbf{X}_i^{\psi}(t) \geq 0$, and with fluoxetine otherwise."

- We use the potential outcome framework (Neyman, 1923; Rubin, 1974)
- Causal estimand: conditional treatment effect

$$\text{CTE} = \mathbb{E}[Y_{i1}(t) - Y_{i0}(t)|\mathbf{X}_\mathbf{i}^{\psi}(t)]$$

Causal assumptions

- Conditional exchangeability:

$$A_i(t) \perp \{Y_{i0}(t), Y_{i1}(t)\} \,|\mathbf{K_i(t)}, \mathbf{V_i(t)}, \mathbf{X}^{\psi}(\mathbf{t}), dN_i(t)$$

- Positivity:

$$0 < \mathbb{P}(A_i(t)|\mathbf{K_i(t)}, \mathbf{X}_{\mathbf{i}}^{\psi}) < 1$$

$$0 < \mathbb{P}(dN_i(t)|\mathbf{V_i(t)}) < 1$$

- Consistency:

$$Y_i(t) = A_i(t)\,Y_{i1}(t) + (1 - A_i(t))\,Y_{i0}(t)$$

Why?

Doubly weighted estimator

$$\mathbb{E}[Y_{i1}(t) - Y_{i0}(t)|\mathbf{X_i^\psi(t)}]$$

$$= \mathbb{E}_{\mathbf{V}}[\mathbb{E}_{\mathbf{K}}[\mathbb{E}[Y_{i1}(t)|\mathbf{K_i(t)}, \mathbf{V_i(t)}, \mathbf{X_i^\psi(t)}]]] - \mathbb{E}_{\mathbf{V}}[\mathbb{E}_{\mathbf{K}}[\mathbb{E}[Y_{i0}(t)|\mathbf{K_i(t)}, \mathbf{V_i(t)}, \mathbf{X_i^\psi(t)}]]]$$

$$= \mathbb{E}_{\mathbf{V}}[\mathbb{E}_{\mathbf{K}}[\mathbb{E}[Y_{i1}(t)|\mathbf{K_i(t)}, A_i(t) = 1, \mathbf{V_i(t)}, dN_i(t) = 1, \mathbf{X_i^\psi(t)}]]]$$

$$- \mathbb{E}_{\mathbf{V}}[\mathbb{E}_{\mathbf{K}}[\mathbb{E}[Y_{i0}(t)|\mathbf{K_i(t)}, A_i(t) = 0, \mathbf{V_i(t)}, dN_i(t) = 1, \mathbf{X_i^\psi(t)}]]]$$

$$= \mathbb{E}_{\mathbf{V}}[\mathbb{E}_{\mathbf{K}}[\mathbb{E}[Y_i(t)|\mathbf{K_i(t)}, A_i(t) = 1, \mathbf{V_i(t)}, dN_i(t) = 1, \mathbf{X_i^\psi(t)}]]]$$

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$$= \ldots$$

$$= \mathbb{E}\left[\frac{\mathbb{I}(A_i(t) = 1, dN_i(t) = 1)Y_i(t)}{\mathbb{P}(A_i(t) = 1|\mathbf{K_i(t)})\mathbb{P}(dN_i(t) = 1|\mathbf{V_i(t)})}|\mathbf{X_i^\psi(t)}\right]$$

$$- \mathbb{E}\left[\frac{\mathbb{I}(A_i(t) = 0, dN_i(t) = 1)Y_i(t)}{\mathbb{P}(A_i(t) = 0|\mathbf{K_i(t)})\mathbb{P}(dN_i(t) = 1|\mathbf{V_i(t)})}|\mathbf{X_i^\psi(t)}\right]$$

- We model observation times using the proportional rate model:

$$\mathbb{E}[dN_i(t)|\mathbf{V_i(t)}] = \xi_i(t)\exp\left\{\gamma'\mathbf{V_i(t)}\right\}\lambda_0(t)dt$$

where γ are estimated using the Andersen and Gill model (1982).

