MANCHESTER 1824
The University of Manchester

MRC Hubs for Trials Methodology Research
North West Hub

Demystifying causal inference in randomised trials

Lecture 4: Mediation using IPW and other methods

ISCB 2016

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Plan

- Introduction to causal mediation parameters
- Causal mediation analysis using parametric regression models
- Causal mediation analysis using inverse probability weighting

Learning objectives

1. Understand the definitions of the causal mediation parameters
2. Understand how these definitions relate to statistical mediation approaches from lecture 3
3. Understand how to estimate these causal parameters using parametric regression methods and IPW
4. Understand the difference between causal mediation analysis and the statistical mediation approaches

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Individual treatment effects

- An **individual causal treatment effect (ITE)** for the *i*th subject with potential outcomes $Y_i(1)$ and $Y_i(0)$ can be defined by the contrast

$$\text{ITE} := Y_i(1) - Y_i(0)$$

- Note that treatment effects are allowed to be **heterogeneous**.
  - ITE is not constrained to be the same for each subject.
  - In principle it can vary from one subject to another.
  - And we might be able to investigate what characteristics of the subject influence the size of the treatment effect; that is look at effect moderation. (Not the subject of today's workshop – but note the use of such "predictive markers/moderators" as instruments in lecture 3.)

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Average treatment effects

- We can now define an average treatment effect in the target populations or in the subpopulations of those who ultimately will (or will not) receive treatment:
  - **Average Treatment Effect (ATE):**

$$\text{ATE} := \text{E(ITE)} = \text{E}[Y(1)-Y(0)]$$

  - **Average Treatment effect on the Treated (ATT):**

$$\text{ATT} := \text{E(ITE} \mid D=1) = \text{E}[\, Y(1)-Y(0) \mid D=1]$$

  - **Average Treatment effect on the Untreated (ATU):**

$$\text{ATU} := \text{E(ITE} \mid D=0) \;\; = \text{E}[\, Y(1)-Y(0) \mid D=0]$$

- Clinicians are often interested in ATT.

Causal mediation parameters

- In analogy with defining causal (total) treatment effects such as ATE we wish to define direct and indirect treatment effects that have a meaning as causal mediation parameters.
- We again employ a potential outcomes framework to define causal treatment effects.
  - But now we need to entertain potential outcomes for hypothetical levels of both the randomisation (Z) and the mediator (M)
- So to start with need to define an individual direct and indirect effect….

Causal effects

- Define outcome Y to be counterfactual in both the level of the randomisation Z and the level of the mediator M; then for individual i:
  - $Y(Z=0, M=m) = Y(0, m)$: The outcome that would be observed if the person was randomised to control $Z=0$ and the level of the mediator was fixed to value $M=m$.
  - $Y(Z=1, M=m) = Y(1, m)$: The outcome that would be observed if the person was randomised to treatment $Z=1$ and the level of the mediator was fixed to value $M=m$.

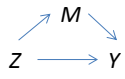
Controlled direct effect

- The individual treatment effect can be written as:

$$\text{ITE} = Y(1) - Y(0) = Y(1, M(1)) - Y(0, M(0))$$

- We can define an individual's controlled direct effect as the direct effect of treatment on outcome at mediator set to $M=m$, i.e. $Y(1, m) - Y(0, m)$ with average value:

$$\text{CDE} = \text{E}[\, Y(1, m) - Y(0, m) \,]$$

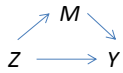


  - In the first term, Z is set to 1
  - In the second term, Z is set to 0
  - In BOTH terms, M is set to m
  - This gives a direct effect, unmediated by M

Natural direct effects

- We might like to know the effect of treatment when the mediator takes its "natural" level under the control condition $M(0)$.
- This leads to the definition of the natural direct effect (NDE):

$$NDE = E[\ Y(1, M(0)) - Y(0, M(0))\ ]$$



  - In the first term, Z is set to 1
  - In the second term, Z is set to 0
  - In BOTH terms, M is set to $M(0)$, the value if $Z=0$ (unexposed)
  - Since M is the same within subject, this gives a direct effect, unmediated by M
  - If no individual level interaction between D and M,

$$CDE(m) = NDE\ \forall\ m$$

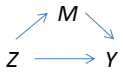
Natural direct and indirect effects

- This leads to the definition of the natural indirect effect (NIE):

$$NDE = E[\ Y(1, M(0)) - Y(0, M(0))\ ]$$

$$NIE = E[\ Y(1, M(1)) - Y(1, M(0))\ ]$$

- The NIE is the effect of change in the mediator on clinical outcome if randomised to treatment ($Z=1$).



