Simplifying Causal Mediation Analysis for Time-to-Event Outcomes using Pseudo-Values

with an application to a clinical trial in Multiple Sclerosis

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Acknowledgements

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Abstract

Mediation analysis for survival outcomes is challenging. Most existing methods quantify the treatment effect using the hazard ratio (HR) and attempt to decompose the HR into the direct effect of treatment plus an indirect, or mediated, effect. However, the HR is not expressible as an expectation, which complicates this decomposition, both in terms

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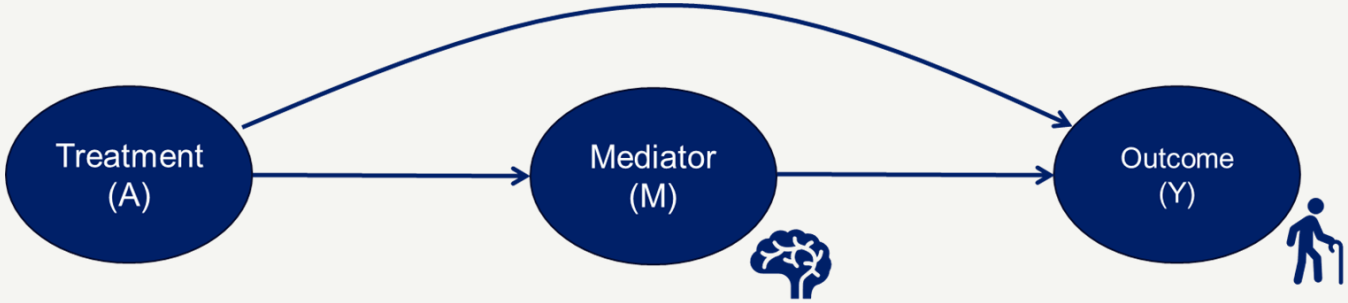
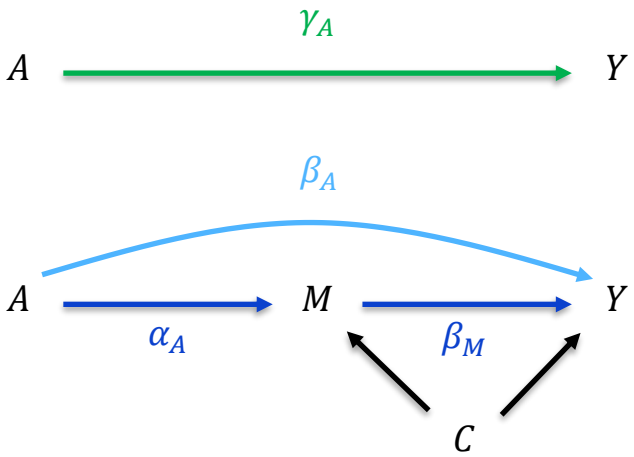
And many others!

Motivation for Mediation



Causal Mediation Analysis

- Causal mediation analysis begins by defining an:
  - treatment (A), mediator (M), and outcome (Y)
- Mediation analysis decomposes a (total) causal effect into two components:
  - 1) Indirect effect: through the mediator pathway
  - 2) Direct effect: through other pathways
- When M and Y are continuous:
  - Direct Effect: β_A
  - Indirect Effect: $\alpha_A\beta_M$
  - Total Effect: $\gamma_A = \beta_A + \alpha_A\beta_M$
  - Proportion Mediated: $\frac{\text{indirect effect}}{\text{total effect}}$
- Even in randomized trials, common causes C of M and Y must be accounted for



Outcome Model

$$E[Y|A,M] = \beta_0 + \beta_A A + \beta_M M + \beta_C C$$

Mediator Model

$$E[M|A] = \alpha_0 + \alpha_A A$$

Why is Mediation Analysis Relevant to Randomized Clinical trials & Pharmaceutical Drug Development?

