Dealing with Treatment-confounder Feedback & Sparse Follow-up in Longitudinal Studies:

Application of a marginal structural model in a multiple sclerosis cohort

Online view: tinyurl.com/epi21ms
Poll: pollev.com/ehsank878

M. Ehsan Karim
ehsan.karim@ubc.ca
UBC School of Population and Public Health

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ehsank.com

Acknowledgements

a place of mind

UBC

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How familiar are you with Multiple Sclerosis (MS) disease?

I do not know about MS at all

I have heard about MS, don't know a lot

I am very familiar with MS

Case Study

Multiple sclerosis (MS)

- damage of nerve cells
- chronic disease
- considerable disability
- has no known cure

Case Study

Multiple sclerosis (MS)

- damage of nerve cells
- chronic disease
- considerable disability
- has no known cure

beta interferon (IFNb)

- regular injections
- long-term use
- potential side effects
- Risk vs. benefit

Data and Measurements

- BC Cohort
  - Relapsing onset MS patients; adults
  - Registered in BC MS clinics 1980-2004: 4 clinics
  - linked administrative data
    - PharmaNet (*prescriptions*)
    - BC vital statistics (*death*)
    - BC Medical Services Plan (*physician visit & diagnoses*)
    - BC Discharge Abstract Database (*hospital admission/discharge*)
    - Registration and Premium Billing Files (*registration, SES*)
- Longitudinal study follow-up
  - **1996-2013** (*universal, publicly funded health-care system*)

Case Study

3 objectives in the case study

Survival advantage associated with **IFNb** exposure?

Effective in **older population**?

How to deal with **sparse follow-up**?

Analytic challenges

3 learning outcomes

Dealing with **time-dependent** confounders [*Most time*]

Effect modification by age, disease duration and sex

Imputation to deal with irregular measurement schedule

3,413
Relapsing onset eligible patients

43 (36-50)
Median age (IQR)

27%
exposed to IFNb (*all preparations*)

66%
Remained unexposed

566
Deaths by the end of follow-up

~76%
Female

1

Survival advantage associated with **IFNb** exposure?

IFNb - Mortality association

How does the process work? 

Understanding of that will dictate our analysis strategy.

1 IFNb - Mortality association

MS Outcomes

- Conventional
  - Relapse
  - Disease progression

- measurement error,
- recall bias and
- differential training

- Time to death (all-cause)
  - Reliable data
  - long-term outcome
  - population-based vital statistics data

1 IFNb - Mortality association

Exposure

- Contiguous IFNb exposure for ≥ 6 months
- Immortal time bias?
  - Ever-never?
  - misclassification?

A recommended treatment algorithm in relapsing multiple sclerosis: report of ar international consensus meeting

D Karussis, LD Biermann, S Bohlega... - European journal of ..., 2006 - Wiley Online Library

An International Working Group for Treatment Optimization in MS met to recommend evidence-based therapeutic options for the management of suboptimal responses or intolerable side-effects in patients treated with disease-modifying drugs (DMDs) for multiple sclerosis (MS). Several DMDs are now available for the treatment of MS that have been shown to alter the clinical course of the disease by decreasing disease activity and delaying the progression of disability. Nevertheless, many patients continue to experience disease ...

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Assumption:
Minimum expected duration of exposure (**6 months**) to yield a clinical response (**survival**).

1 IFNb - Mortality association

- Goodin et al. (2012):
  - 366 RRMS,
  - 81 deaths
  - 21 years
  - post hoc analyses
- Tsai and Lee (2013):
  - 1,149 MS,
  - 88 deaths;
  - immortal time
- Kingwell et al. (2019):
  - nested case control
  - Baseline covariates

Survival in MS: a randomized cohort study 21 years after the start of the pivotal IFNβ-1b trial

DS Goodin, AT Reder, GC Ebers, G Cutter… - Neurology, 2012 - AAN Enterprises

Objective: To examine the effects of interferon beta (IFNβ)-1b on all-cause mortality over 21 years in the cohort of 372 patients who participated in the pivotal randomized clinical trial (RCT), retaining (in the analysis) the original randomized treatment-assignments. Methods: For this randomized long-term cohort study, the primary outcome, defined before data collection, was the comparison of all-cause mortality between the IFNβ-1b 250 μg and placebo groups from the time of randomization through the entire 21-year follow-up interval …

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Impact of disease-modifying therapies on the survival of patients with multiple sclerosis in Taiwan, 1997–2008

CP Tsai, CTC Lee - Clinical drug investigation, 2013 - Springer

Background Little is known about the impact of disease-modifying therapies (DMTs) on the survival of patients with multiple sclerosis (MS) throughout the world. Objective We conducted this study to investigate the association between DMTs and the survival of patients with MS in Taiwan. Methods A total of 1,240 individuals who had a primary diagnosis of MS and a seriously disabling disease certificate in Taiwan between 1 January 1997 and 1 December 2008 were followed up until 31 December 2009 to check what …

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Multiple sclerosis: effect of beta interferon treatment on survival

E Kingwell, E Leray, F Zhu, J Petkau, G Edan, J Oger… - Brain, 2019 - academic.oup.com

Worldwide, the beta interferons remain the most commonly prescribed disease-modifying drugs for multiple sclerosis. However, it is unclear if they alter survival. We investigated the association between beta interferon and mortality in the 'real-world'setting. This was a multi-centre population-based observational study of patients with relapsing-onset multiple sclerosis who were initially registered at a clinic in British Columbia, Canada (1980–2004) or Rennes, France (1976–2013). Data on this cohort were accessed from the clinical …

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1 IFNb - Mortality association

IFNb → Death

Primary association of interest

Examining the effects of comorbidities on disease-modifying therapy use in multiple sclerosis

T Zhang, H Tremlett, S Leung, F Zhu, E Kingwell… - Neurology, 2016 - AAN Enterprises

Objective: Comorbidities are common in multiple sclerosis (MS) and adversely affect health outcomes. However, the effect of comorbidity on treatment decisions in MS remains unknown. We aimed to examine the effects of comorbidity on initiation of injectable disease-modifying therapies (DMTs) and on the choice of the initial DMT in MS. Methods: We conducted a retrospective observational analysis using population-based health administrative and linked clinical databases in 3 Canadian provinces. MS cases were …