  - In the first term, M is set to M(1)
  - In the second term, M is set to M(0)
  - In both terms, Z is set to 1
  - Z is only allowed to influence Y through its influence on M

Natural direct, indirect and total effects

- For a continuous outcome, these definitions allow us to partition the average treatment effects:

$$ATE = NDE + NIE$$

- Also after conditioning on $\boldsymbol{X}=x$:

$$ATE|\boldsymbol{X} = NDE|\boldsymbol{X} + NIE|\boldsymbol{X} = ATE$$

- For a binary outcome, we have:

$$ATE = NDE * NIE$$

- After conditioning on $\boldsymbol{X}=x$:

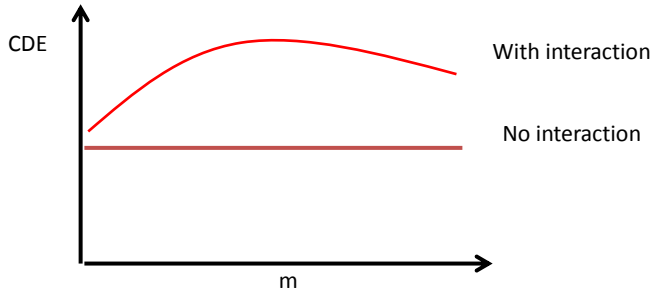
$$ATE\ |\boldsymbol{X} = NDE\ |\boldsymbol{X} * NIE|\boldsymbol{X}$$

Suitable methods for 'target' and 'nuisance' mediators

- Controlled direct effects are a natural question for 'nuisance' mediators:
  - What is the direct effect of randomisation on outcome if everyone in the population has the value M=m?
  - Interaction between R and M on Y might be important.
- For 'true' mediators, depends on question/subject matter:
  - Issues of confounding; non-linearity; interaction; etc.

CDE with and without interaction

- **Controlled direct effect:** $Y(1,m)$ - $Y(0,m)$
  - Direct effect of randomisation on outcome at mediator level *m*.



Policy implications of controlled direct effects

- Take the antidepressant medication example (PROSPECT):
  - Binary *M* (*M*=1, receives AD; *M*=0, does not receive AD)
  - Possible to intervene on *M* and set this to a value
- What is the direct effect of randomisation on outcome if everyone in the population receive antidepressant?
  $Y(1,1)$ - $Y(0,1)$
- What is the direct effect of randomisation on outcome if no-one in the population receives antidepressant?
  $Y(1,0)$ - $Y(0,0)$

Traditional regression approach

- It is based on two regression models:
  - Model for mediator (*M*): $E[M|Z,X] = \mu + \alpha Z + \delta X$
  - Model for outcome (*Y*): $E[Y|Z,M,X] = \tau + \gamma Z + \beta M + \varphi X$
  - (**X** are baseline covariates that act as observed confounders.)
- Under these two linear regression models the indirect effect is given by:

$$\text{Natural indirect effect (NIE)} = \alpha * \beta$$

- In the absence of a *Z* x *M* interaction the controlled direct effect equals the natural direct effect and is given by:

$$\text{CDE=NDE=} \gamma$$

Traditional regression approach: problem with interaction

- It is based on two regression models:
  - Model for mediator (*M*):
$$E[M|Z,X] = \mu + \alpha Z + \delta X$$
  - Model for outcome (*Y*):
$$E[Y|Z,M,X] = \tau + \gamma Z + \beta M + \omega Z * M + \varphi X$$
- What is the direct effect?
  - Depends on the level of *M*
- What is the indirect effect?
  - Depends on the level of *R*