- Mediation analysis can generate evidence that provides the pharmaceutical statistician with three main utilities:

1. Explaining a treatment's mechanism of action

Clinical trials aim to answer "if" a treatment works. The natural follow-up question is "how" the drug works. Mediation can provide evidence that the treatment works in part via specific pathways.

2. Justifying a surrogate endpoint

If a biomarker etc. lies on the causal pathway between treatment and clinical outcome, this is supportive evidence for using the biomarker as a surrogate endpoint in clinical trials (Joffe, 2009; Vanderweele, 2013, Fleming, 2022)

3. Accounting for Intercurrent Events

Intercurrent events can be treated as mediators and the natural direct effect calculated. This estimates the treatment effect had the trial's overall IE rate been that observed in the reference arm. Named the "*balanced estimand*" by Michiels, 2021. The controlled direct effect is described as the hypothetical strategy in the ICH E9(R1) addendum.

Pseudo-Value Mediation for Time-to-Event Outcomes

Survival Estimands & Estimators

Interpretable Summary Measures

Estimand (θ)	Estimator ($\hat{\theta}$)	Interpretation	Total Effect
Survival Probability	**Kaplan-Meier Curve**	**Probability**	**Difference**
$S(t) = P(T > t)$	$\hat{S}(t) = \prod_{U_i \le t} \left\{1 - \frac{dN(U_i)}{Y(U_i)}\right\}$	Probability of survival (or event free) at time t	$S_1(t) - S_0(t)$
Restricted Mean Survival Time	**Area under the Kaplan-Meier Curve**	**Time**	**Difference**
$\mu(\tau) = E[\min(T, \tau)]$	$\hat{\mu} = \int_0^\tau \hat{S}(u)du$	Average survival time up to time τ	$\mu_1(\tau) - \mu_0(\tau)$
Cumulative Incidence Curve (with competing risks)	**Aalen-Johansen Estimator**	**Probability**	**Difference**
$F_j(t) = P(T \le t, \delta = j)$	$\hat{F}_j(t) = \int_0^t \prod_{U_i \le u} \left\{1 - \frac{dN(U_i)}{Y(U_i)}\right\} \frac{dN_j(u)}{Y(u)}$	Probability of having the event at time t	$F_{j,1}(t) - F_{j,0}(t)$

- **Advantages**: non-parametric, no proportional hazards assumption, collapsible, model-free, interpretable
- **Disadvantage**: the incorporation of covariates

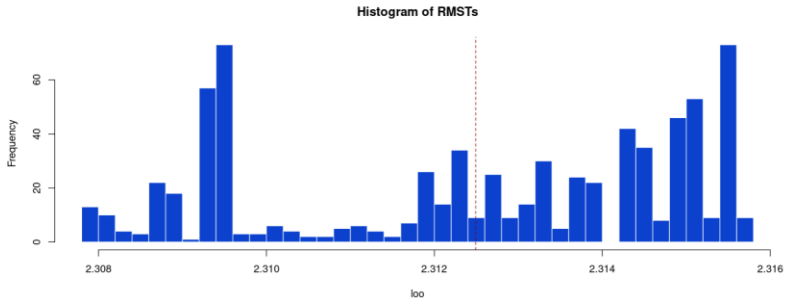
Pseudo-Values

What are pseudo-values?

- The pseudo-value captures how much the full sample estimate $\hat{\theta}$ changes due to subject i
- We estimate the pseudo value θ_i for any estimator $\hat{\theta}$ of θ is defined as:

$$\hat{\theta}_i \coloneqq n\hat{\theta} - (n-1)\hat{\theta}_{(-i)}$$

- Where $\hat{\theta}_{(-i)}$ is defined as the statistic after leaving out observation i (jackknife estimate)



Pseudo-values for covariate adjustment

- Then, if we use the pseudo-values as the outcome in a linear regression, the coefficients coincide with their effect on the non-parametric estimate (Andersen, 2004; Andersen, 2010)

$$\hat{\theta}_i = \beta_0 + \beta_1 A_i + \epsilon_i$$

- Why? Because the pseudo-value is an estimate of the conditional expectation

$$\theta_i = \theta_i(A_i) = E_{T|A}[g(T_i)|A_i]$$

Step-by-Step Guide to Pseudo-Value Mediation

Step 1: Calculate the full sample estimate

For a given survival estimand, calculate the estimate $\hat{\theta}$ for the entire sample (not separately in each treatment arm).

