Bayesian Causal Mediation Analysis with Stan – A g-formula approach

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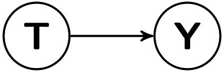
Mediation analysis

- Many scientific studies aim to infer if a given treatment or intervention influences a given outcome.



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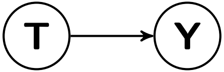
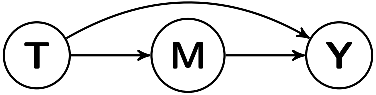
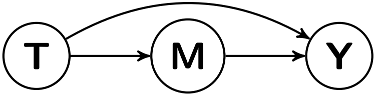


- Increasingly, many studies are interested in disentangling the pathways that link exposure to the outcome to get insight into the mechanism.
  - Why/how does the treatment/intervention affect outcome?

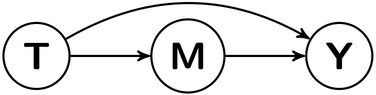


Mediation analysis



- Mediation analysis can be helpful in identifying
  - the effect of the intervention that acts through a given set of intermediate variables (indirect effect), and
  - the effect of the intervention unexplained by those same intermediate variables (direct effect).

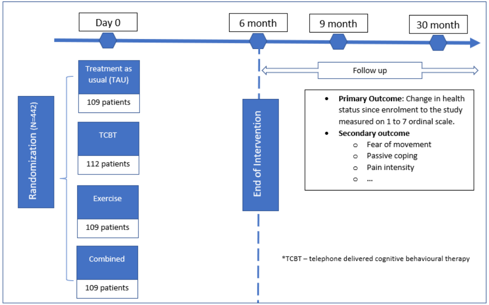
Mediation analysis



- Mediation analysis can be helpful in identifying
  - the effect of the intervention that acts through a given set of intermediate variables (indirect effect), and
  - the effect of the intervention unexplained by those same intermediate variables (direct effect).
- Question: How can we make inference about these causal effects from experimental and observational studies?

Motivating example — MUSICIAN trial

- The Managing Unexplained Symptoms (CWP) In Primary Care: Involving Traditional and Accessible New Approaches – a 2 × 2 factorial randomized controlled trial (McBeth et al., 2012)



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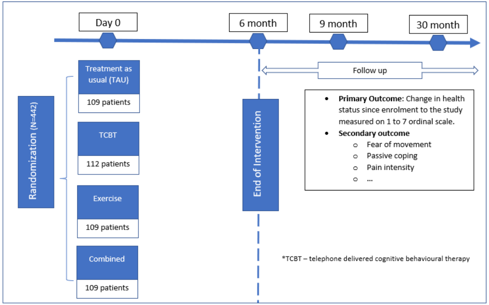
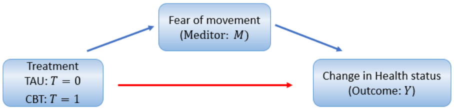


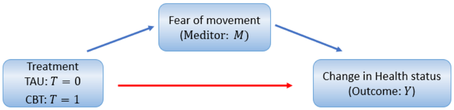
- CBT was associated with substantial improvements in patient global assessment.

Research questions



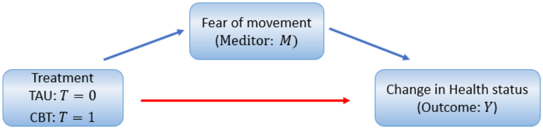
- To what extent does the treatment improve health status by inducing a change in fear of movement?
- To what extent the treatment improve health status independent of changing fear of movement?

Effect definition



	CBT ($T_i = 1$)	TAU ($T_i = 0$)
Fear of movement if CBT ($M_i(1)$)		
Fear of movement if TAU ($M_i(0)$)		

Effect definition



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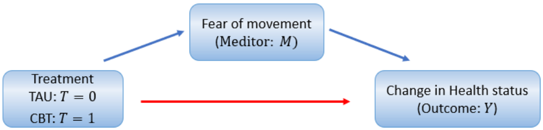

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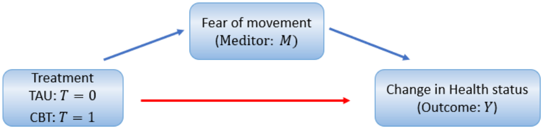