IV and causal mediation parameter

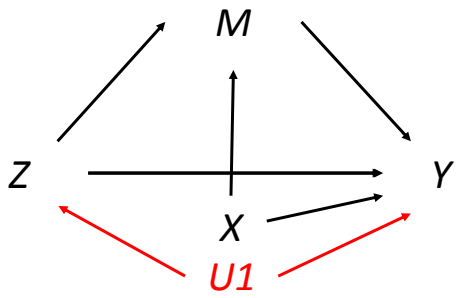
- IV methods applied to fit the regression model for Y estimate the controlled direct effect of treatment (CDE).
- Because we are assuming no interaction between randomised treatment and mediator in the model for Y the CDE is equal to the natural direct effect (NDE).
- We can derive an estimate of the natural indirect effect (NIE) by making use of e.g. NIE = ATE – NDE
  - May need bootstrapping to get inferences for NIE.

Estimating causal parameters

- Wide range of options for most combinations of *M* and *Y*
- Work on identification and estimation of direct and indirect causal effects using parametric regression models
  - VanderWeele and Vansteelandt (2009, 2010):
  - Outcomes can be continuous, binary, poisson or negative binomial.
  - Mediators can binary or continuous.
- G-computation is flexible and efficient but requires parametric modelling assumptions:
  - correct specification of all relevant conditional expectations and distributions
  - gformula command in Stata (Daniel et al., 2011)
- Semi-parametric methods make fewer parametric assumptions:
  - Inverse probability of treatment weighting (IPTW):
  - G-estimation

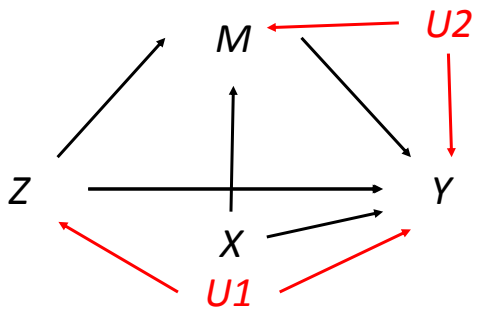
Assumptions for identification

- Total effects require:
  - A1: no unmeasured Z-Y confounding (U1);
  - (satisfied by randomisation ☺)



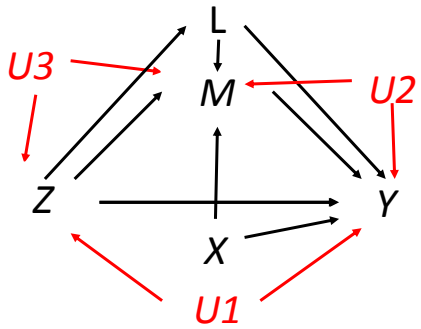
Assumptions for identification

- Controlled direct effects require:
  - A1: no unmeasured *Z-Y* confounding (*U1*);
  - A2: no unmeasured *M-Y* confounding (*U2*).



Assumptions for identification

- Natural direct and indirect effects require A1, A2 and
  - A3: no unmeasured treatment-mediator confounding (*U3*);
  - (satisfied by randomisation ☺)
- Either
  - A4a: no mediator-outcome confounder affected by treatment (*L*)
  - A4b: restrictions on the *Z*-*M* interactions



Estimating causal parameters using parametric regression models

- Assume a continuous mediator and continuous outcome.
- Traditional method would use two regression models:

$$E[M|Z=z, X=x] = \mu + \alpha z + \delta x$$

$$E[Y|Z=z, M=m, X=x] = \tau + \gamma z + \beta m + \omega x$$

- The NIE is the usual indirect effect ($\alpha\beta$), the NDE=CDE and is the usual direct effect (γ).
- Allowing for interactions gives a new outcome model:

$$E[Y|Z=z, M=m, X=x] = \tau + \gamma z + \beta m + \omega z * m + \varphi x$$

Estimating causal parameters using parametric regression models

- Using parameters from models 1 and 3, we can obtain the causal parameters as:

$$CDE = (\gamma + \omega m)(z - z')$$
$$NDE = (\gamma + \omega\tau + \omega\alpha r' + \beta\delta x)(z - z')$$
$$NIE = (\beta + \alpha + \omega\alpha \mathrm{r})(\mathrm{z} - \mathrm{z}')$$