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- IIV weights are combined with inverse probability of treatment (IPT) weights:

$$e_i(\omega, \mathbf{K_i(t)}) = \frac{\mathbb{I}(A_i(t)=1)}{\mathbb{P}(A_i(t)=1|\mathbf{K_i(t)};\omega)} + \frac{\mathbb{I}(A_i(t)=0)}{\mathbb{P}(A_i(t)=0|\mathbf{K_i(t)};\omega)}.$$

- The estimating equation to solve (extension of the dWOLS proposed by Wallace and Moodie (2015)):

$$U(\boldsymbol{\beta}, \boldsymbol{\psi}; \hat{\boldsymbol{\gamma}}, \hat{\boldsymbol{\omega}}) = \sum_{i=1}^{n} \int_0^{\tau} \varphi_i(\hat{\boldsymbol{\gamma}}, \mathbf{V_i(t)}) e_i(\hat{\boldsymbol{\omega}}, \mathbf{K_i(t)})$$

$$\times \begin{bmatrix} \frac{\partial f\left\{\mathbf{X}_i^{\beta}(t); \boldsymbol{\beta}\right\}}{\partial \boldsymbol{\beta}} \\ A_i(t)\mathbf{X}_i^{\psi}(t) \end{bmatrix} \left[Y_i(t) - f\left\{\mathbf{X}_i^{\beta}(t); \boldsymbol{\beta}\right\} - A_i(t)\boldsymbol{\psi}'\mathbf{X}_i^{\psi}(t) \right] dN_i(t) = \mathbf{0}.$$

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- Note 1: Requires acute treatment effect, no carryover effect of subsequent treatments (Dong et al., 2021)
- Note 2: Doubly robust if the weights satisfy the balancing property and the blip is correctly specified (Wallace and Moodie, 2015) and if the observation model is correct

Simulation study

$$\mathbf{K_i} = \{K_{1i}, K_{2i}, K_{3i}\} \sim \{N(1,1), Bern(0,55), N(0,1)\}$$

$$A_i \sim Bern(p_i) \text{ with } p_i = \text{expit}\{0{,}5 + 0{,}55K_{1i} - 0{,}2K_{2i} - 1K_{3i}\}$$

$$Z_i(t) \sim \begin{cases} N(2,1) \text{ if } A_i = 1 \\ N(4,2) \text{ if } A_i = 0 \end{cases}$$

$$Q_i(t) \sim Bern(0.5)$$

$$Y_i(t) = \sqrt{(t/100)} - 2\, A_i + 2.5\{Z_i(t) - \mathbb{E}[Z_i(t)|A_i]\} +$$
$$0{,}4K_{i1i} + 0{,}05K_{2i} - 0{,}6K_{3i} + 0.5\{A_i \times Q_i(t)\} - 1\{A_i \times K_{1i}\} + \epsilon_i(t)$$

$$\text{where } \epsilon_i(t)|\phi_i \sim N(\phi_i, 0{,}01), \phi_i \sim N(0, 0{,}04)$$

$$dN_i(t) \sim Poisson(\lambda_i(t)),\ \lambda_i(t) = \eta_i \exp\{\gamma_A A_i + \gamma_Z Z_i(t) + \gamma_{K2} K_2 + \gamma_{K3} K_3\}$$

where η_i is a random effect, $(\gamma_A, \gamma_Z, \gamma_{K2}, \gamma_{K3})$ the dependence parameters

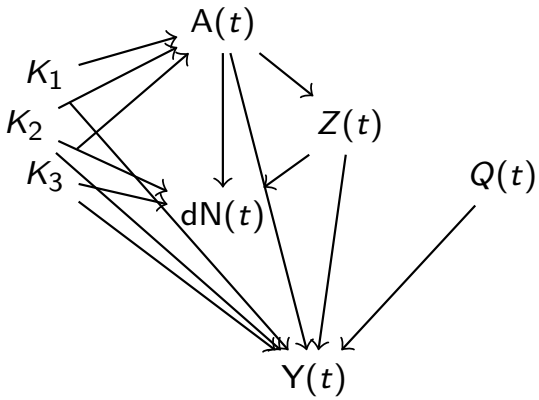
Estimators that were compared

To assess the method's robustness, we compare:

