Introduction to causal inference and causal mediation analysis

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Outline

- Introduction to causal inference
- Introduction to causal mediation analysis.
- Unified framework for the difference method in GLMs
- *g*-linkability results
- Data duplication algorithm
- Simulations, an example and summary.

Counterfactual outcomes

- An intervention, X, and an outcome which it may cause, Y. Y can be a health outcome or a process outcome.
- Counterfactuals: $Y_i(x)$ defined for each value of x.
- We observe one value only for each participant i. If X is binary, we observe either $Y_i(0)$ or $Y_i(1)$. This is the "fundamental problem of causal inference"

  Neyman (1923); Rubin (1974,1980); Holland (1986); Robins (1986)

Average causal effect

- The causal effect of a binary treatment for subject i is $Y_i(1) - Y_i(0)$, and the population averaged causal effect is

$$E(Y_i(1)) - E(Y_i(0)),$$

  where the expectation is over the distribution of counterfactual outcomes of a population about whom causal inference for the intervention is of interest

- When

$$E(Y|X = x) = Y(x) \qquad \textbf{consistency}$$

  The expected value of the outcome observed given the intervention status assigned is equal to the partipant's counterfactual outcome corresponding to that intervention status.

Average causal effect

- **exchangeability/no confounding**
- Exchangeability occurs when
  - the risk of outcome, Y, among those who received the exposure, X, is the same as the risk of outcome that would have occured had those who didn't receive the exposure did receive it, and
  - the risk of outcome Y, among those who didn't receive the exposure is the same as the risk of outcome that would have occurred had those who received the exposure didn't get it, i.e.

$$([Y_i(1)|X_i = 1] = [Y_j(1)|X_j = 0])$$
$$\&$$
$$([Y_i(0)|X_i = 0] = [Y_j(0)|X_j = 1]), \forall i, j, i \neq j$$

Thus, if participants' probabilities of receiving the intervention depend on risk factors for the outcome, exchangeability is not satisfied, and confounding occurs

Conditional exchangeability

- Conditional exchangeability is a more plausible assumption in observational studies.

$$Y(x) \perp\!\!\!\perp X | W \quad \text{for all } x$$

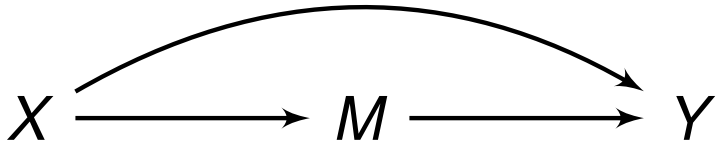
where W is a group of confounders.

- Confounding: A "back-door" path between the exposure and the outcome. A flow of association other than the causal pathway.

- Confounder: a variable (or a group of variables) that can be used to eliminate confounding in an estimate (when conditioned on).

Mediation Analysis

- So a causal effect of X on Y was established, but we want more!



- The directed acyclic graph (DAG) above encodes assumptions. Nodes are variables, directed arrows depict causal pathways
- Here M is caused by X, and Y is caused by both M and X.
- DAGs can be useful for causal inference: clarify the assumptions taken and facilitate the discussion.

Examples of mediation in practice

- Does cognitive behavioral therapy (X) targeting worry reduce delusions (Y)? Via worry reduction (M) ?

  (Freeman et al., The Lancet Psychiatry, 2015)

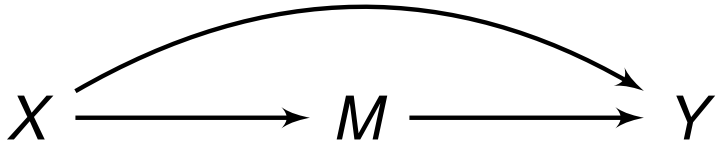
- Does tumor subtype and stage at diagnosis (M) mediate the effect of race (X) on post-diagnosis survival (Y)?

  (Warner et al., J. Clin. Oncol., 2015)

- Does percentage Mammographic Density (M) mediates risk factor effects (e.g., BMI at age 18, X) on post-menopausal breast cancer (Y)?

  (Rice et al., Breast Cancer Res., 2016)

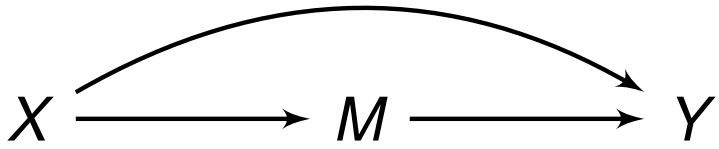
Causal mediation analysis



- We need more counterfactuals: $M_i(x)$ and $Y_i(x, m)$ for all relevant x, m values.
- Composite counterfactuals: $Y_i(x) = Y_i(x, M_i(x))$
- For every x, the value of M_i is set according to the value $X = x$, $M_i(x)$, and then $Y_i(x, M_i(x))$ is obtained.
- For example: If $M_i(0) = 1$, $Y_i(0) = Y_i(0, 1)$.
- The **total** effect of X on Y

$$\begin{aligned} TE(x, x') &= E[Y(x')] - E[Y(x)] \\ &= E[Y(x', M(x'))] - E[Y(x, M(x))] \end{aligned}$$