Step 2: Calculate pseudo-values

$$\hat{\theta}_i := n\hat{\theta} - (n-1)\hat{\theta}_{(-i)}$$

Step 3: Fit linear regression mediation models

Fit one linear regression model for the pseudo-values (θ_i) and another for the mediator M.

Step 4: Combine estimates to obtain mediation effects

- Direct effect = β_A
- Indirect effect = $\alpha_A\beta_M$

Step 5: Inference

Inference can be conducted via bootstrapping steps 2-4 above. Alternatively, the delta method or closed form expression:

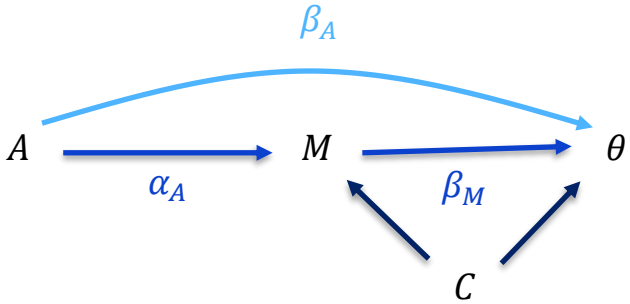
$$\sigma_{NIE} = \sqrt{\alpha_A^2 V(\beta_M) + \beta_M^2 V(\alpha_A) + V(\beta_M)V(\alpha_A)}$$

Outcome Model

$$E[\theta|A,M] = \beta_0 + \beta_A A + \beta_M M + \beta_C C$$

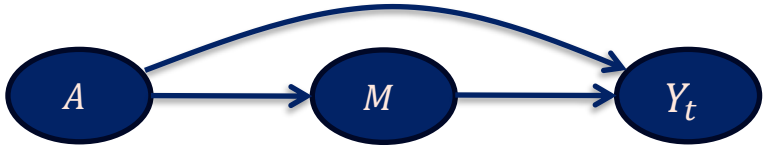
Mediator Model

$$E[M|A] = \alpha_0 + \alpha_A A$$



Simulation Study

Simulation Setup



Data generating scheme

- $A \in \{0,1\}$
- $(M|A=a) \sim N(-a,1)$
- Time to event $(Y_t|A=a,M=m) \sim Exp(\lambda)$, $\lambda = \exp(\beta_0 + a\beta_A + m\beta_M)$ with independent censoring.

What are the true mediation effects?