- Without interactions (ω=0), these become the parameters obtained from the traditional method multiplied by levels of the exposure Z
  - For a binary exposure, Z={0,1}, (z-z')=1 so this term disappears.
  - For continuous exposure, we can compare multiple levels of the exposure

Estimating causal parameters using parametric regression models

- With a binary mediator, the model for the mediator becomes:

$$logit[\Pr(M = 1|Z = z, X = x)] = \mu + \alpha z + \delta x$$
$$E[Y|Z = z, M = m, X = x] = \tau + \gamma z + \beta m + \omega z * m + \varphi x$$

- And the causal parameters are:

$$CDE = (\gamma + \omega m)(z - z')$$

$$NDE = \{\gamma(z - z')\} + \{\omega(z - z')\}\frac{\exp[\mu + \alpha z' + \delta]}{1 + \exp[\mu + \alpha z' + \delta]}$$

$$NIE = (\mu + \omega z)\left\{\frac{\exp[\mu + \alpha z + \delta]}{1 + \exp[\mu + \alpha z + \delta]} - \frac{\exp[\mu + \alpha z' + \delta]}{1 + \exp[\mu + \alpha z' + \delta]}\right\}$$

Estimating causal parameters using parametric regression models

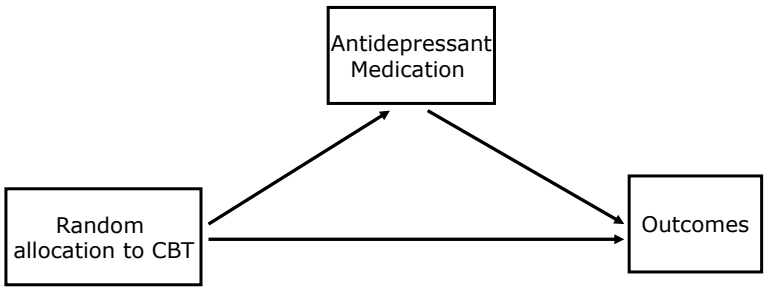
- With a binary mediator and outcome, the models are:

$$logit[\Pr(M = 1|Z = z, X = x)] = \mu + \alpha z + \delta x$$
$$logit[\Pr(Y = 1)|Z = z, M = m, X = x] = \tau + \gamma z + \beta m + \omega z * m + \varphi x$$

- And the causal parameters are:

$$\log\{OR^{CDE|x}\} = (\gamma + \omega m)(z - z')$$
$$\log\{OR^{NDE|x}\} = \frac{\exp(\gamma z)\{1 + \exp(\beta + \omega z + \mu + \alpha z' + \delta x)\}}{\exp(\gamma z')\{1 + \exp(\beta + \omega z' + \mu + \alpha z' + \delta x)\}}$$
$$\log\{OR^{NIE|x}\} = \frac{\{1 + \exp(\mu + \alpha z' + \delta x)\}\{1 + \exp(\beta + \omega z + \mu + \alpha z + \delta x)\}}{\{1 + \exp(\mu + \alpha z + \delta x)\}\{1 + \exp(\beta + \omega z + \mu + \alpha z' + \delta x)\}}$$

Example: SMaRT trial



- Trial of CBT for depression in patients with cancer diagnosis.
- The intervention is either randomisation to usual care or usual care plus the intervention (Depression Care for People with Cancer).
- We examine the role of therapeutic dose of AD. This is recorded for all participants at baseline, 3 and 6 months, and takes the form of a binary variable (therapeutic dose received, yes or no).

Example: SMaRT trial

- The outcomes were measured at 3, 6 and 12 months. We consider the 6 month outcomes in this initial analysis.
  - Depression score (SCL-20)
  - Anxiety score (mean of items derived from SCL-90)
  - Fatigue score (EORTC QLQ C30).
- We use the following baseline variables:
  - sex
  - age (≤39, 40-79, and ≥80 years),
  - primary cancer site (breast, colorectal, gynaecological, and other cancer)
  - extent of disease (disease-free after initial treatment, local disease, and metastatic disease)
  - Measurements of outcome at baseline
  - whether the participants were receiving a therapeutic dose of AD at baseline.