Natural direct and indirect effects



The **natural direct** effect $NDE = E[Y(1, M(0))] - E[Y(0, M(0))]$

The **natural indirect** effect

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

Robins and Greenland (1992); Pearl (2001)

The mediation proportion

- $TE = E(Y(1, M(1))) - E(Y(0, M(0)))$
- We have the following decomposition

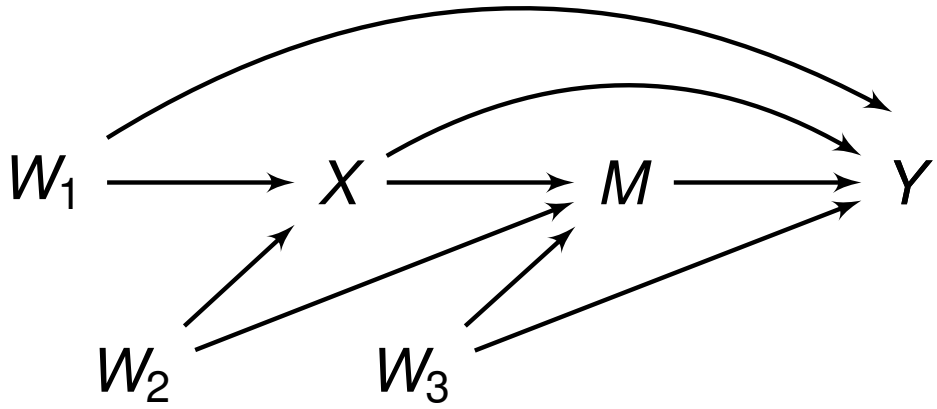
$$TE = NDE + NIE$$

- In practice, researchers prefer the **mediation proportion**

$$MP = \frac{NIE}{TE} = \frac{NIE}{NIE + NDE}$$

- Proportion if $MP \in [0, 1]$.

Mediation analysis with confounders



Let $\boldsymbol{W} = \{W_1, W_2, W_3\}$ and consider the following set of assumptions

(I) $Y(x,m) \perp\!\!\!\perp X | \boldsymbol{W}$ for all x and m

(II) $Y(x,m) \perp\!\!\!\perp M | \boldsymbol{W}, X$ for all x and m

(III) $M(x) \perp\!\!\!\perp X | \boldsymbol{W}$ for all x

(IV) $Y(x,m) \perp\!\!\!\perp M(x') | \boldsymbol{W}$ for all x, x' and m

Under assumptions (I)–(IV), NDE and NIE are identified from the data.

Linear models for mediation

In addition to assumptions (I)–(IV), assume the following linear models

$$E(Y|X, M, \boldsymbol{W}) = \beta_0 + \beta_1 X + \beta_2 M + \boldsymbol{\beta}_3^T \boldsymbol{W}$$
$$E(M|X, \boldsymbol{W}) = \gamma_0 + \gamma_1 X + \boldsymbol{\gamma}_3^T \boldsymbol{W}$$
$$E(Y|X, \boldsymbol{W}) = \beta_0^\star + \beta_1^\star X + \boldsymbol{\beta}_3^{\star T} \boldsymbol{W}$$

Simple calculations show:

$$NDE = \beta_1$$
$$NIE = \gamma_1 \beta_2 = (\beta_1^\star - \beta_1)$$
$$TE = \beta_1 + \gamma_1 \beta_2 = \beta_1^\star$$

The product method and the difference method

$$
\begin{aligned}
E(Y|X, M, \boldsymbol{W}) &= \beta_0 + \beta_1 X + \beta_2 M + \boldsymbol{\beta}_3^T \boldsymbol{W} \\
E(M|X, \boldsymbol{W}) &= \gamma_0 + \gamma_1 X + \boldsymbol{\gamma}_3^T \boldsymbol{W} \\
E(Y|X, \boldsymbol{W}) &= \beta_0^\star + \beta_1^\star X + \boldsymbol{\beta}_3^{\star T} \boldsymbol{W} \\
NIE &= \gamma_1 \beta_2 = \beta_1^\star - \beta_1 \\
MP &= \frac{\gamma_1 \beta_2}{\gamma_1 \beta_2 + \beta_1} = \frac{\beta_1^\star - \beta_1}{\beta_1^\star}
\end{aligned}
$$

- The NIE estimates $\hat{\beta}_2 \hat{\gamma}_1$ and $\hat{\beta}_1^\star - \hat{\beta}_1$ are the same, algebraically.
- If Y is binary and we replace the outcome linear regressions by logistic regressions this is no longer the case.
- Asymptotic normality and variance: delta method and/or bootstrap.