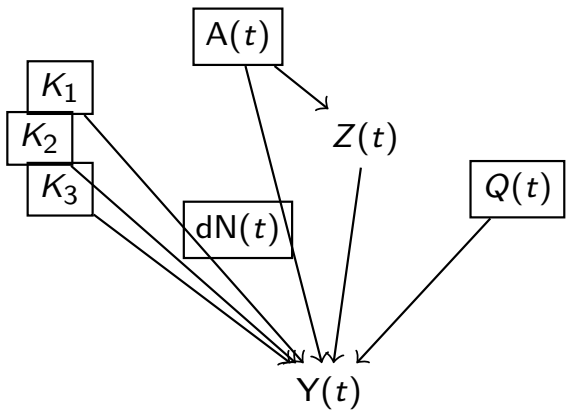
	Misspecified model (x)			
Estimator	Visit (partial[1])	Visit (full[2])	Treatment[3]	Outcome[4]
$\hat{\psi}_{DW1}$				
$\hat{\psi}_{DW2}$	x			x
$\hat{\psi}_{DW3}$	x		x	
$\hat{\psi}_{DW4}$		x		
$\hat{\psi}_{OLS}$		x	x	
$\hat{\psi}_{IPT}$		x		

1. Adjusted for the important variables (treatment and mediator)
2. Not adjusted for the mediator, adjusted for the treatment and K_2
3. Wrong functional form (squared terms) for the linear terms of K_1 and K_3
4. Misses the adjustment for K_2

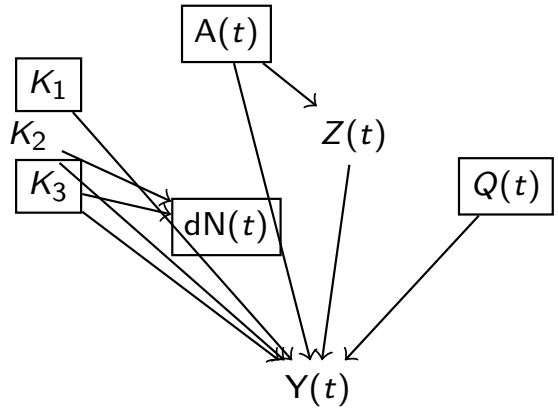
Corresponding causal diagrams



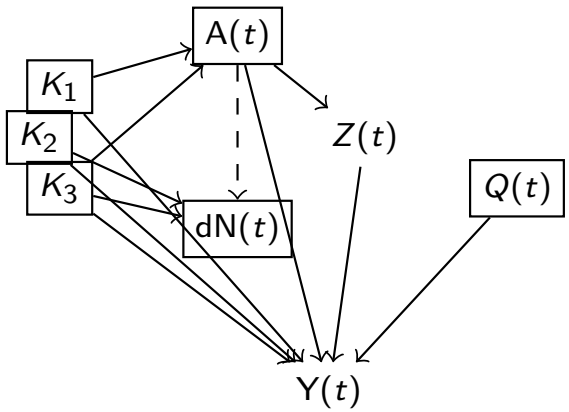
(a) Data generating mechanism



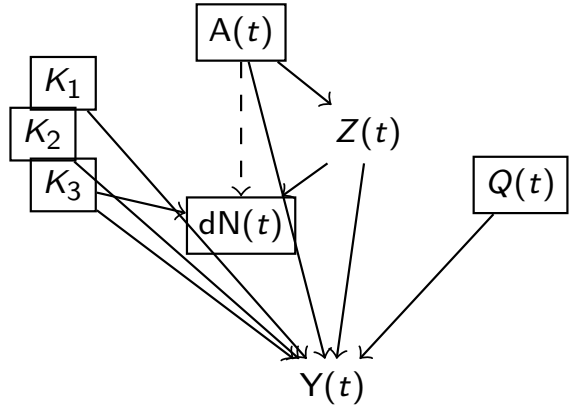
(b) Proposed estimator



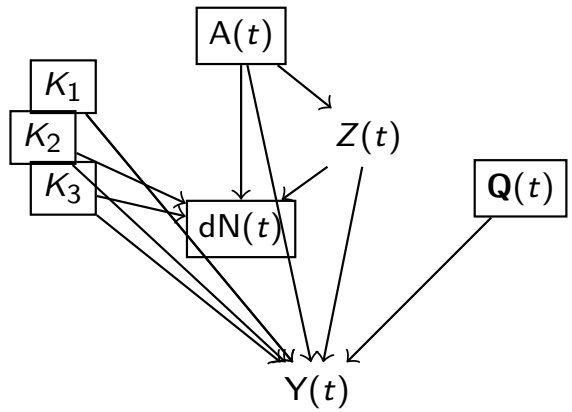
(c) Wrong observation and outcome models



(d) Wrong observation and treatment models



(e) Fully wrong observation model ($dN_i(t) \sim A(t) + K_2$)



(f) Only adjusted with IPT weights

Note: A box means that we condition upon that variable.