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1 IFNb - Mortality association

- MS population: higher comorbidity

Comorbidity

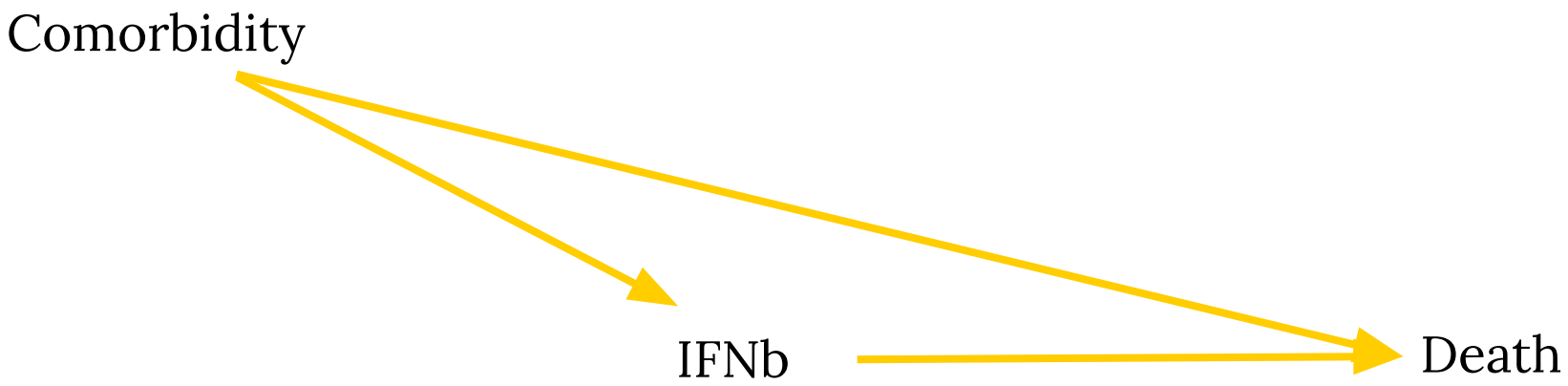
- Likelihood of initiating IFNb vs. burden of comorbidity
- cumulative comorbidities impact survival