Mediation analysis with GLMs

- The difference method.

$$E(Y|X, M, \boldsymbol{W}) = g^{-1}(\beta_0 + \beta_1 X + \beta_2 M + \boldsymbol{\beta}_3^T \boldsymbol{W})$$
$$E(Y|X, \boldsymbol{W}) = g^{-1}(\beta_0^\star + \beta_1^\star X + \boldsymbol{\beta}_3^{\star T} \boldsymbol{W})$$

- $g(\cdot)$ is a known *link function*. Examples: $g(u) = u$, $g(u) = \log(u)$ and $g(u) = \text{logit}(u) = \log(u/(1-u))$.
- TE, NIE and NDE can be defined **on the coefficient scale** (on the link function scale):

$$NIE = \beta_1^\star - \beta_1 \qquad \text{and} \qquad MP = (\beta_1^\star - \beta_1)/\beta_1^\star$$

- For example, for logistic regression, we have the same decomposition, different interpretation:

$$\log OR_{TE} = \log OR_{NDE} + \log OR_{NIE}$$

VanderWeele and Vansteelandt (2010)

Generalized linear models (GLMs)

$$E(Y|X, M, \boldsymbol{W}) = g^{-1}(\beta_0 + \beta_1 X + \beta_2 M + \boldsymbol{\beta}_3^T \boldsymbol{W})$$
$$E(Y|X, \boldsymbol{W}) = g^{-1}(\beta_0^\star + \beta_1^\star X + \boldsymbol{\beta}_3^{\star T} \boldsymbol{W})$$

- Estimate $\boldsymbol{\beta} = (\beta_0, \beta_1, \beta_2, \boldsymbol{\beta}_3)$ and $\boldsymbol{\beta}^\star = (\beta_0^\star, \beta_1^\star, \boldsymbol{\beta}_3^\star)$ by solving

$$U(\boldsymbol{\beta}) = \left\{ \begin{array}{l} \sum_{i=1}^n \boldsymbol{D}_i^T v_i^{-1}[Y_i - E(Y_i|X_i, M_i, \boldsymbol{W}_i)] \\ \sum_{i=1}^n \boldsymbol{D}^{\star T}_i v_i^\star - 1[Y_i - E(Y_i|X_i^\star, \boldsymbol{W}_i^\star)] \end{array} \right\} = 0$$

  where $\boldsymbol{D}_i = \partial E(Y_i|X_i, M_i, \boldsymbol{W}_i)/\partial \boldsymbol{\beta}$ and v_i is the variance of Y_i.

- **Question:** Does the same link function g hold for both models?

g-linkability

Definition

When both the marginal and conditional models hold with the same link function *g*, we say we have *g-linkability*

g-linkability

Definition

When both the marginal and conditional models hold with the same link function g, we say we have *g-linkability*

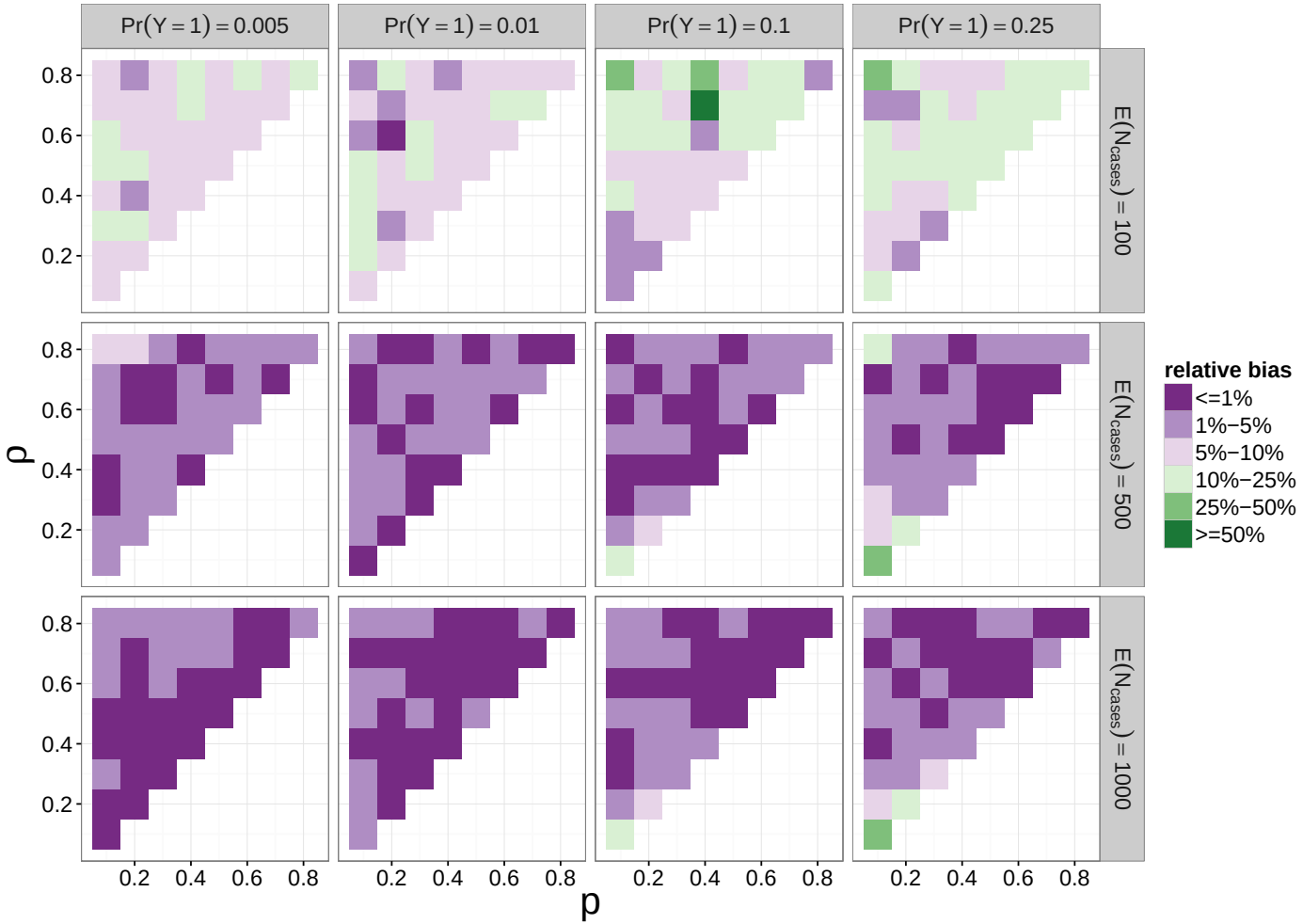
g-linkability holds under the following simple conditions:

- *Identity* link: When $E(M|X, \boldsymbol{W}) = a_0 + a_1 X + \boldsymbol{a}_2^T \boldsymbol{W}$
- *Log* link: When $\log E(\exp(\beta_2 M)|X, \boldsymbol{W}) = b_0 + b_1 X + \boldsymbol{b}_2^T \boldsymbol{W}$
- *Logit* link: When $\log E(\exp(\beta_2 M)|X, \boldsymbol{W}) = b_0^* + b_1^* X + \boldsymbol{b}_2^{T^*} \boldsymbol{W}$ and the outcome is rare (approximate *g*-linkability)

Question: How rare should the outcome be for the logit link function?

Nevo, D., Liao, X. and Spiegelman, D., 2017. Estimation and inference for the mediation proportion. *International Journal of Biostatistics*, 2017, 13(2).

Rare outcome assumption



Binary outcome; $TE = \log(\beta_1^\star) = \log(1.5)$. (X, M) jointly normal, $\rho = cor(X, M)$. Relative bias: $|mean(\widehat{MP}) - MP|/MP$.

Inference for mediation parameters: difference method

- Testing for mediation: $H_0 : NIE = \beta_1^\star - \beta_1 = 0$ or $H_0 : MP = (\beta_1^\star - \beta_1)/\beta_1^\star = 0$. CIs are also of interest.
- Asymptotic normality and variance by the delta method

$$\widehat{Var(NIE)} = Var(\hat{\beta}_1^\star) + Var(\hat{\beta}_1) - 2Cov(\hat{\beta}_1^\star, \hat{\beta}_1)$$

$$\widehat{Var(MP)} = \frac{\beta_1^2 Var(\hat{\beta}_1^\star)}{(\beta_1^\star)^4} + \frac{Var(\hat{\beta}_1)}{(\beta_1^\star)^2} - 2\frac{\beta_1}{(\beta_1^\star)^3} Cov(\hat{\beta}_1, \hat{\beta}_1^\star)$$

- If we had estimates for $\widehat{Var(MP)}$ and $\widehat{Var(NIE)}$, we could have constructed confidence intervals and (one-sided) Z-tests for mediation.
- How to estimate $Cov(\hat{\beta}_1^\star, \hat{\beta}_1)$? Must bootstrap?

Inference: Data duplication algorithm

- How to estimate $Cov(\hat{\beta}_1^\star, \hat{\beta}_1)$?
- The **idea**: Fit a single model that includes $\beta_1^\star$ and β_1. For $j = 1, 2$:

$$E(Y_{ij}|X_i, M_i, \boldsymbol{W}_i) =$$

$$g^{-1}\left[I\{j=1\}(\beta_0 + \beta_1 X_i + \beta_2 M_i + \boldsymbol{\beta}_3^T \boldsymbol{W}_i) + I\{j=2\}(\beta_0^\star + \beta_1^\star X_i + \boldsymbol{\beta}_3^{\star T} \boldsymbol{W}_i)\right]$$

- Use generalized estimating equations (GEE) to estimate (β^T, β^{*T}) from the duplicated data.
- Create a duplicated dataset: each observation is represented by two pseudo-observations and each of the covariates appears twice. The mediator is not duplicated. Set values to zeros according to the above model.
- The SAS macro `%mediate` implements the data duplication algorithm.

Data duplication

i	j	Intercept	Intercept*	X	$X^\star$	M	$\boldsymbol{W}$	$\boldsymbol{W}^\star$	Y
1	1	1	0	x_1	0	m_1	$\boldsymbol{w}_1$	0	y_1
1	2	0	1	0	x_1	0	0	$\boldsymbol{w}_1$	y_1
2	1	1	0	x_2	0	m_2	$\boldsymbol{w}_2$	0	y_2
2	2	0	1	0	x_2	0	0	$\boldsymbol{w}_2$	y_2
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$

- For each i, $j = 1$ observation comes from the conditional model and $j = 2$ from the marginal model.
- Fit for the duplicated data the model

$$E(Y_{ij}|X_i, X_i^\star, M_i, \boldsymbol{W}_i, \boldsymbol{W}_i^\star) =$$

$$g^{-1}\left(\beta_0 I\{j=1\} + \beta_1 X_i + \beta_2 M_i + \boldsymbol{\beta}_3^T \boldsymbol{W}_i + \beta_0^\star I\{j=2\} + \beta_1^\star X_i^\star + \boldsymbol{\beta}_3^{\star T} \boldsymbol{W}_i^\star\right)$$

- We get a consistent estimator for $Cov(\hat{\beta}, \hat{\beta}^\star)$, just by looking in the right place in the sandwich estimator matrix.