Results

Table 1: Results of the simulation study ($M = 1000$ simulations) - error rate for the optimal treatment decision

Sample size	Parameters γ^{υ}	No. obs. times mean (IQR)	Error rate $\hat{\psi}_{DW1}$	$\hat{\psi}_{DW2}$	$\hat{\psi}_{DW3}$	$\hat{\psi}_{DW4}$	$\hat{\psi}_{OLS}$	$\hat{\psi}_{IPT}$
250	1	3 (1-3)	0.02	0.01	0.01	0.04	0.03	0.04
	2	3 (2-5)	0.05	0.06	0.05	0.16	0.15	0.16
	3	6 (3-9)	0.06	0.03	0.03	0.26	0.25	0.26
	4	10 (8-12)	0.01	0.01	0.00	0.01	0.00	0.01
500	1	3 (1-3)	0.01	0.01	0.01	0.03	0.03	0.03
	2	3 (1-5)	0.02	0.03	0.02	0.14	0.13	0.14
	3	6 (3-9)	0.04	0.02	0.02	0.25	0.25	0.25
	4	10 (8-12)	0.00	0.00	0.00	0.00	0.00	0.00

υ.1. (-2, -0.3, 0.2, -1.2); 2. (0.3, -0.6, -0.4, -0.3); 3. (0.4, -0.8, 1, 0.6); 4. (0, 0, 0, 0).
Abbrev.: IQR, interquartile range.

Illustration

- Treatment rule to choose between citalopram (1) and fluoxetine (0) to reduce BMI variations
- Outcome definition:

$$U(t) = 100 - 5 \times \mathbb{I}[\,\text{Detrimental change in BMI}(t)\text{ category}\,]$$
$$+ \mathbb{I}[\,\text{BMI}(0) < 18.5 \cup (18.5 \leq \text{BMI}(0) \leq 24.9 \cap \text{BMI}(t) < 20)\,] \times \{\%\text{ increase BMI}(t)\}$$
$$- \mathbb{I}[\,\text{BMI}(0) \geq 25 \cup (18.5 \leq \text{BMI}(0) \leq 24.9 \cap \text{BMI}(t) > 23.5)\,] \times \{\%\text{ increase BMI}(t)\}\,,$$

  where $\mathbb{I}$ is the indicator function.
- 31,120 patients and 48,388 measures of $U(t)$
- There is indication of confounding and informative visits

Treatment rule

$$\text{Treat with citalopram if } -1.45 + 0.16 \times \mathbb{I}[\text{Male sex}]$$

$$+0.13 \times [\text{Index Multiple Deprivation}] + 0.08 \times \mathbb{I}[\text{Has been smoker}]$$

$$+0.42 \times \mathbb{I}[\text{Alcohol abuse}] + 1.31 \times \mathbb{I}[\text{Psychiatric disease}]$$

$$+0.35 \times \mathbb{I}[\text{Anxiety}] - 0.91 \times \mathbb{I}[\text{Use of antipsychotics}]$$

$$+0.30 \times \mathbb{I}[\text{Other psychotropics}] + 0.21 \times \mathbb{I}[\text{Lipid lowering drugs}] > 0$$

Table 2: Comparison of fitted outcomes, CPRD, 1998-2017

	Mean fitted outcome (SE)			
Treatment	$\hat{\psi}_{OLS}$	$\hat{\psi}_{IPT}$	$\hat{\psi}_{IIV}$	$\hat{\psi}_{DW1}$
Received	98.2 (0.001)	98.2 (0.001)	98.3 (0.001)	98.3 (0.001)
Optimal	98.9 (0.001)	98.9 (0.001)	99.1 (0.001)	99.0 (0.001)

Abbrev.: SE, standard error.