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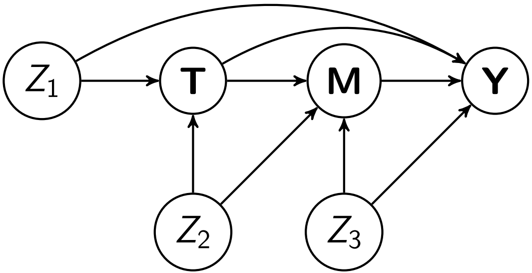
Population Average Natural direct effect: $E[Y(1, M(0))] - E[Y(0, M(0))]$

Identification of causal effects

To estimate natural direct and indirect effect we need:

- There are no unmeasured exposure-outcome confounder given $\boldsymbol{Z}$
- There are no unmeasured mediator-outcome confounder given $(T, \boldsymbol{Z})$
- There are no unmeasured exposure-mediator confounder given T
- There are no mediator-outcome confounder affected by exposure



Identification of causal effects

Under the four identification assumptions, natural direct and indirect effects are given by

$$E\left[Y(1, M(0)) - Y(0, M(0))\right] = \int\int \{E\left[Y \mid t = 1, m, z\right] - E\left[Y \mid t = 0, m, z\right]\} dF_{M|t=1,z}(m) dF_Z(z)$$

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Estimation

- Analytical integration (Valeri, L., and VanderWeele, T. J. (2013))
  - Parametric regression model for Y and M and computing the integration analytically
  - `SAS` and `SPSS macros` available
  - Frequentest approach
- Sampling (Imai et al., 2010)
  - Proposed to use a broad class of parametric or semiparametric model for Y and M
  - Use simulations to calculate NIE and NDE and the standard errors for this using bootstrap
  - Popular `R` - package `mediation`
  - Quasi-Bayesian approach

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- We propose to use Bayesian framework for estimation of NIE and NDE.
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- We propose to use Bayesian framework for estimation of NIE and NDE.
- Why bayes?
  - Full posterior inference for any function of model parameters, hence, point and interval estimates can be easily constructed for causal risk ratios, odds ratios, and risk differences
  - Priors can help us compute causal effects under sparsity - avoid *ad hoc* approaches
  - Probabilistic sensitivity analysis

Estimation — How it works?

- $\boldsymbol{D} = \{Y_i, T_i, M_i, \boldsymbol{Z}_i\}$
- T_i is a binary treatment assignment $t \in \{0, 1\}$
- Y is binary and M is continuous
- Assume IA (1) – IA (4) hold, the following regression models are correctly specified
  - $\text{logit}(P(Y_i = 1 \mid T_i, M_i, \boldsymbol{Z}_i)) = \alpha_0 + \boldsymbol{\alpha}_Z \boldsymbol{Z}_i + \alpha_T T_i + \alpha_M M_i,$
  - $E\left[M_i \mid T_i, \boldsymbol{Z}_i\right] = \beta_0 + \boldsymbol{\beta}_Z \boldsymbol{Z}_i + \beta_T T_i$
- $\boldsymbol{\theta} = (\alpha_0, \boldsymbol{\alpha}_Z, \alpha_T, \alpha_M, \beta_0, \boldsymbol{\beta}_Z, \beta_T)$
- Appropriate prior is assumed for elements of $\boldsymbol{\theta}$.
- The model is fitted in `stan`.

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- Draw the potential outcome values
  - Potential values of M: $M(t)^{(i,b)} \sim \text{Normal}(\beta_0^{(b)} + \beta_Z^{(b)} \boldsymbol{Z}^{(i,b)} + \beta_T^{(b)} t, \sigma^{(b)})$

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  - Given, the potential values of M, draw potential values of Y: $Y(t, M(t)^{(i,b)})^{(i,b)} \sim$ $\text{Bernoulli}(\text{logit}^{-1}(\alpha_0^{(b)} + \alpha_Z^{(b)}\boldsymbol{Z}^{(i,b)} + \alpha_T^{(b)}t + \alpha_M^{(b)}M(t)^{(i,b)}))$

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- Compute NIE and NDE
  - $NDE^{(b)} = \frac{1}{n}\sum_{i=1}^{n}\{Y(1, M(0)^{(i,b)})^{(i,b)} - Y(0, M(0)^{(i,b)})^{(i,b)}\}$
  - $NIE^{(b)} = \frac{1}{n}\sum_{i=1}^{n}\{Y(1, M(1)^{(i,b)})^{(i,b)} - Y(1, M(0)^{(i,b)})^{(i,b)}\}$
- Compute average and quartiles of NDE and NIE