Example: SMaRT trial – ITT analysis

Outcome at 6 months	Effect Size	N	p-value
Depression score (0-4)	-0.55 (-0.77 to -0.33)	183	<0.001
Anxiety score (0-4)	-0.30 (-0.43 to -0.17)	172	<0.001
Fatigue score (0-100)	-11.68 (-18.61 to -4.75)	170	0.001

Data are differences (95% CI). Calculated from ANCOVA (mean differences as effect sizes).

Example: SMaRT trial – mediators

Therapeutic Dose of AD	Usual Care (N=99)	Intervention (N=101)	Missing values
Baseline	20 (20%)	17 (17%)	0
3 months	42 (42%)	68 (69%)	2
6 months	32 (34%)	62 (65%)	12

We will use the 3 month measure of therapeutic dose. These are generally retrospective, but when considering 6 month outcomes this ensures temporality (mediator before outcome).

Example: SMaRT trial – depression outcomes

Controlled Direct Effects: What is the direct effect of random allocation if everyone in the sample had the value M=m?

Outcome scale: 0-4

Time	Parameter	Effect	SE	P-value	95% CI
6 months	CDE at M=0	-0.538	0.178	0.002	-0.887, -0.190
	CDE at M=1	-0.630	0.162	<0.001	-0.948, -0.311
	NDE	-0.548	0.123	<0.001	-0.788, -0.307
	NIE	0.018	0.442	0.968	-0.848, 0.883

Example: SMaRT Trial

- Evidence for unmeasured confounding:

  wrong direction on coefficient for therapeutic dose;

  suggests detrimental effect!

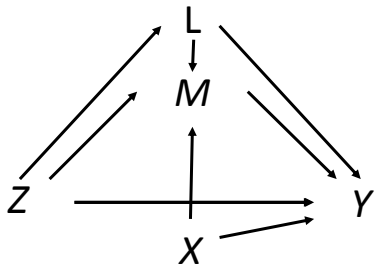
dep6	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
interven	-.5383036	.1779271	-3.03	0.003	-.8895495	-.1870577
dose3	.1877437	.1754722	1.07	0.286	-.1586561	.5341435
__000001	-.0914497	.2432662	-0.38	0.707	-.5716816	.3887823
dep0	.5485273	.1273208	4.31	0.000	.2971833	.7998714
dose0	-.0950172	.1551008	-0.61	0.541	-.4012018	.2111674

Software for mediation analysis

- Statistical mediation analysis:
  - Stata: sgmediation, binary_mediation
  - Mplus, EQS, AMOS, R – any SEM package
  - SPSS: PROCESS (Hayes, Preacher)
- Causal mediation analysis in software;
  - Stata: paramed (Emsley et al.), mediation (Imai et al.), gformula (Daniel et al.)
  - SAS: gformula (Robins et al.), mediation (VanderWeele)
  - SPSS: mediation (VanderWeele)
  - R: mediation (Imai et al.)
  - Mplus: (Muthen)
  - Lange et al. (2012) and Vansteelandt et al. (2012).

Assumptions for identification

- To estimate natural direct and indirect effects using the parametric regression models, we need the assumption that there is no effect of exposure that confounds the mediator-outcome relationship
  - this would be violated in the following causal diagram:



Identification of Direct and Indirect Effects

- If there are effects of the exposure that confound the mediator-outcome relationship such as *L,* using the regression approach we can still estimate controlled direct effects but not natural direct and indirect effects (Avin et al., 2005).
- However, techniques such as marginal structural models for mediation (VanderWeele, 2009) or structural nested models for mediation (Vansteelandt, 2009) will be needed.
- Previously for controlled direct effects we required:
  - A1: no unmeasured *Z*-*Y* confounding;
  - A2: no unmeasured *M*-*Y* confounding.
- We need to extend the definition in A2 to control for *L* as well.