Discussion

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- Individualized treatment rules can be used to optimize a treatment decision according to patient characteristics
- In a standard analysis, we condition on the indicator of being observed (the causal diagram is a useful tool!)
- The methods discussed rely on the following assumptions:
  - causal assumptions
  - on the data generating mechanism
  - time window for the treatment effect
  - on the several models
- Extension: Rule for a sequence of treatments (multiple time points)

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HEALTHY BRAINS HEALTHY LIVES

NIH National Institute of Mental Health

McGill UNIVERSITY

Contact:
janie.coulombe@umontreal.ca

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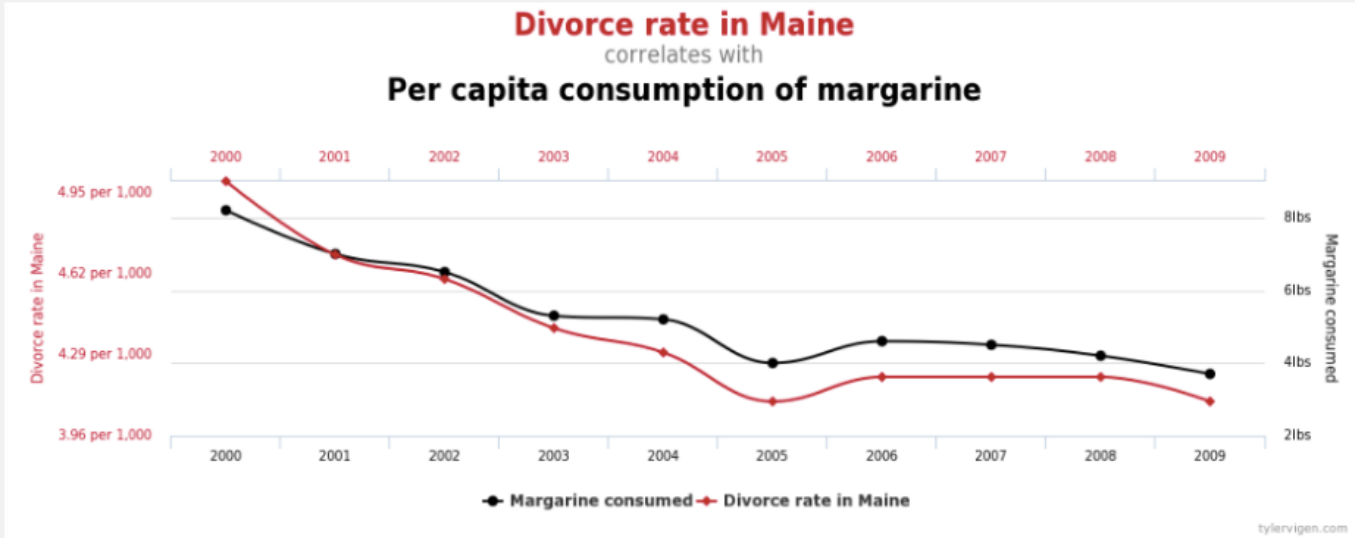
Blip evaluated in different patients

Male sex (yes)	IMD (1 to 5)	Ever smoker (yes)	Alcohol abuse (yes)	Psychiatric diagnosis (yes)	Anxiety (yes)	Antipsy. drug (yes)	Psychotro. drug (yes)	Lipid lowering drug (yes)	Value blip function
0	1	0	0	0	0	1	0	0	-2.23
1	1	0	0	0	0	1	0	0	-2.07
0	3	0	0	0	0	1	1	1	-1.46
0	1	0	0	0	0	0	0	0	-1.32
1	3	0	0	0	0	1	1	1	-1.30
1	1	0	0	0	0	0	0	0	-1.16
0	3	1	0	0	0	0	0	0	-0.98
1	3	1	0	0	0	0	0	0	-0.82
0	5	0	0	0	0	0	0	0	-0.80
0	3	0	0	0	1	0	0	0	-0.71
1	5	0	0	0	0	0	0	0	-0.64
0	3	1	1	0	0	0	0	0	-0.56
1	3	0	0	0	1	0	0	0	-0.55
1	3	1	1	0	0	0	0	0	-0.40
0	5	1	1	0	0	0	0	0	-0.30
1	5	1	1	0	0	0	0	0	-0.14
0	3	0	1	1	0	0	0	0	0.67
0	3	1	1	1	0	0	0	0	0.75
1	3	0	1	1	0	0	0	0	0.83
0	3	1	0	1	1	0	0	1	0.89
1	3	1	1	1	0	0	0	0	0.91
0	3	0	1	1	1	0	0	0	1.02
0	5	1	1	1	0	0	0	0	1.01
1	3	1	0	1	1	0	0	1	1.05
1	5	1	1	1	0	0	0	0	1.17
1	3	0	1	1	1	0	0	0	1.18
1	5	1	1	1	1	0	1	1	2.03