IFNb → Death

- anti-oxidative properties
- reduce risk of infections

Addressing confounding

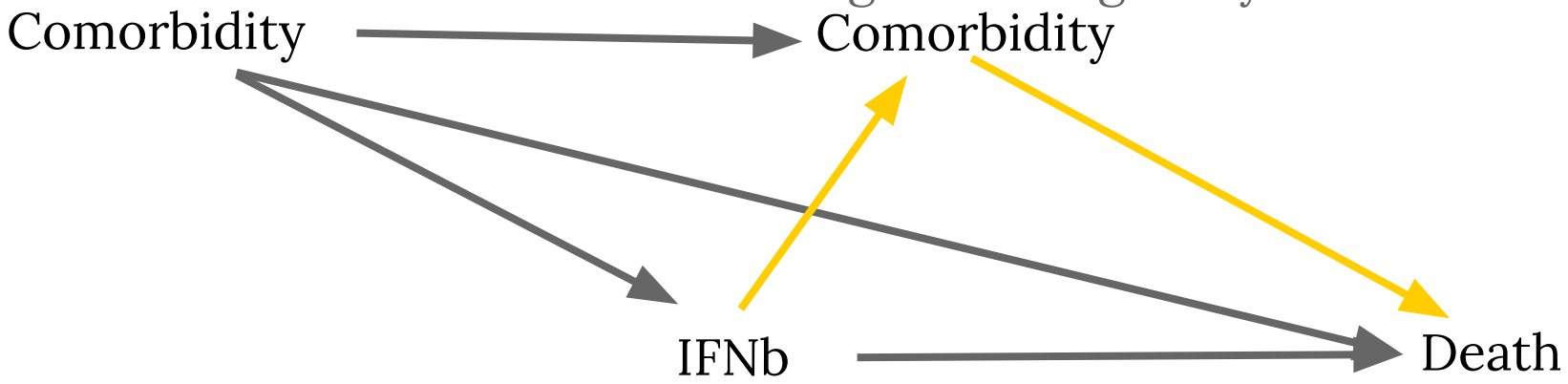
1 IFNb - Mortality association



Addressing confounding: Death ~ IFNb + Comorbidity

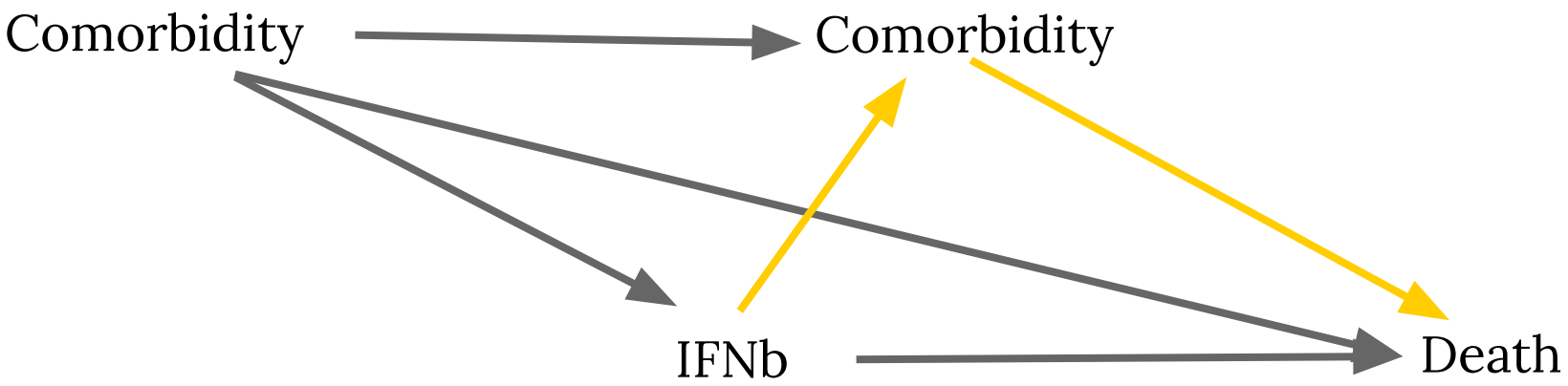
1 IFNb - Mortality association

- IFNb side effects
- Long term usage may influence risk



Addressing confounding + Mediator: Time-varying confounding

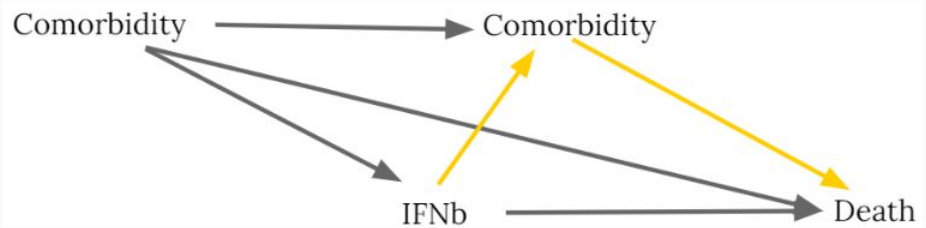
1 IFNb - Mortality association



Addressing confounding + Mediator:

(1) Death ~ IFNb + Comorbidity?
(2) Death ~ IFNb?
(3) None of the above

What should be the analytic strategy?



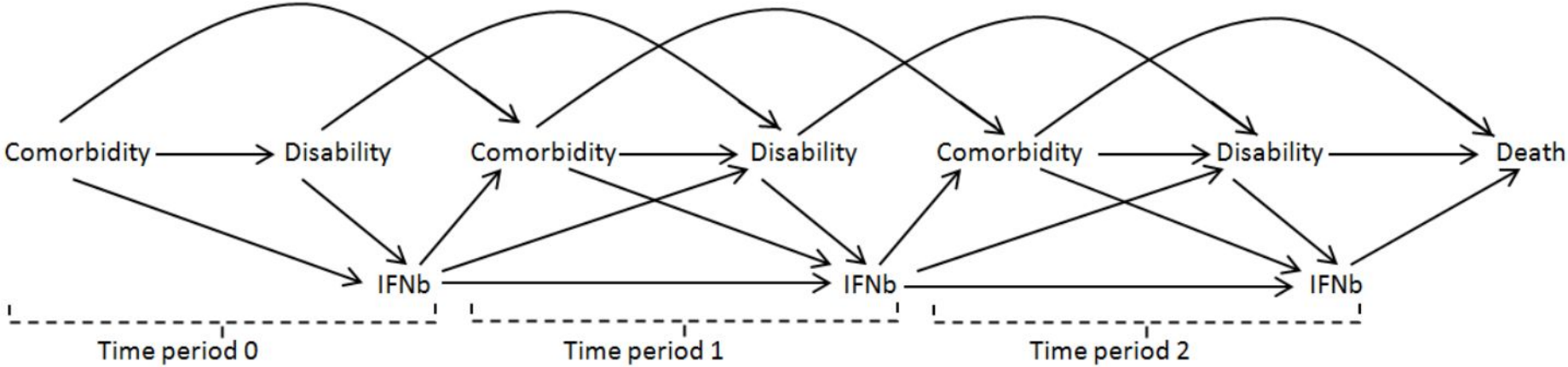
Death ~ IFNb + Comorbidity

Death ~ IFNb

None of the above

Marginal Structural Model

1 IFNb - Mortality association



- IFNb reduces relapse; which may contribute to lower disability
- Relapse used as an eligibility criteria to reimburse IFNb

Treatment-confounder feedback

How familiar are you with Marginal Structural Models (MSM)?

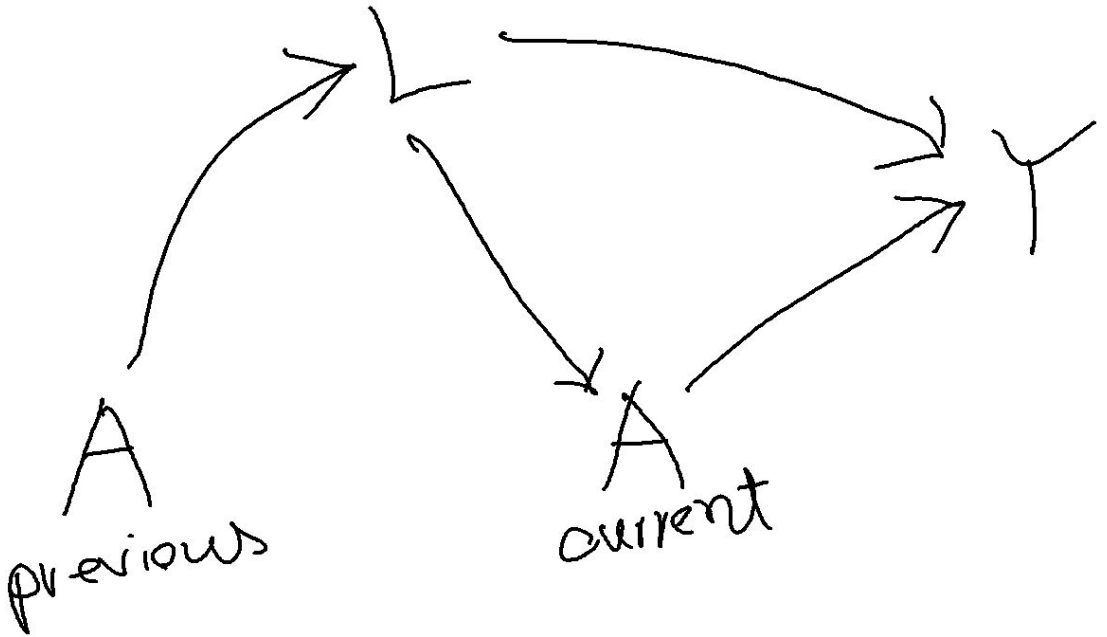
I am an expert in MSM: applied MSM in studies