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Marginal structural models for direct effects

- A marginal structural model for controlled direct effects is given by:

$$E[Y(z,m)] = \beta_0+\beta_1 z+\beta_2 m+\beta_3 zm$$

- Once we have fit the marginal structural model the controlled direct effect is simply given by:

$$CDE(z,z';m) = E[Y(z,m)] - E[Y(z',m)] = (\beta_1+\beta_3 m)(z-z')$$

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Marginal structural models for direct effects

- We regress *Y* on *Z*, *M*, *Z*M* where each subject is weighted by the product of the weights:

$$w_i^z = \frac{\Pr(Z = z_i)}{\Pr(Z = z_i|X = x_i)}$$

$$w_i^m = \frac{\Pr(M = m_i|Z = z_i)}{\Pr(M = m_i|Z = z_i, X = x_i, L = l_i)}$$

- If the mediator M is continuous then we have to replace the probabilities for the weight obtained by logistic regression with probability density functions obtained from linear regression

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Marginal structural models for direct effects

- For binary outcomes we could instead fit a marginal structural model logistic regression to obtain controlled direct effect odds ratios.
- We would calculate weights the same way but fit a weighted logistic regression rather than a weighted linear regression.

$$Logit\{\Pr(Y(z,m)=1)\} = \beta_0 + \beta_1 z + \beta_2 m + \beta_3 zm$$

- We might want to use the MSM approach even if we do not have time-dependent confounding if:
  (i) We want marginal rather than conditional estimates
  (ii) We might prefer to model *Z* and *M* (weights) rather than *M* and *Y*

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Mediation analysis in survival analysis

- Suppose we aim to decompose a total effect comparing *r* and *r′* into direct and indirect effects, but we have a time-to-event outcome.
- Which of the methods that we have discussed can we use?
- It turns out, that we can estimate causal mediation parameters using survival analysis, under the same set of assumptions A1-A4.
- The interesting thing in survival data is that there are multiple scales we can use to decompose the total effect:
  - Survival function
  - Hazard function
  - Mean survival times

Mediation analysis in survival analysis (2)

- Let T be the time-to event outcome.
  - $T(z)$ is the counterfactual event time if Z is set to z.
  - $T(z,m)$ is the counterfactual event time if Z is set to z and M is set to m.
  - $M(z)$ is the counterfactual mediator if Z is set to z (as before).
  - $T(z,M(z'))$ is the nested counterfactual if Z is set to z, and the mediator is set to the value it would have been had Z been set to z'.

Mediation analysis in survival analysis (3)

- Let $S_T(t)$ be the survival function at time t,
  - $S_T(t)=\Pr(T>t)$
  - Conditional on covariates: $S_T(t|X)= \Pr(T>t|X=x)$
- We could decompose a comparison of the survival functions $S_{T(z)}(t)$ and $S_{T(z')}(t)$ as follows:

$$S_{T(z)}(t)-S_{T(z')}(t) = [S_{T(z,M(z))}(t)-S_{T(z,M(z'))}(t)] + [S_{T(z,M(z'))}(t)-S_{T(z',M(z'))}(t)]$$

  - The first expression is the **natural indirect effect** on the survival function scale;
  - the second expression is the **natural direct effect** on the survival function scale.

Mediation analysis in survival analysis (4)

- Let $\lambda_T(t)$ and $\lambda_T(t|X)$ be the hazard functions at time t.
  - i.e. the instantaneous rate of the event given T≥t.
- Then we could decompose the total effect on the hazard function scale as:

$$\lambda_{T(z)}(t)-\lambda_{T(z')}(t) =[\lambda_{T(z,M(z))}(t)-\lambda_{T(z,M(z'))}(t)] + [\lambda_{T(z,M(z'))}(t)-\lambda_{T(z',M(z'))}(t)]$$

- On the mean survival times, the decomposition would be:

$$\begin{aligned}E[T(z)]-E[T(z`)]=&[E[T(z,M(z))]-E[T(z,M(z`))]]\\&+[E[T(z,M(z`))]-E[T(z`,M(z`))]]\end{aligned}$$

- Each of these decompositions could be made conditional on covariates as well.