GEE for the duplicated data

- Testing: Reject two-sided test $H_0 : MP = 0$ if

$$\left| \widehat{MP} / \sqrt{\widehat{Var}(\widehat{MP})} \right| > z_{1-\alpha/2}$$

alternative test:

$$\left| \widehat{NIE} / \sqrt{\widehat{Var}(\widehat{NIE})} \right| > z_{1-\alpha/2}$$

- Confidence interval:

$$\widehat{MP} \pm \sqrt{\widehat{Var}(\widehat{MP})} \cdot z_{1-\alpha/2}$$

Software for causal mediation analysis

SAS Macro `%mediate` and R package (on CRAN) `GEEmediate` implement the data duplication algorithm, and reports point estimates, CIs and *p*-values for MP and NIE. Very fast implementation because they take advantage of existing software (PROC GENMOD or `gee` package).

Nevo, D., Liao, X. and Spiegelman, D., 2017. Estimation and inference for the mediation proportion. International Journal of Biostatistics, 2017, 13(2)

Macro available at:
`https://www.hsph.harvard.edu/donna-spiegelman/software`

```
%mediate(
DATA      = The name of the dataset. REQUIRED
ID        = The name(s) of >= 1 variable(s) that uniquely
identifies each record (e.g id or id period). REQUIRED
EXPOSURE = The main exposure or treatment variable of interest,
expressed as ONE VARIABLE, or alternately you may use
a set of indicators for an EXPOSURE. REQUIRED
INTERMED = The intermediate variable(s). This can be a set of
indicators, or any other representation of the intermediate
variable, such as a set of spline indicators. REQUIRED
COVARS    = List of covariates in the model, if any. OPTIONAL
INTMISS   = Whether you want to use missing indicators for unknown
of the INTERMED variable vs the model-specific complete case
analysis. Default=F OPTIONAL
WHERE     = A subsetting clause, if desired
NOTE:  if any of the variables named in WHERE is not among TIME,
EVENT, EXPOSURE, INTERMED, COVARS, then they should be listed
in EXTRAV (see next). OPTIONAL
EXTRAV    = A list of variables used in the WHERE clause that
are not part of the model or strata (see above) OPTIONAL
SURV      = If this is a survival analysis set to T, if a
generalized linear model, set to F (default=T) OPTIONAL
```

SURV=T Options

TIME = The survival time variable (time to outcome or censoring) REQUIRED if surv=T
EVENT = The event variable (1=yes, 0=no)
REQUIRED if surv = T
STRATA = Strata for the PROC PHREG, if desired.
These would usually be the same as the strata used
in the original PROC PHREG or MPHREG9 analysis,
typically AGEMO and year of questionnaire return. OPTIONAL
MODPRINT = Whether you want to print the results of the
PROC PHREG used in the macro. Default=F OPTIONAL
TIES = Ties option for phreg (default=breslow) OPTIONAL
PROCOPT = Procedure options for phreg OPTIONAL
MODOPT = Model options for phreg OPTIONAL
SURV=F Options

OUTCOME = The name of the dependent variable when surv
(see above) = F REQUIRED if surv = F
TYPE = If using a log-binomial(relative risk) regression
model, indicates if relrisk9 macro should be used to help with
convergence. type=1 indicates that relrisk9 should be used.
Type = 0 indicates relrisk9 should not be used.default=1 OPTIONAL

```
DIST      = proc genmod distribution option for use with type=0
(default=nor) OPTIONAL
LINK      = proc genmod distribution option for use with type=0
(default=identity) OPTIONAL
RR2       = If using a log-binomial(relative risk) regression
model, the percent mediation is normally calculated from the
coefficients and is 1-(b/a) where b is the coefficient of the
EXPOSURE in the model with the proposed mediator(s), and a is
the coefficient  of the EXPOSURE in the model without the
proposed mediator(s). Setting RR2=1 tells the macro to calculate
the mediation proportion from the relative risks using a method
described in the literature (RRa-RRb)/(RRa-1). One issue with
this estimator is that it depends on whether the EXPOSURE is
coded as a risk factor or a protective factor. The results of
this estimator are displayed in addition to the percent
mediation, and are labeled pctmed_RR. Another alternative
method using the relative risks is also reported, calculating
1-RRb/RRa. This method gives does not depend on the coding of
EXPOSURE, but is a new idea, not described in the literature.
The results are labeled pctmed_RR2_alt.
debugdv   = Option is used for debugging.  optional );
```

MD as a mediator for distal BC risk factors (1)

- Established risk factors for breast cancer (BC) incidence: history of benign breast disease, family history, BMI, ...
- A different type of risk factor: **mammographic density**, which is a well-established risk factor. However, it is unknown if

> "...*mammographic density is an intermediate phenotype or whether BC risk factors influence BC risk and MD separately*".