I have heard about MSM; but tell me more

I don't know about it; tell me

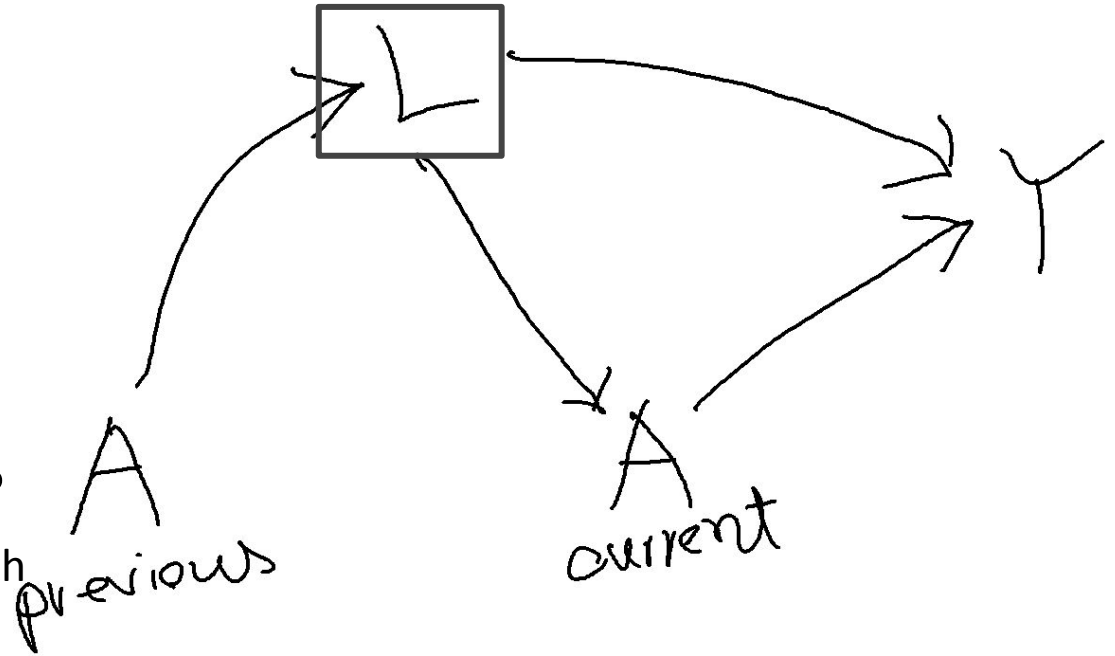
1 Brief Tutorial: Notations

- A = Treatment
- Y = Outcome
- L = Time-varying confounder



1 Cox regression?

- A = Treatment
- Y = Outcome
- L = Time-varying confounder



Solution 1: Conditioning?

(Why not Cox regression with time-updated covariates?)

Simulation from a known Cox MSM using standard parametric models for the g-formula

JG Young, EJ Tchetgen Tchetgen - Statistics in medicine, 2014 - Wiley Online Library

It is routinely argued that, unlike standard regression-based estimates, inverse probability weighted (IPW) estimates of the parameters of a correctly specified Cox marginal structural model (MSM) may remain unbiased in the presence of a time-varying confounder affected by prior treatment. Previously proposed methods for simulating from a known Cox MSM lack knowledge of the law of the observed outcome conditional on the measured past. Although unbiased IPW estimation does not require this knowledge, standard regression-based …

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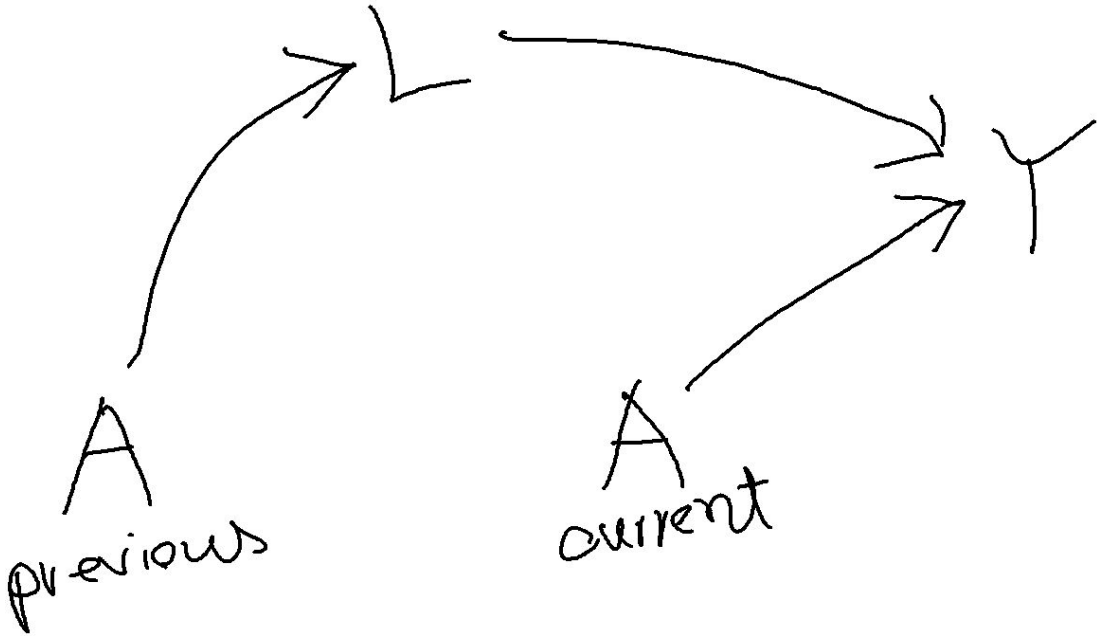
1 Simulation as a tool to explain!

Simplistic simulation: https://ehsanx.github.io/MSMsim/

- A = Treatment
- Y = Outcome
- L = Time-varying confounder

Solution 2: MSM

(*in pseudo-population*)



1 Data Setup

id	Month	A	L	Y
1	$t_0=0$	$a_0=0$	$l_0=0$	$y_0=0$
1	$t_1=1$	$a_1=0$	$l_1=0$	$y_1=0$
1	$t_2=2$	$a_2=0$	$l_2=1$	$y_2=0$
1	$t_3=3$	$a_3=1$	$l_3=1$	$y_3=0$
1	$t_4=4$	$a_4=1$	$l_4=0$	$y_4=1$

- Long format data set up
- Multiple observations per patient
- Data for subject 1
- Warning:
  Equations in next few slides!!