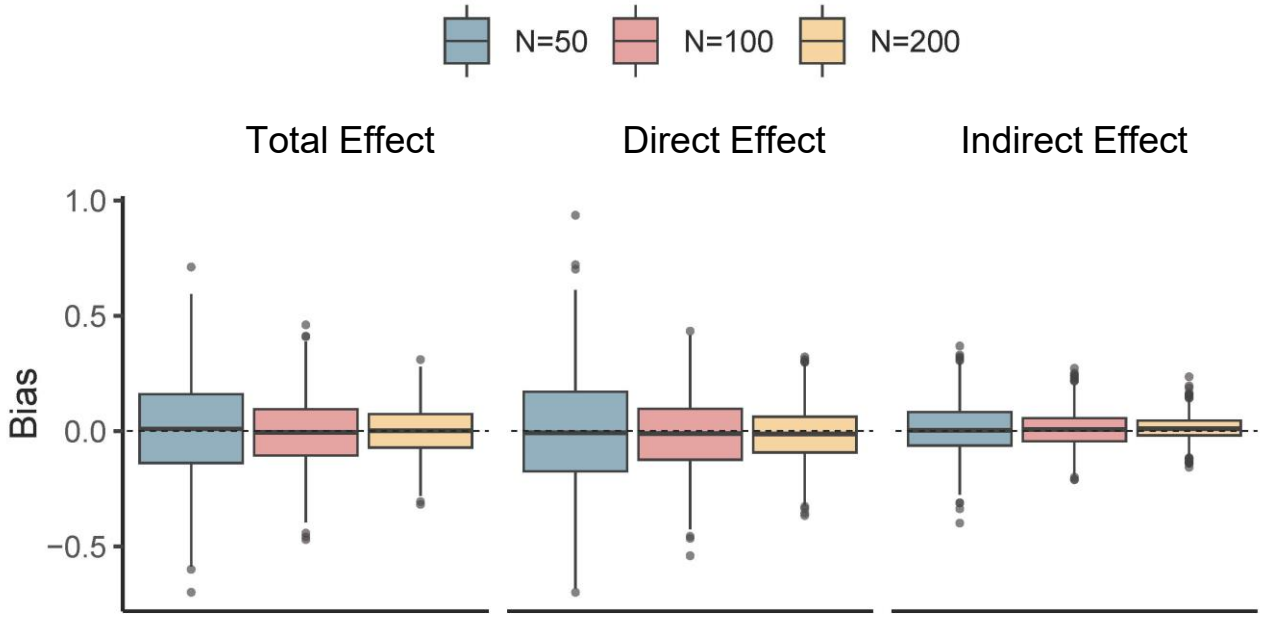
- Indirect effect (IE) for RMST is $\mathbb{E}_{M_1}[\mathrm{RMST}(M_1, A=1)] - \mathbb{E}_{M_0}[\mathrm{RMST}(M_0, A=1)]$

$$\mathbb{E}_M[\mathrm{RMST}(M, A=1)] = \int_{-\infty}^{\infty} \mathrm{RMST}(m, A=1)\phi(m)\, dm$$

- Since $(M|A=a) \sim N(a,1)$, expectations can be computed via Gaussian-Hermite quadrature:

$$\int_{-\infty}^{\infty} \mathrm{RMST}(m, A=1)\phi(m)\, dm \approx \sum_{j=1}^{J} w_j\, \mathrm{RMST}\big(m_j, A=1\big).$$

Results

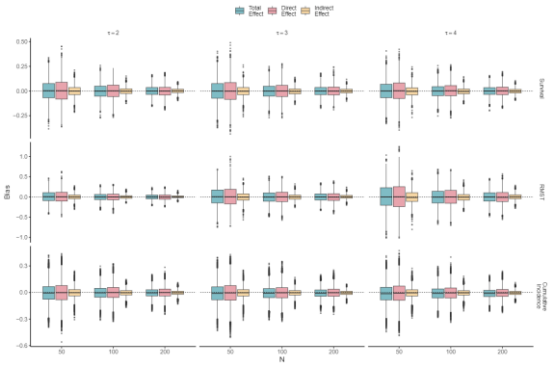


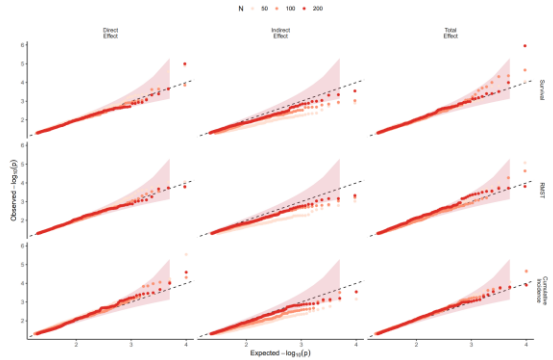
- Pseudo-value approach is unbiased for all RMST mediation estimands