Causal mediation analysis with an additive hazard model

- Lange and Hansen (2011) describe mediation analysis under an additive hazard model for *T*:

$$\lambda_T(t/z,m,x)=\theta_0+\theta_1 z+\theta_2 m+\theta_4 x$$

- With a linear model for *M* as before,

$$E[M|Z=z,X=x]=\beta_0+\beta_1 z+\beta_2 x$$

- Then:

$$NIE=\lambda_{T(z,M(z))}(t)-\lambda_{T(z,M(z'))}(t)=\beta_1\theta_2(z-z')$$

$$NDE=\lambda_{T(z,M(z'))}(t)-\lambda_{T(z',M(z'))}(t)=\theta_1(z-z')$$

- Note that this is the same as we found in the statistical mediation analysis (Baron and Kenny).

Causal mediation analysis with an accelerated failure time model

- Assuming an accelerated failure time model for *T* whilst allowing for an interaction between *Z* and *M*:

$$\log(T) = \theta_0 + \theta_1 z + \theta_2 m + \theta_3 zm + \theta_4 x + \nu\epsilon$$

where *v* is a scale parameter, and *ε* can take any distribution. and a linear model for *M* and σ^2 the variance of the error term:

$$E[M|Z = z, X = x] = \beta_0 + \beta_1 z + \beta_2 x$$

- VanderWeele (2011) derived the following results:

$$NIE = log\{E[T(z, M(z)|x)]\} - log\{E[T(z, M(z')|x)]\} = (\beta_1\theta_2 + \theta_3\beta_1 z)(z - z')$$

$$NDE = log\{E[T(z, M(z')|x)]\} - log\{E[T(z', M(z')|x)]\} = \{\theta_1 + \theta_3(\beta_0 + \beta_1 z' + \beta_2 x + \theta_2\sigma^2)\}(z - z') + 0.5\theta_3{}^2\sigma^2(z^2 - z'^2)$$

Causal mediation analysis with an accelerated failure time model

- These results hold for arbitrary distributions for ε but require a normally distributed mediator *M*.
- When there is no interaction (so that θ_3=0), the expressions reduce to those we produced previously.
- These are also analogous to the results we had previously for a binary outcome.

Causal mediation analysis with a proportional hazards model

- Assuming a proportional hazards model for *T* whilst allowing for an interaction between *Z* and *M*:

$$\lambda_T(t|z,m,x) = \lambda_T(t|0,0,0)e^{\theta_1 z+\theta_2 m+\theta_3 zm+\theta_4 x}$$

and a linear model for *M* and σ^2 the variance of the error term:

$$E[M|Z=z,X=x] = \beta_0 + \beta_1 z + \beta_2 x$$

- VanderWeele (2011) derived the following results:

$$NIE = log\left\{\lambda_{T(z,M(z))}(t|x)\right\} - log\left\{\lambda_{T(z,M(z'))}(t|x)\right\} = (\beta_1\theta_2 + \theta_3\beta_1 z)(z-z')$$

$$NDE = log\left\{\lambda_{T(z,M(z'))}(t|x)\right\} - log\left\{\lambda_{T(z',M(z'))}(t|x)\right\} =$$
$$\{\theta_1 + \theta_3(\beta_0 + \beta_1 z' + \beta_2 x + \theta_2\sigma^2)\}(z-z') + 0.5\theta_3{}^2\sigma^2(z^2 - z'^2)$$

Causal mediation analysis with a proportional hazards model

- These results **only** hold for a rare outcome.
- When there is no interaction (so that θ_3=0), the expressions reduce to those we produced previously.
- Again, these are also analogous to the results we had previously for a binary outcome.
- For a non-rare outcome, there is no clear interpretation of the indirect effect, so the recommendation is that the PH model should not be used.

Software for mediation analysis in survival analysis

- Lange and Hansen (2011) present a general approach to performing these analysis in standard software:
  - Approach based on inverse probability weighting.
- The analysis could be performed manually by estimating the two regressions separately, and combining the results as described here:
  - Bootstrapping could be used for the standard errors, or the analytic terms from paramed.
- Valeri and VanderWeele have extended their SAS macro to include survival outcomes.
- We are aiming to produce a Stata command (survmed) to perform this analysis (in 2017).

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