(Rice et al., Breast Cancer Res., 2016)

- Nested case-control study (within the Nurses' Health studies) : 559 cases and 1727 controls.
- Outcome: Binary - BC.
- Analysis restricted to post-menopausal women. All exposures measured before the mammography.

MD as a mediator for distal BC risk factors (2)

- Matching of each case to one or two controls on age, current hormone therapy use, and variables related to the technical aspects of the mammography.
- Analysis adjusted for: age, current BMI, adolescent somatotype and technical issues related to the mammography.
- Sensitivity analysis for unmeasured confounding has shown that a confounder needs to be strongly associated with BC (1.8) to make a meaningful change in NIE estimates

The SAS macro `%mediate` call

Sample macro call (effect of BMI on breast cancer incidence, mediated by mammographic density):

```
 %mediate(data=premen, id=id, exposure=BMI,
intermed=pct_MD covars=age_mam_c bmi18_c bbd_mam nullip
par_mam_c afbc_c menarch_c avgadol_c readbatch2 readbatch3
time1 time3 fast2, intmiss=F, outcome=caco, modprint=t,
notes=nonotes, where=, extrav=, procopt=, modopt=,
link=logit, dist=bin, type = 0, surv=F);
```

Macro available on:
https://www.hsph.harvard.edu/donna-spiegelman/software/mediate/

Parameter estimates for PROC GENMOD

Obs	Parm	Estimate	Stderr	LowerCL	UpperCL	Z	ProbZ
2	intercept1	-1.2537	0.1483	-1.5443	-0.9630	-8.45	<.0001
3	intercept2	-1.2673	0.1448	-1.5512	-0.9834	-8.75	<.0001
4	exposure1_1	0.2516	0.1023	0.0511	0.4521	2.46	0.0139
5	exposure2_1	0.3517	0.1003	0.1551	0.5483	3.51	0.0005
6	intm1_1	0.2572	0.0393	0.1801	0.3343	6.54	<.0001
7	intm2_1	0.0000	0.0000	0.0000	0.0000	.	.
8	age_mam_c_1	0.0049	0.0133	-0.0211	0.0310	0.37	0.7096
9	age_mam_c_2	-0.0055	0.0131	-0.0311	0.0202	-0.42	0.6764
10	cbmi_mam_c_1	0.1987	0.0651	0.0711	0.3263	3.05	0.0023
11	cbmi_mam_c_2	0.0278	0.0600	-0.0898	0.1454	0.46	0.6430
12	bmi18_c_1	-0.1498	0.1432	-0.4304	0.1309	-1.05	0.2956
13	bmi18_c_2	-0.1731	0.1394	-0.4464	0.1001	-1.24	0.2143
14	nullip_1	0.1854	0.2063	-0.2190	0.5898	0.90	0.3690
15	nullip_2	0.1819	0.2032	-0.2163	0.5801	0.90	0.3705
16	par_mam_c_1	0.0318	0.0594	-0.0846	0.1481	0.54	0.5924
17	par_mam_c_2	-0.0022	0.0574	-0.1147	0.1103	-0.04	0.9693
18	afbc_c_1	0.1491	0.0722	0.0076	0.2907	2.06	0.0390
19	afbc_c_2	0.1565	0.0709	0.0176	0.2954	2.21	0.0272
20	menarch_c_1	-0.1786	0.0740	-0.3237	-0.0336	-2.41	0.0158
21	menarch_c_2	-0.1554	0.0723	-0.2971	-0.0136	-2.15	0.0317
22	avgadol_c_1	-0.1123	0.1852	-0.4753	0.2506	-0.61	0.5441
23	avgadol_c_2	-0.2049	0.1809	-0.5595	0.1498	-1.13	0.2576
24	readbatch2_1	0.0286	0.1859	-0.3357	0.3929	0.15	0.8776
25	readbatch2_2	-0.0773	0.1815	-0.4330	0.2783	-0.43	0.6700
26	readbatch3_1	-0.2298	0.1384	-0.5011	0.0415	-1.66	0.0969
27	readbatch3_2	-0.2486	0.1362	-0.5156	0.0184	-1.82	0.0681
28	time1_1	0.1485	0.1424	-0.1305	0.4276	1.04	0.2968
29	time1_2	0.2099	0.1395	-0.0635	0.4833	1.51	0.1323
30	time3_1	0.2363	0.1353	-0.0290	0.5015	1.75	0.0808
31	time3_2	0.2476	0.1343	-0.0155	0.5108	1.84	0.0651
32	fast2_1	0.0447	0.1244	-0.1991	0.2884	0.36	0.7195
33	fast2_2	0.0460	0.1223	-0.1938	0.2858	0.38	0.7069

```
Effect for outcome: caco, exposure:  HBBD
Calculating the proportion of treatment effect mediated by pct_MD
Adjusted for:  age_mam_c cbmi_mam_c bmi18_c   nullip par_mam_c
afbc_c menarch_c avgadol_c readbatch2 readbatch3 time1 time3
fast2
Exposure effect unadjusted for the hypothesized intermediates
pct_MD:
0.352 (     0.155 --      0.548)
Exposure effect adjusted for the hypothesized intermediates
pct_MD:
0.252 (     0.051 --      0.452)
Proportion of HBBD effect mediated by
pct_MD:
PTE =     28.459% (     8.949% --     47.969%)   p = 0.0042
```