Simulation Summary

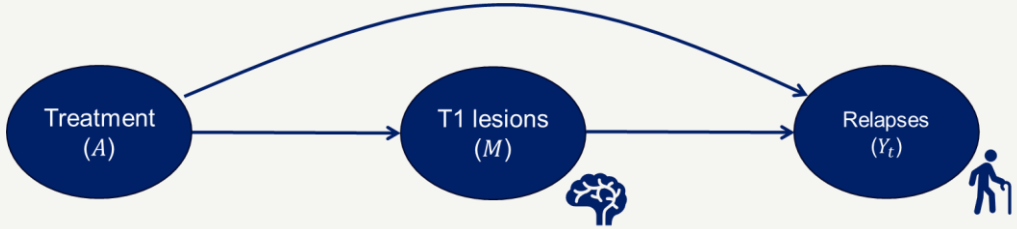
We repeated simulations for several estimands and scenarios:

- RMST, survival probabilities and cumulative incidence curves.
- Different time-points ($\tau = 2,3,4$).
- Different sample sizes ($N = 50, 100, 200$)
- Four different effect hypotheses:
  - No IE only, no DE only, no IE and DE.
- Three mediation estimands for each scenario
  - Natural Direct Effect, Natural Indirect Effect, Total Effect
- For each, checked coverage of confidence intervals.
- Pseudo-values computed via the influence function are fast and very accurate ($R^2 \approx 1.00$)





Estimates remain unbiased and control type I error across all 324 simulated scenarios/estimands.



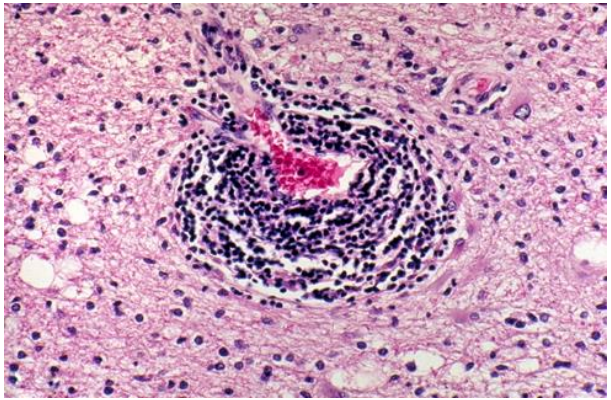
Clinical Trial Data Application

Clinical Trial in pediatric Multiple Sclerosis

Pathobiology of Multiple Sclerosis

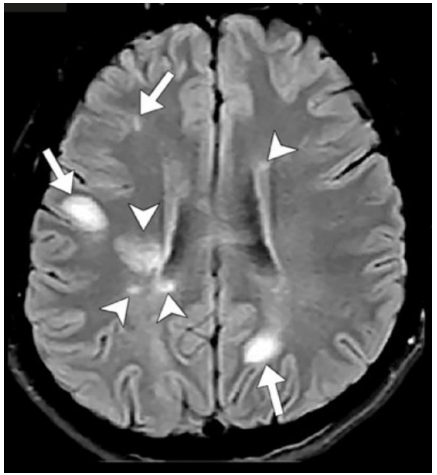
Gadolinium-enhancing T1 lesions can cause MS relapses

Inflammatory MS lesion: Immune cells invade the brain from a vein



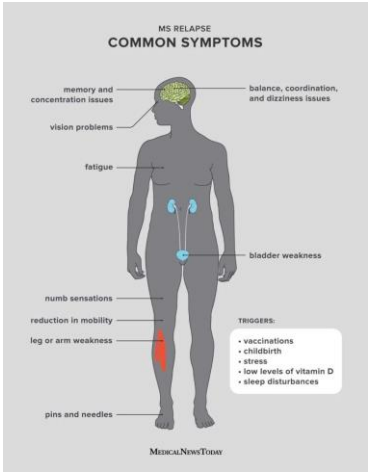
This histological image shows an acute inflammatory Multiple Sclerosis lesion where immune cells (in black) such as monocytes, T cells, and B cells have migrated from the blood vessel (in red), initiating an inflammatory process in the central nervous system (CNS).