Confounder variable

Divorce And Margarine

Posted on April 10, 2017 by annahaensch

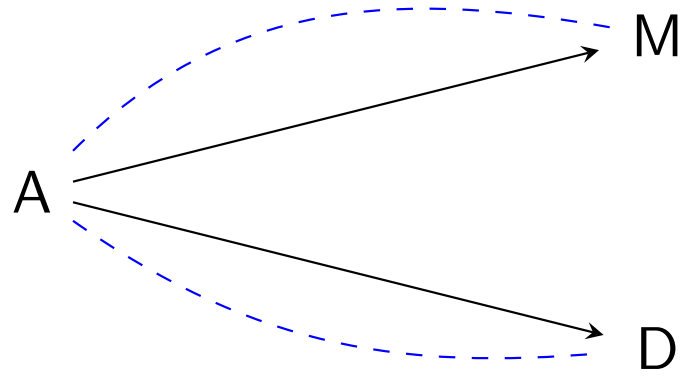


A spurious correlation involving a spurious butter substitute. Via tylervigen.com.

Source: blogs.ams.org

Confounder A: Interest in the relationship M-D

No adjustment: M and D dependent



If we model $M|A$ and adjust (e.g., IPT weights):

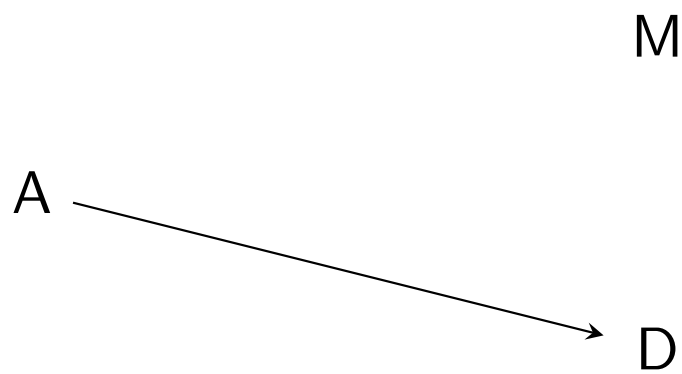


Table 3: Coefficients of the blip function (95% bootstrap CIs) for the optimal treatment rules as estimated by four alternative models: OLS which does not adjust for confounding or observation process, IPW which accounts only for confounding, IIV which accounts only for the observation process, and the proposed doubly-weighted estimator which accounts for both processes, CPRD, UK, 1998-2017, n=31,120 individuals.