Controlling for time-dependent confounding using marginal structural models
Z Fewell, MA Hernán, F Wolfe, K Tilling… - The Stata …, 2004 - journals.sagepub.com
Longitudinal studies in which exposures, confounders, and outcomes are measured repeatedly over time have the potential to allow causal inferences about the effects of exposure on outcome. There is particular interest in estimating the causal effects of medical treatments (or other interventions) in circumstances in which a randomized controlled trial is difficult or impossible. However, standard methods for estimating exposure effects in longitudinal studies are biased in the presence of time-dependent confounders affected by …
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1 (Exposure) weight models

id	Month	A	L	Y	Denominator model	IPW (unstabilized)
1	$t_0=0$	$a_0=0$	$l_0=0$	$y_0=0$		
1	$t_1=1$	$a_1=0$	$l_1=0$	$y_1=0$	$p_1 = P(A=a_1 \mid a_0,l_0,l_1)$	$w_1=1/p_1$
1	$t_2=2$	$a_2=0$	$l_2=1$	$y_2=0$		
1	$t_3=3$	$a_3=1$	$l_3=1$	$y_3=0$		
1	$t_4=4$	$a_4=1$	$l_4=0$	$y_4=1$		

Controlling for time-dependent confounding using marginal structural models
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1	$t_1=1$	$a_1=0$	$l_1=0$	$y_1=0$	$p_1 = P(A=a_1 \mid a_0,l_0,l_1)$	$w_1=1/p_1$
1	$t_2=2$	$a_2=0$	$l_2=1$	$y_2=0$	$p_2 = P(A=a_2 \mid a_1,l_0,l_1,l_2)$	$w_2=1/(p_1*p_2)$
1	$t_3=3$	$a_3=1$	$l_3=1$	$y_3=0$		
1	$t_4=4$	$a_4=1$	$l_4=0$	$y_4=1$		

Controlling for time-dependent confounding using marginal structural models
Z Fewell, MA Hernán, F Wolfe, K Tilling… - The Stata …, 2004 - journals.sagepub.com
Longitudinal studies in which exposures, confounders, and outcomes are measured repeatedly over time have the potential to allow causal inferences about the effects of exposure on outcome. There is particular interest in estimating the causal effects of medical treatments (or other interventions) in circumstances in which a randomized controlled trial is difficult or impossible. However, standard methods for estimating exposure effects in longitudinal studies are biased in the presence of time-dependent confounders affected by …
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1 (Exposure) weight models

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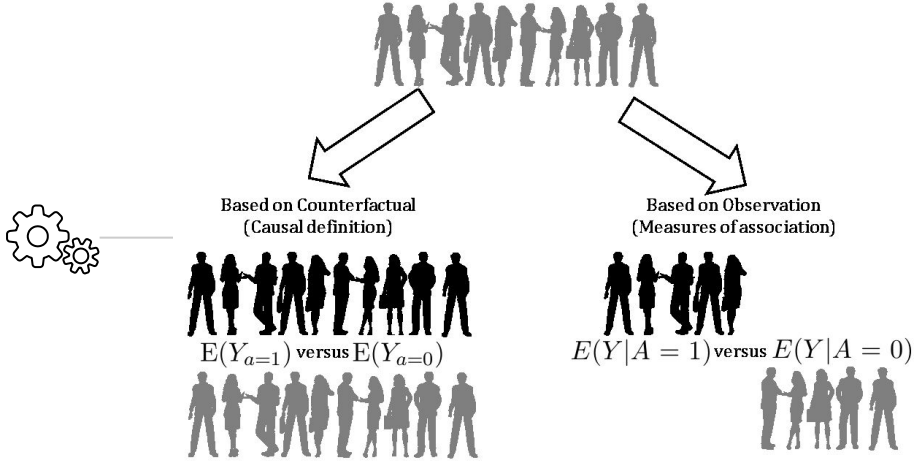
1	$t_0=0$	$a_0=0$	$l_0=0$	$y_0=0$		
1	$t_1=1$	$a_1=0$	$l_1=0$	$y_1=0$	$p_1 = P(A=a_1 \mid a_0,l_0,l_1)$	$w_1=1/p_1$
1	$t_2=2$	$a_2=0$	$l_2=1$	$y_2=0$	$p_2 = P(A=a_2 \mid a_1,l_0,l_1,l_2)$	$w_2=1/(p_1*p_2)$
1	$t_3=3$	$a_3=1$	$l_3=1$	$y_3=0$	$p_3 = P(A=a_3 \mid a_2,l_0,l_2,l_3)$	$w_3=1/(p_1*p_2*p_3)$
1	$t_4=4$	$a_4=1$	$l_4=0$	$y_4=1$	$p_4 = 1$	$w_4=1/(p_1*p_2*p_3*p_4)$

1 (Exposure) weight models

id	Month	Numerator model	Denominator model	IPW (stabilized)
1	$t_0=0$			
1	$t_1=1$	$p_{10} = P(A=a_1 \mid a_0,l_0)$	$p_1 = P(A=a_1 \mid a_0,l_0,l_1)$	$w_1=p_{10}/p_1$
1	$t_2=2$	$p_{20} = P(A=a_2 \mid a_1,l_0)$	$p_2 = P(A=a_2 \mid a_1,l_0,l_1,l_2)$	$w_2=(p_{10}*p_{20})/(p_1*p_2)$
1	$t_3=3$	$p_{30} = P(A=a_3 \mid a_2,l_0)$	$p_3 = P(A=a_3 \mid a_2,l_0,l_2,l_3)$	$w_3=(p_{10}*p_{20}*p_{30})/(p_1*p_2*p_3)$
1	$t_4=4$	$p_{40} = 1$	$p_4 = 1$	$w_4=(p_{10}*p_{20}*p_{30}*p_{40})/(p_1*p_2*p_3*p_4)$

1 MSM steps



MSM Fitting:

Step 1: Denominator weight model: $A \sim t + A_{lag} + L_0 + L + L_{lag}$

Step 2: Numerator weight model: $A \sim t + A_{lag} + L_0$

Step 3: Obtain predictions from the model fits

Step 4: Convert them using IPW formula and multiply over time

Step 5: Weighted outcome model $Y \sim A + L_0$

Estimates from pseudo-population (impact of L reduced)