...which can be visualized on MRI scans as Gd-T1 lesions.



Inflammatory lesions can be visualized on an magnetization resonance image (MRI). Patients receive gadolinium, a contrast agent, which leaks into the brain in MS patients with active lesions, appearing as white spots on the T1 sequence.

Lesions can cause MS relapses, acute neurological symptoms



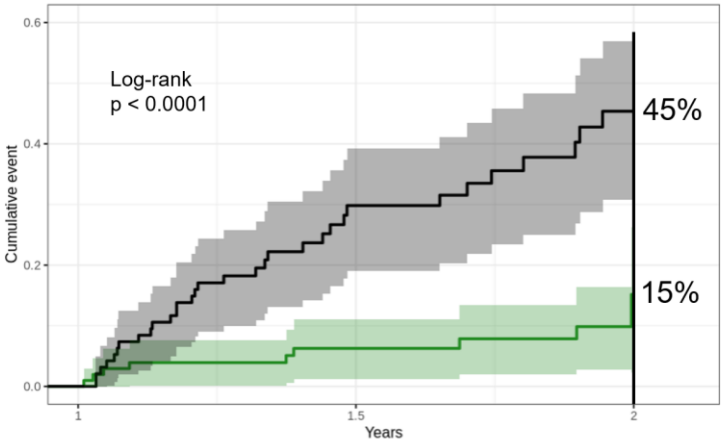
Patients with acute CNS lesions may experience various neurological symptoms, depending on the location of inflammatory lesion in the CNS. (Although most brain lesions are 'clinically silent' and symptom-free, they still contribute to the cumulative damage to the CNS and have downstream severity.

Time-to-relapse in the 2nd Year mediated by Gd-T1 lesions at Year 1

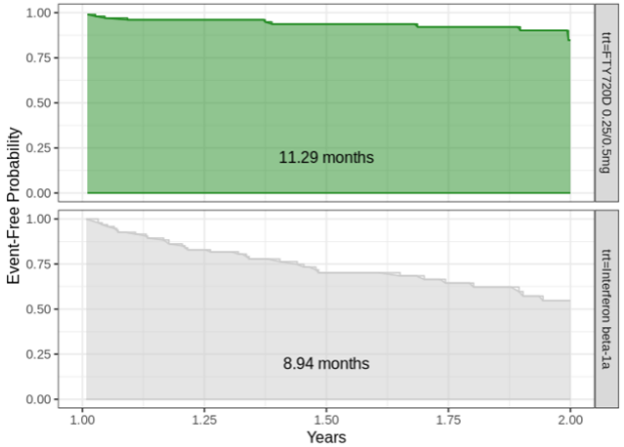
Total Treatment Effect Summary

- MS relapses are the primary endpoint in Relapsing Multiple Sclerosis (RMS) trials
- The mediator (Gd-T1 lesions on MRI) is collected in an MRI scan at year 1; therefore, for the mediation analysis the outcome is time-to-first relapse in the 2nd year (i.e. after the MRI scan)

Probability of an MS relapse decreases by 30%:
Risk difference 0.30, 95% CI (0.18, 0.41), p<0.001



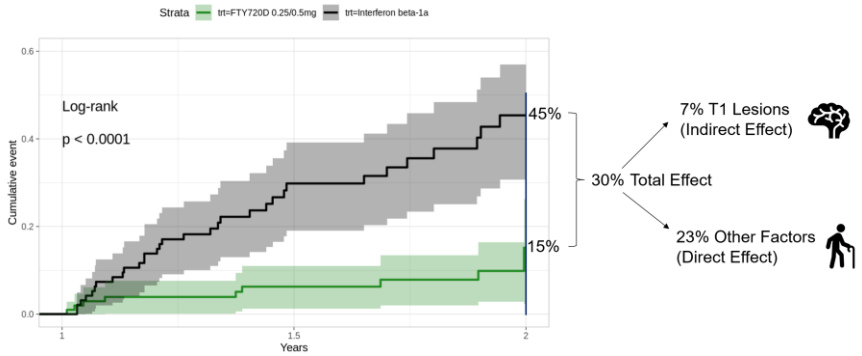
Mean relapse-free time is extended by 2.4 months:
RMST 2.4 months, 95% (1.3, 3.4), p<0.001