Variable	$\hat{\psi}_{OLS}$	$\hat{\psi}_{IPT}$	$\hat{\psi}_{IIV}$	$\hat{\psi}_{DW}$
Intercept	-1.66 (-2.69, -0.46)	-1.38 (-2.62, -0.11)	-1.68 (-2.84, -0.58)	-1.45 (-2.66, -0.22)
Age	0.01 (-0.01, 0.03)	0.00 (-0.01, 0.03)	0.01 (-0.01, 0.03)	0.00 (-0.02, 0.03)
Male sex	-0.08 (-0.67, 0.55)	0.03 (-0.59, 0.62)	0.03 (-0.54, 0.65)	0.16 (-0.48, 0.76)
IMD	0.14 (-0.09, 0.31)	0.14 (-0.13, 0.32)	0.12 (-0.10, 0.31)	0.13 (-0.13, 0.31)
Ever smoker	0.23 (-0.38, 0.66)	0.13 (-0.47, 0.65)	0.21 (-0.41, 0.66)	0.08 (-0.50, 0.60)
Alcohol abuse	1.03 (-0.11, 2.24)	0.68 (-0.48, 1.88)	0.78 (-0.26, 1.99)	0.42 (-0.70, 1.60)
Psychiatric disease†	0.44 (-1.83, 2.10)	1.02 (-1.23, 2.84)	0.58 (-1.73, 1.93)	1.31 (-0.88, 3.05)
Anxiety	0.29 (-0.07, 1.12)	0.31 (-0.02, 1.21)	0.32 (-0.05, 1.15)	0.35 (0.00, 1.26)
Medication				
Antipsychotics	-0.73 (-1.56, 0.17)	-0.82 (-1.75, 0.10)	-0.78 (-1.61, 0.10)	-0.91 (-1.91, 0.03)
Other psychotropic drugs‡	0.03 (-0.81, 0.66)	0.07 (-0.73, 0.64)	0.22 (-0.49, 0.86)	0.30 (-0.47, 0.93)
Lipid lowering drugs	-0.16 (-0.73, 0.76)	0.04 (-0.70, 0.97)	-0.02 (-0.57, 0.95)	0.21 (-0.49, 1.23)

Abbreviations: CI, confidence interval; CPRD, Clinical Practice Research Datalink; UK, United Kingdom; IMD, Index of Multiple Deprivation.

†. An indicator for a diagnosis of either autism spectrum disorder, obsessive compulsive disorder, bipolar disorder, or schizophrenia.

‡. Which include benzodiazepine drugs, anxiolytics, barbiturates and hypnotics.

Doubly robust - intuition

Using correctly specified IPT weights make $A_i(t)$ and $\mathbf{X}_i^{\beta}(t)$ independent in

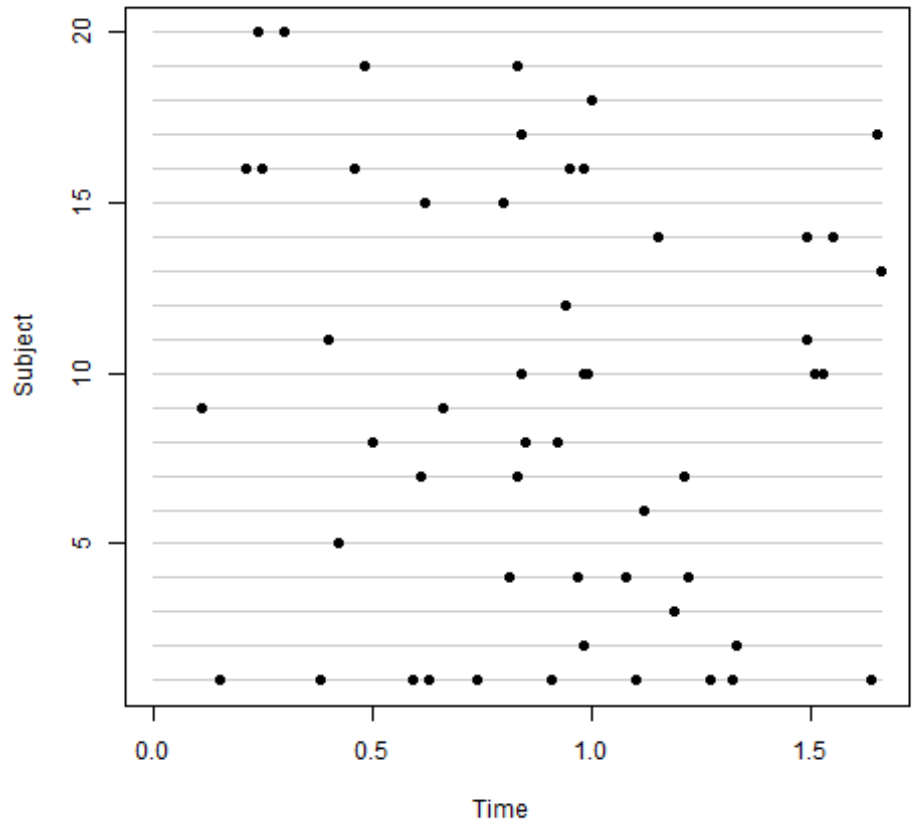
$$\mathbb{E}[Y_i(t)|A_i(t), \mathbf{X}_i(t)] = \underbrace{f\left\{\mathbf{X}_i^{\beta}(t); \boldsymbol{\beta}\right\}}_{\text{contains confounders}} + A_i(t)\boldsymbol{\psi}'\mathbf{X}_i^{\psi}(t).$$