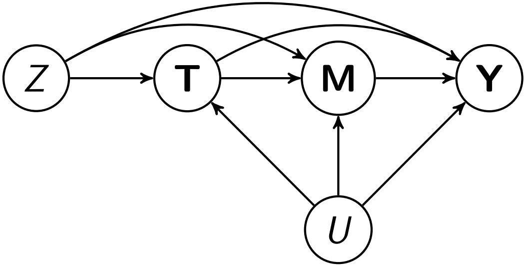
Application to MUSICIAN trial

- The Bayesian g-formula approach and the approach by Imai et al, 2010 (R-package `mediation`) leads to a comparable result.
- The effect of CBT on change in health status is mainly through mechanisms other than fear of movement.

Estimand	Imai et al. 2010	Bayesian g-formula
Direct effect	0.217 (0.107, 0.350)	0.224 (0.078, 0.369)
Indirect Effect	0.040 (-0.02, 0.100)	0.037 (-0.071, 0.142)

Bayesian sensitivity analysis

- The identification assumptions are often too strong
- Need to assess the robustness of findings via sensitivity analysis
- Question: How large a departure from the key assumption must occur for the conclusions to no longer hold?



Bayesian sensitivity analysis

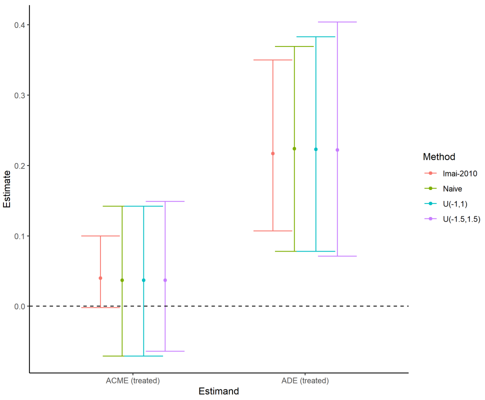
- We follow the approach by McCandless et al, 2007

$$Y|T, M, \boldsymbol{Z} \sim \text{Bernoulli}(\text{expit}(\alpha_0 + \boldsymbol{\alpha}_Z \boldsymbol{Z} + \alpha_T T + \alpha_M M + \alpha_U U))$$
$$M|T, \boldsymbol{Z}, \sigma \sim \text{Normal}(\beta_0 + \boldsymbol{\beta}_Z \boldsymbol{Z} + \beta_T T + \beta_U U, \sigma^2)$$
$$U|\boldsymbol{Z} \sim \text{Bernoulli}(\text{expit}(\gamma_0 + \gamma_Z \boldsymbol{Z}))$$

- We assign Uniform mean-zero bounded priors for the sensitivity parameters.

$$\alpha_U \sim U(-\delta, \delta)$$
$$\beta_U \sim U(-\delta, \delta)$$
$$\gamma_Z \sim U(-\delta, \delta)$$
$$\gamma_0 \sim U(-\delta, \delta)$$

Bayesian sensitivity analysis



Summary

- We have demonstrated the application of g-formula to Bayesian models for conducting mediation analysis.
- We show a flexible Bayesian model to explore sensitivity to unmeasured confounding in causal mediation analysis.
- Our goal is to make the methodology accessible to practitioners.
  - The development version of the R-package, `BayesGmed`, are available at https://github.com/belayb/BayesGmed.

Selected references

- McBeth, J., Prescott, G., Scotland, G., Lovell, K., Keeley, P., Hannaford, P., ... & Macfarlane, G. J. (2012). Cognitive behavior therapy, exercise, or both for treating chronic widespread pain. Archives of internal medicine, 172(1), 48-57.
- Imai, K., Keele, L., & Yamamoto, T. (2010). Identification, inference and sensitivity analysis for causal mediation effects. Statistical science, 25(1), 51-71.
- Valeri, L., & VanderWeele, T. J. (2013). Mediation analysis allowing for exposure–mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. Psychological methods, 18(2), 137.
- McCandless, L. C., Gustafson, P., & Levy, A. (2007). Bayesian sensitivity analysis for unmeasured confounding in observational studies. Statistics in medicine, 26(11), 2331-2347.