Risk factor	$\hat{\beta}^{\star}$ ($\widehat{RR}_{total}$)	p-value	$\hat{\beta}$ ($\widehat{RR}_{direct}$)
HBBD	0.35 (1.42)	< 0.001	0.25 (1.28)
BC family history	0.42 (1.52)	0.01	0.42 (1.52)
BMI (age 18)	-0.23 (0.79)	0.02	-0.05 (0.95)
Age at first birth	0.15 (1.17)	0.03	0.15 (1.16)
Age at menarche	-0.16 (0.86)	0.03	-0.18 (0.84)

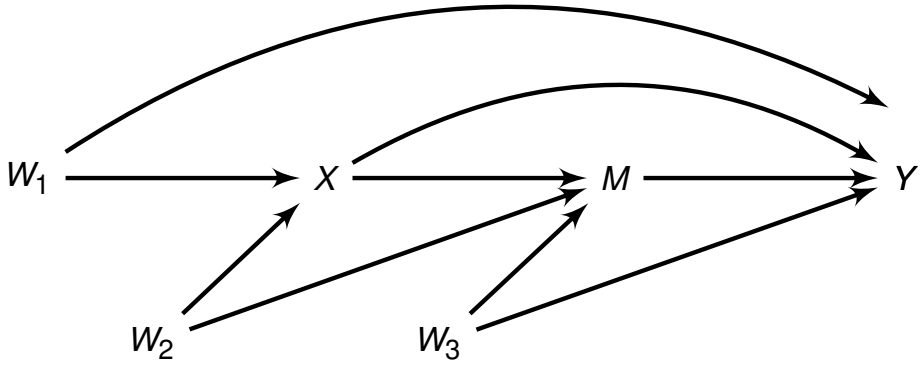
BMI (age18): per 5 units increase; Age at first birth: per 5 years increase; Age at menarche: per 2 years increase

Risk factor	$\widehat{MP}$	CI95%	p-value	
			MP test	*NIE* test
HBBD	0.28	0.09–0.48	0.004	$< 10^{-6}$
BC family history	0.004	-0.10–0.11	0.94	0.94
BMI (age 18)	0.78	0.06–1.50	0.03	$< 10^{-7}$
Age at first birth	0.03	-0.09–0.15	0.31	0.30
Age at menarche	-0.16	-0.36–0.04	0.12	0.04

HBBD: History of benign breast disease

Discussion

- Strengths of mediation analysis
  - Mediation analysis provide answers to well-defined causal questions.
  - I presented an easy to apply algorithm based on the difference method, which is valid under simple moment conditions.
  - Inference for parameters of interest: NIE and more commonly used MP.
- Limitations of mediation analysis
  - Data cannot help differentiate between a confounder and a mediator.
  - The estimator for the parameter of interest in applications is quite variable.



Thank you!

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Confidence intervals for MP logit link ($P(Y = 1) = 0.01$)

			$E(N_{cases}) = 500$ RR^{TE}			$E(N_{cases}) = 1000$ RR^{TE}		
			1.25	1.5	2	1.25	1.5	2
$p = 0.1$	$\rho = 0.1$	CR	0.95	0.95	0.87	0.96	0.93	0.80
		LEN	0.13	0.07	0.04	0.08	0.05	0.03
	$\rho = 0.5$	CR	0.97	0.96	0.94	0.96	0.95	0.96
		LEN	0.49	0.26	0.15	0.33	0.19	0.11
$p = 0.3$	$\rho = 0.3$	CR	0.96	0.95	0.92	0.95	0.95	0.94
		LEN	0.39	0.20	0.11	0.26	0.13	0.08
	$\rho = 0.5$	CR	0.96	0.95	0.93	0.96	0.96	0.95
		LEN	0.55	0.29	0.17	0.37	0.20	0.12
$p = 0.5$	$\rho = 0.5$	CR	0.95	0.95	0.94	0.96	0.96	0.94
		LEN	0.65	0.34	0.20	0.45	0.24	0.14

CR = Empirical Coverage rate of 95% CI. LEN = CI length

$$\widehat{MP} \pm \sqrt{\widehat{Var}(\widehat{MP})} \cdot 1.96$$

Extras: The Kenny and Baron mediation approach

The traditional approach (Baron and Kenny, 1986) (cited about 63k times!) suggested the following series of models and strategy for mediation analysis

$$E(Y|X, M, \boldsymbol{W}) = \beta_0 + \beta_1 X + \beta_2 M \quad (1)$$

$$E(M|X, \boldsymbol{W}) = \gamma_0 + \gamma_1 X \quad (2)$$

$$E(Y|X) = \beta_0^\star + \beta_1^\star X \quad (3)$$

- Establish an association between M and X in (2).
- Establish an association between Y and X in (3).
- Establish an association between Y and M in (1).