Mediation Analysis Results (Survival probability)

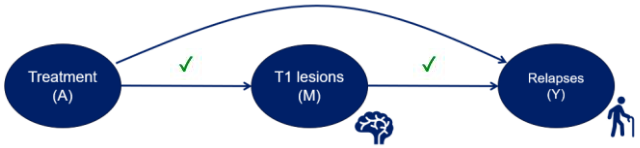
- We find evidence of an indirect effect of treatment mediated through T1-gd lesions
- Estimated proportion mediated is 24%
- The pseudo-value mediation using linear models makes the total effect additive
- Total Effect = NIE + NDE
  0.30 = 0.07 + 0.23
- Adjusted for covariates
  - age, number of relapses in the last year, normalized brain volume, sex, duration since first symptoms, and previous treatment usage at baseline
- Bootstrap inference -1,000 replicates

Effect	Estimate	95% CI	p-value
Indirect Effect	0.07	(0.02, 0.14)	0.022
Direct Effect	0.23	(0.03, 0.42)	0.009
Total Effect	0.30	(0.11, 0.48)	<0.001
Proportion Mediated	**24%**		



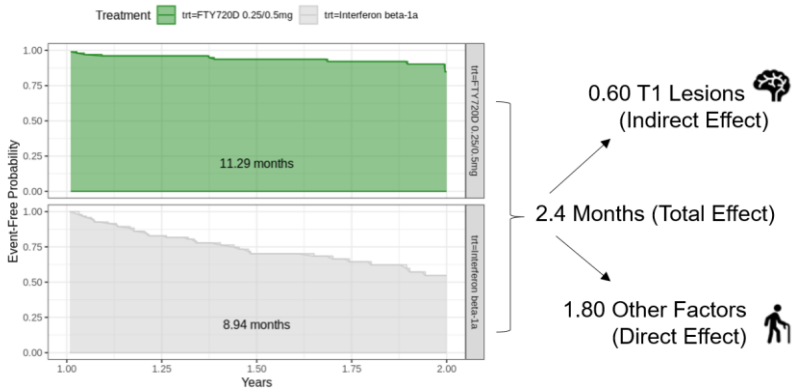
Mediation Analysis Results (Survival time: RMST)

- We find evidence of an indirect effect of treatment mediated through T1-gd lesions using RMST as well



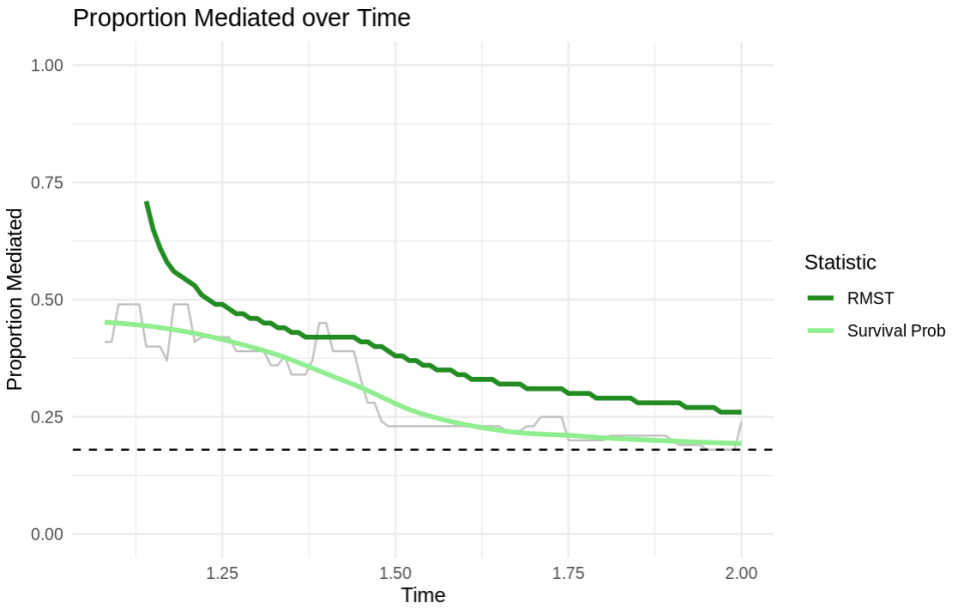
- Estimated proportion mediated is 26%
- Similar to the 24% mediated with survival probabilities
- The conclusion from the mediation analysis is consistent on both scales