Hence, the coefficients $\boldsymbol{\psi}$ can be estimated consistently even if $f\left\{\mathbf{X}_i^{\beta}(t); \boldsymbol{\beta}\right\}$ is wrongly specified (and vice versa if $f\left\{\mathbf{X}_i^{\beta}(t); \boldsymbol{\beta}\right\}$ is correctly specified, but not the IPT weights).

Of note, the observation model must be correctly specified, at least w.r.t. a set of important variables ("**partial**" double robustness).

Simulation study

Visits are simulated according to a **proportional rate model**:



Abacus plot produced with the `IrregLong` package in R (Pullenayegum, 2022)

Résultats

Table 4: Results of the simulation study ($M = 1000$ simulations) - absolute bias of the blip evaluated at the values of $Q(t)$ and K_1

Sample size	Parameters γ^{υ}	No. obs. times mean (IQR)	Absolute bias $\hat{\psi}_{DW1}$	$\hat{\psi}_{DW2}$	$\hat{\psi}_{DW3}$	$\hat{\psi}_{DW4}$	$\hat{\psi}_{OLS}$	$\hat{\psi}_{IPT}$
250	1	3 (1-3)	0.58	0.50	0.42	0.76	0.74	0.76
	2	3 (1-5)	1.00	1.07	0.97	1.57	1.53	1.57
	3	6 (3-9)	1.14	0.87	0.83	2.04	2.06	2.06
	4	10 (8-12)	0.24	0.24	0.21	0.24	0.19	0.24
1000	1	3 (1-3)	0.33	0.27	0.21	0.68	0.72	0.67
	2	3 (1-5)	0.55	0.60	0.53	1.50	1.49	1.50
	3	6 (3-9)	0.69	0.48	0.46	2.03	2.04	2.04
	4	10 (8-12)	0.12	0.12	0.10	0.12	0.09	0.12
2500	1	3 (1-3)	0.23	0.18	0.14	0.66	0.71	0.66
	2	3 (2-5)	0.36	0.40	0.35	1.51	1.51	1.50
	3	6 (3-9)	0.52	0.34	0.32	2.04	2.05	2.05
	4	10 (8-12)	0.08	0.08	0.07	0.08	0.06	0.08

υ.1. (-2, -0.3, 0.2, -1.2); 2. (0.3, -0.6, -0.4, -0.3); 3. (0.4, -0.8, 1, 0.6); 4. (0, 0, 0, 0).
Abbrev.: IQR, interquartile range.

Note. The bias of the blip evaluated at $Q(t)$ and K_1 depends on the values of $Q(t)$ and K_1. It might be more relevant to study the coefficients bias (results not shown).

Table 5: Characteristics of the 31,120 patients, n (%), CPRD, 1998-2017

Variable	Citalopram (n=18,671)	Fluoxetine (n=12,449)
Year of cohort entry		
1998-2005	3751 (20)	4896 (39)
2006-2011	10,279 (55)	5703 (46)
2012-2017	4641 (25)	1850 (15)
Anxiety	5956 (32)	2987 (24)
Antipsychotics	2836 (15)	1675 (13)
Other psychotropics	4476 (24)	2546 (20)
Lipid-lowering drugs	3360 (18)	1614 (13)

Table 6: Rate ratios (95% CIs) for the observation of $U(t)$, CPRD, 1998-2017

Variable	RR (95% CI)
Citalopram treatment	0.9 (0.9, 0.9)
Sex (M)	0.9 (0.9, 0.9)
Index of Multiple Deprivation	1.0 (1.0, 1.0)
Year of cohort entry (ref.= <2006)	
2006-2011	0.9 (0.9, 1.0)
2012-2017	0.9 (0.9, 0.9)
Has been a smoker	1.7 (1.6, 1.7)
Antipsychotics	1.1 (1.0, 1.2)
Other psychotropics	1.2 (1.2, 1.3)
Lipid-lowering drugs	1.2 (1.2, 1.3)