1 MSM coding

MSM Fitting: https://ehsanx.github.io/MSMsim/

```r
# Step 1: Weight denominator model
ww <- glm(A ~ tpoint + Alag + L0 + L + Llag, family = binomial(logit),
          data = aggregate.data)
# Step 2: Weight numerator model
ww0 <- glm(A ~ tpoint + Alag + L0, family = binomial(logit),
           data = aggregate.data)
# Step 3: Obtain predictions from the models
aggregate.data$wwp <- with(aggregate.data,
                           ifelse(A == 0, 1 - fitted(ww), fitted(ww)))
aggregate.data$wwp0 <- with(aggregate.data,
                            ifelse(A == 0, 1 - fitted(ww0),fitted(ww0)))
# Step 4: Calculate time-dependent IPWs
aggregate.data$sw <- unlist(tapply(aggregate.data$wwp0/aggregate.data$wwp,
                                   aggregate.data$id, cumprod))
# Step 5: Weighted outcome model
fit.msm <- coxph(Surv(tpoint0, tpoint, Y) ~ A + L0 + cluster(id),
                 data = aggregate.data, weight = sw, robust = TRUE)
```

Simulation from a known Cox MSM using standard parametric models for the g-formula

JG Young, EJ Tchetgen Tchetgen - Statistics in medicine, 2014 - Wiley Online Library

It is routinely argued that, unlike standard regression-based estimates, inverse probability weighted (IPW) estimates of the parameters of a correctly specified Cox marginal structural model (MSM) may remain unbiased in the presence of a time-varying confounder affected by prior treatment. Previously proposed methods for simulating from a known Cox MSM lack knowledge of the law of the observed outcome conditional on the measured past. Although unbiased IPW estimation does not require this knowledge, standard regression-based …

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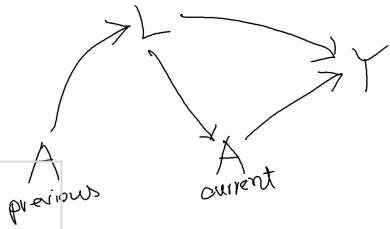
1 Marginal Structural Model



Simplistic simulation: https://ehsanx.github.io/MSMsim/

Method	Weight max	Percent Bias
Unadjusted Cox	-	5.8%
L Adjusted Cox	-	-2.3%
MSM (unstabilized)	134,166	4.5%
MSM (stabilized)	3	< 0.6 %

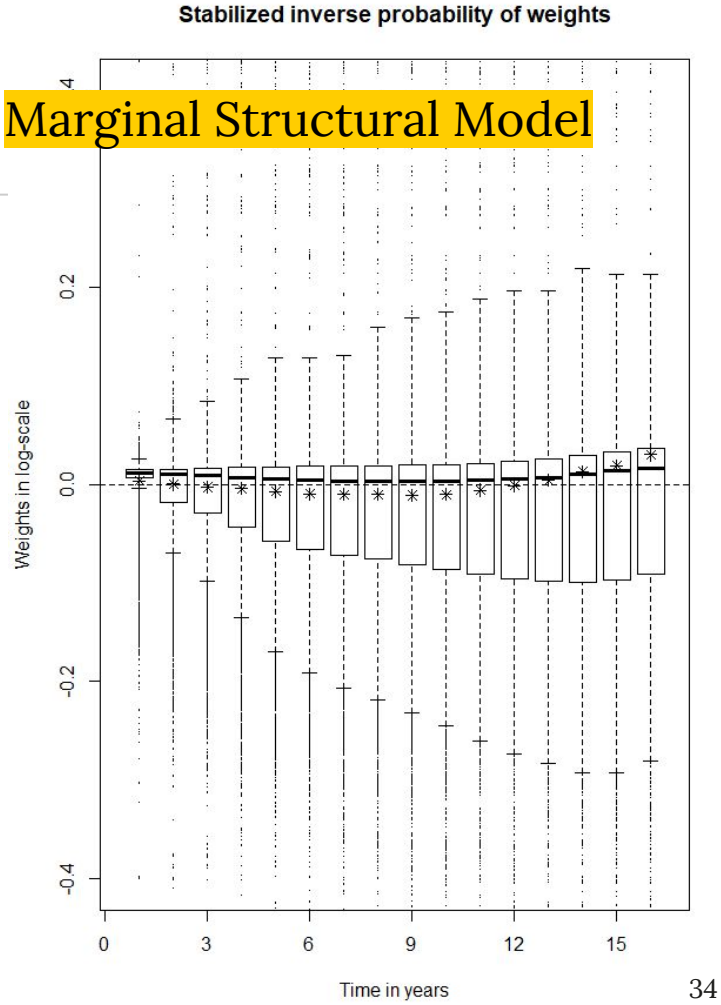
Data and Measurements: Covariates

- Baseline measures
  - age, disease duration, calendar year, sex, & SES quintile
- Time-varying confounder
  - Other drugs (similar definition as IFNb)
    - glatiramer acetate & fingolimod
- Time-varying confounders affected by prior treatment
  - **Comorbidity burden**: Charlson's Comorbidity Index [17]
  - **Disability**: Expanded Disability Status Scale [EDSS]

1 IFNb - Mortality association

- Treatment Weights
  - baseline covariates,
  - natural cubic spline of time;
  - lag of IFNb, other MS drugs, EDSS score & comorbidity
- Censoring weights
- Combined and stabilized
  - Confounding due to time-dependent confounders minimized

Marginal Structural Model



Marginal Structural Model

1 IFNb - Mortality association

Exposure	Exposure % (IFNb)	Weight (max)	Hazard ratio	95% CI
IFNb for ≥ 6 months	27%	7.74	0.63	0.47 - 0.86

* Stabilized weight used, baseline covariates further adjusted

** Disability scores imputed by linear interpolation approach & then LOCF

*** Robust estimators of the standard error

**** Causal contrast: the counterfactual survival times of the full cohort,
had every- body been exposed versus
had everybody not been exposed to the defined exposure of interest.