Effect	Estimate	95% CI	p-value
Indirect Effect	0.60	(0.24, 1.20)	0.023
Direct Effect	1.80	(0.60, 2.76)	<0.001
Total Effect	2.40	(1.20, 3.48)	<0.001
Proportion Mediated	**26%**		



What if we vary the time horizon? (τ)

- The proportion mediated is stronger initially after the MRI scan, and fades as the time horizon is extended.
- Characterizes the “reach” of the mediator.
- T1-gd lesions explain most of the treatment effect in the subsequent 6 months
- Pseudo-value mediation can vary τ, which is an advantage as it provides information about causal effects over time.
- Can inform future studies as to what frequency a biomarker should be collected

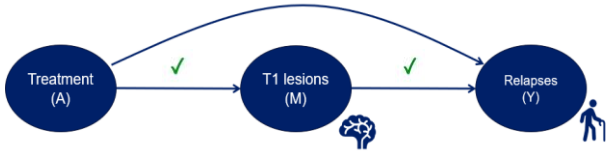


Conclusions

Conclusions

Mediation Analysis is a powerful tool to explain treatment effect

- Can explain MoA, justify surrogates, and handle intercurrent events
- Gaining interest across the pharmaceutical industry
- R package **`CMAverse`** is a great starting point



Pseudo-value mediation provides a simple approach for time-to-event outcomes

- Simplify the approach by allowing the mediation to be conducted with linear models
- Simulation studies demonstrate the approach is unbiased for a wide range of scenarios
- Mediation for interpretable estimands fills a gap in the mediation literature

Data application supports evidence of Gadolinium Enhancing T1 lesions being on the causal pathway between treatment and clinical relapses

- The MoA is in part due to T1 lesions and is supportive justification for use as a surrogate
- The mediation analysis was robust to choice of summary measure (survival probability or RMST)
- Varying the time horizon τ allows one to assess the reach of a mediator

Thank you

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Backup

Influence Function Approximation of Pseudo-values

Influence Function

- The influence function of a statistical functional $\theta = T(F)$ is defined as the instantaneous relative influence of X_i as $\epsilon \downarrow 0$

$$\varphi_{T,F}(X_i) = \lim_{\epsilon \downarrow 0} \frac{T((1-\epsilon)F + \epsilon\delta_{X_i}) - T(F)}{\epsilon}$$

- where $\delta_x = I(X < x)$ corresponds with a point-mass distribution on x

Relationship to pseudo-values

- Stefanski & Boos show that the pseudo-value is expressible as:

$$Y_i - \hat{\theta} = -(n-1)(\hat{\theta}_{(-i)} - \hat{\theta}) = \frac{T((1-\epsilon_n)F_n + \epsilon_n\delta_i) - T(F_n)}{\epsilon_n}$$

- where $\epsilon_n = -(n-1)^{-1}$ and F_n is the empirical CDF so that $T(F_n) = \hat{\theta}$
- Therefore, if the expression for the influence function is known, the pseudo-value can be approximated as:

$$Y_i \approx \hat{\theta} + \varphi(X_i)$$

- Influence function approximations of pseudo-values are more efficient

Asymptotic Distribution of the Proportion Mediated