Marginal Structural Model

1 IFNb - Mortality association

Exposure	Exposure % (IFNb)	Weight (max)	Hazard ratio	95% CI
IFNb for ≥ 6 months	27%	7.74	0.63	0.47 - 0.86

Simplified treatment model:

- Exposed to IFNb for 6+ contiguous months?
- once exposed, always exposed

Effect of highly active antiretroviral therapy on time to acquired immunc syndrome or death using marginal structural models

SR Cole, MA Hernán, JM Robins… - American journal of …, 2003 - academic.oup.com

To estimate the net (ie, overall) effect of highly active antiretroviral therapy (HAART) on time to acquired immunodeficiency syndrome (AIDS) or death, the authors used inverse probability-of-treatment weighted estimation of a marginal structural model, which can appropriately adjust for time-varying confounders affected by prior treatment or exposure. Human immunodeficiency virus (HIV)-positive men and women (n= 1,498) were followed in two ongoing cohort studies between 1995 and 2002. Sixty-one percent (n= 918) of the …

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Marginal Structural Model

1 IFNb - Mortality association

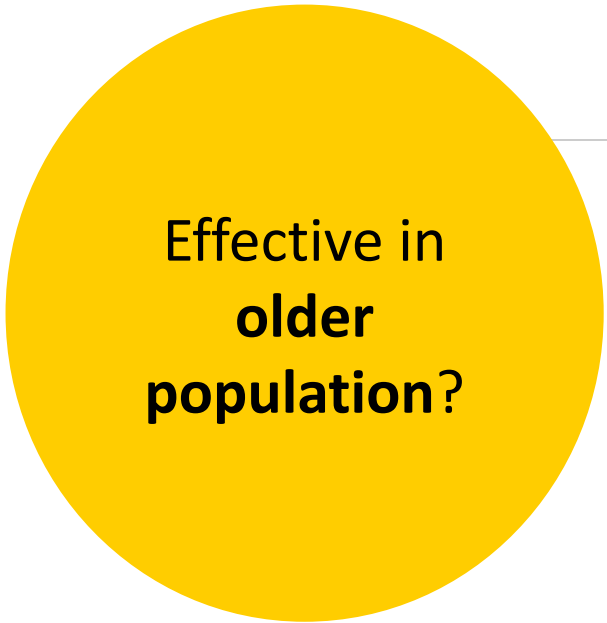
Exposure	Exposure % (IFNb)	Weight (max)	Hazard ratio	95% CI
IFNb for ≥ 6 months	27%	7.74	0.63	0.47 - 0.86
IFNb for ≥ 12 months	24%	7.37	0.62	0.45 - 0.87
IFNb for ≥ 18 months	22%	7.91	0.54	0.38 - 0.77
IFNb for ≥ 24 months	20%	7.60	0.49	0.33 - 0.73
IFNb for ≥ 36 months	16%	8.87	0.42	0.27 - 0.65
IFNb for ≥ 48 months	13%	10.18	0.38	0.22 - 0.66
IFNb for ≥ 60 months	11%	9.97	0.31	0.15 - 0.63

* Dose-response relationship

2

Effect modification

IFNb effective in older population?



2 Effect modification

- Drugs approved based on evidence from **RCTs that excluded older patients**
  - age of 50 or 55.
- Older MS patients are frequently prescribed IFNb.
- **Insufficient evidence**.

2 Effect modification

	Same weights as the main analysis	**Hazard ratio (IFNb)**	**95% Confidence interval**
Primary analysis	Main effects only	0.63	0.47 - 0.86
Effect Modification	One interaction term per model		
Sex	Male	0.45	0.26 - 0.78
	Female	0.71	0.50 - 1.01
Age at entry	Age ≥ 40	0.48	0.33 - 0.70
Disease duration	Disease duration ≥ 5	0.52	0.36 - 0.76

2 Effect modification

	Same weights as the main analysis	**Hazard ratio (IFNb)**	**95% Confidence interval**
Effect Modification	One interaction term per model		
Sex	Male	0.45	0.26 - 0.78
	Female	0.71	0.50 - 1.01
Age at entry	Age ≥ 50	0.52	0.31 - 0.85
Disease duration	Disease duration ≥ 10	0.42	0.26 - 0.66

2 Effect modification

	Newly calculated weights per group	**Hazard ratio (IFNb)**	**95% Confidence interval**
Effect Modification	Subgroup analysis		
Sex	Male *(N = 803)*	0.45	0.25 - 0.81
	Female *(N = 2,610)*	0.73	0.52 - 1.04
Age at entry	Age ≥ 40 *(N = 2,165)*	0.47	0.32 - 0.69
Disease duration	Disease duration ≥ 5 *(N = 2,351)*	0.49	0.33 - 0.73

[HTML] When to initiate combined antiretroviral therapy to reduce mortality and AIDS-defining illness in HIV-infected persons in developed countries: an observational …

HIV-Causal Collaboration - Annals of internal medicine, 2011 - ncbi.nlm.nih.gov

Background Most clinical guidelines recommend that AIDS-free, HIV-infected persons with CD4 cell counts below 0.350× 10 9 cells/L initiate combined antiretroviral therapy (cART), but the optimal CD4 cell count at which cART should be initiated remains a matter of debate. Objective

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2 Effect modification

Technical Note:

- Cut-points are based on age recorded at study entry
- Results should not be interpreted as the impact of early-or-late initiation of IFNb.
- Dynamic marginal structural models to determine the optimal therapeutic window.

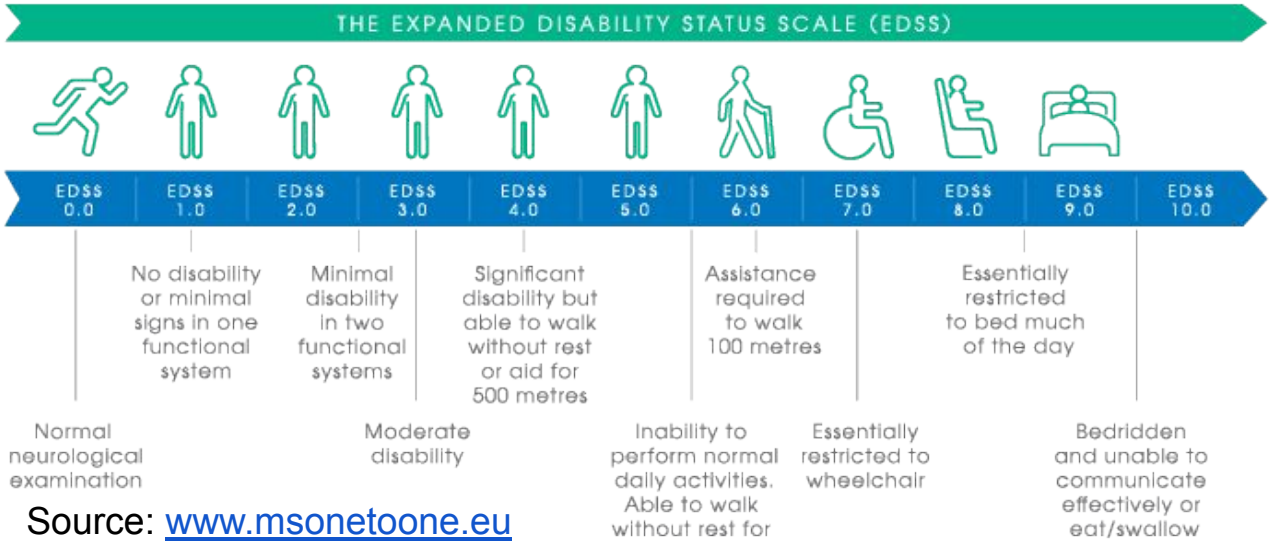
3 Sparse follow-up

Imputing unobserved measurements?

How to deal with **sparse follow-up**?

3 Sparse follow-up

- Disability (EDSS) measurements at a clinic:
  - from 0 (no disability) to 9.5 (bedbound; fully dependent)



Source: www.msonetoone.eu

The impact of sparse follow-up on marginal structural models for time-t
data

N Mojaverian, EEM Moodie, A Bliu… - American journal of …, 2015 - academic.oup.com

The impact of risk factors on the amount of time taken to reach an endpoint is a common parameter of interest. Hazard ratios are often estimated using a discrete-time approximation, which works well when the by-interval event rate is low. However, if the intervals are made more frequent than the observation times, missing values will arise. We investigated common analytical approaches, including available-case (AC) analysis, last observation carried forward (LOCF), and multiple imputation (MI), in a setting where time-dependent …

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3 Sparse follow-up

- Disability (EDSS) measurements at a clinic:
  - from 0 (no disability) to 9.5 (bedbound; fully dependent)
  - recorded during a **face-to-face physician visit**
  - Clinic visits may be **irregular**.
  - **Less / more visits** associated with health outcome?
- Data sparsity issue
  - Previous literature suggests **imputation**
  - **Multi-level imputation** methods incorporate the **clustered nature** of the data
    - Never been assessed.

3 Data setup

- Imputed only for denominator weight models
  - $A \sim t + A_{lag} + L_0 + L + L_{lag}$

id	Month	A	L	Y
1	$t_0=0$	$a_0=0$	$l_0=0$	$y_0=0$
1	$t_1=1$	$a_1=0$	$l_1=0$	$y_1=0$
1	$t_2=2$	$a_2=0$	NA	$y_2=0$
1	$t_3=3$	$a_3=1$	NA	$y_3=0$
1	$t_4=4$	$a_4=1$	$l_4=0$	$y_4=1$

Imputing missing covariate values for the Cox model
IR White, P Royston - Statistics in medicine, 2009 - Wiley Online Library
Multiple imputation is commonly used to impute missing data, and is typically more efficient than complete cases analysis in regression analysis when covariates have missing values. Imputation may be performed using a regression model for the incomplete covariates on other covariates and, importantly, on the outcome. With a survival outcome, it is a common practice to use the event indicator D and the log of the observed event or censoring time T in the imputation model, but the rationale is not clear. We assume that the survival outcome …
☆ 99 Cited by 653 Related articles All 11 versions Import into BibTeX

3 Multiple imputation by chained equations

- Imputation Model for EDSS
  - **Baseline variables**:
    - sex, age, disease duration, calendar year, SES
  - **Survival related variables**:
    - event of death, Nelson–Aalen estimate of cumulative hazard,
  - **Time-varying variables**:
    - concurrent IFNb exposure, other disease-modifying drug exposure, comorbidity burden, and follow-up index

* Collection of visits for each individual person as a cluster
** 30 imputation combined using Rubin's rules

3 Sparse follow-up

		Hazard ratio (IFNb)	95% Confidence interval
Ad hoc **approaches**	Linear interpolation	0.63	0.47 - 0.86
	LOCF only	0.65	0.47 - 0.89
Multiple Imputation (MI)	Proportional odds logistic regression	0.53 **	0.35 - 0.79
	Predictive mean matching (PMM)	0.53 **	0.35 - 0.79
MI with cluster	PMM using linear mixed model	0.53 **	0.35 - 0.79

Sensitivity analysis in observational research: introducing the **E-value**
TJ VanderWeele, P Ding - Annals of internal medicine, 2017 - acpjournals.org
Sensitivity analysis is useful in assessing how robust an association is to potential unmeasured or uncontrolled confounding. This article introduces a new measure called the "**E-value**," which is related to the evidence for causality in observational studies that are …
☆ 99 Cited by 1163 Related articles All 12 versions Import into BibTeX

Sensitivity analysis

- SES missing for 3.2% patients
  - Q1, M, Q3 imputed: HR, conclusion same
- Excluded 4% patients with switched from/to IFNb
  - HR, conclusion same
- Changed study end date to June, 2009:
  - Fewer deaths (*381*) vs. main analysis deaths (*566*)
  - HR slightly smaller, wider 95% CI but conclusion same.
- E-value
  - HR 2.10 for null value 1 with common outcome assumption

Strengths and Limitations

- Mortality
  - well-defined outcome.
- Exposure definition
  - depends on minimal exposure duration assumption.
- List of variables for MSM / imputation:
  - Limited
  - cognition, health behaviors (smoking, diet, or exercise)
- Multilevel imputation within MSM
  - Further simulation necessary.
- Several sensitivity analyses were run:
  - conclusions remained the same.

Summary

IFNb-Mortality

- hazard of mortality was 37% lower.
- Consistent with prior findings.

Effect modification

- Older MS patients had significant survival advantage.
- Early-vs-late? No.

Sparse follow-up

- MI makes more sense than *ad hoc*
  - MCAR vs. MAR
- MI with cluster did not have much impact.

Thanks!

ehsan.karim@ubc.ca

www.**ehsank**.com