Extras: the controlled direct effect

- The **controlled direct** effect

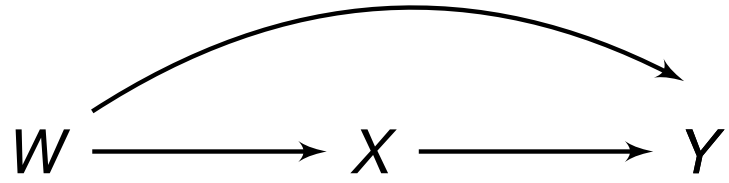
$$CDE(x, x', m) = E(Y(x', m)) - E(Y(x, m))$$

- The effect of changing (modifying, intervening on) $X = x$ to $X = x'$ while fixing the mediator to a prespecified value m.
- Relevant when such joint interventions are feasible.
- $CDE(m)$ is identified under assumptions I + II.
- Identified under less assumptions (only (I) and (II) are needed).

Robins and Greenland (1992); Pearl (2001)

DAGs NP-SEM

In the following DAG, W is a confounder, and the X-Y relationship is confounded.



- Markovian assumption: Every variable on the DAG is independent of its non descendants given its parents.
- Nonparametric Structural Equation Modeling (NP-SEM): Each node (variable) on the graph is coupled with a function and a random variable in the following way:
  - $W = f_W(\epsilon_W)$
  - $X = f_X(W, \epsilon_X)$
  - $Y = f_Y(W, X, \epsilon_Y)$
  - ϵ_W, ϵ_X and ϵ_Y are independent.

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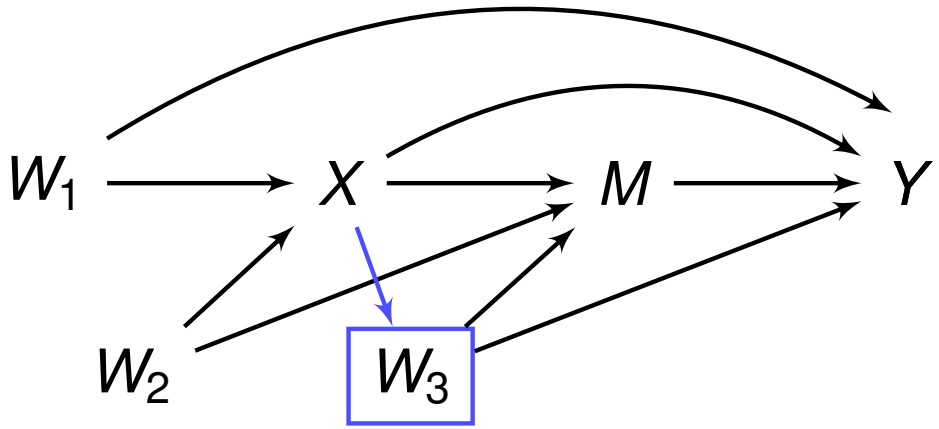
Extras: on mediation analysis with confounders



Let $\boldsymbol{W} = \{W_1, W_2, W_3\}$ and consider the following set of assumptions

(I) $Y(x,m) \perp\!\!\!\perp X | \boldsymbol{W}$ for all x and m

(II) $Y(x,m) \perp\!\!\!\perp M | \boldsymbol{W}, X$ for all x and m

(III) $M(x) \perp\!\!\!\perp X | \boldsymbol{W}$ for all x

(IV) $Y(x,m) \perp\!\!\!\perp M(x') | \boldsymbol{W}$ for all x, x' and m

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Extras: Simulation Design

- Simulate X and M from a bivariate normal distribution with correlation ρ.
- (Binary outcome) Fix $\beta_1^\star$ (TE), MP (mediation proportion) and $Pr(Y = 1)$ (outcome rate), $E(\#cases)$ (number of cases)
- (Continuous outcome) Fix $\beta_1^\star$ (TE), MP and β_0.
- Calculate other model parameters: $\beta_1 = (1 - p)\beta_1^\star$. $\beta_2 = \frac{MP}{\rho}\beta_1^\star$.
- For binary outcome, β_0 by solving $Pr(Y = 1) = q$ for the desired q (e.g., $q = 0.1$).
- Simulate Y given X and M using the conditional model.

Extras: Type I error and power: Binary outcome with logit link

		$E(\#cases) = 100$				$E(\#cases) = 500$			
		$\beta_1^\star = \log(1.25)$		$\beta_1^\star = \log(1.5)$		$\beta_1^\star = \log(1.25)$		$\beta_1^\star = \log(1.5)$	
MP	ρ	R_{MP}	R_{NIE}	R_{MP}	R_{NIE}	R_{MP}	R_{NIE}	R_{MP}	R_{NIE}
0.0	0.1	0.01	0.06	0.03	0.04	0.04	0.05	0.03	0.04
	0.5	0.02	0.04	0.03	0.05	0.05	0.06	0.04	0.05
0.1	0.1	0.35	0.69	0.98	0.99	1.00	1.00	1.00	1.00
	0.5	0.04	0.09	0.15	0.20	0.18	0.20	0.47	0.48

- $\rho = Corr(X, M)$. Testing $H_0 : MP = 0$ or $H_0 : NIE = 0$.
- $Pr(Y = 1) = 0.005 \qquad (\Rightarrow n = 20000, 100000)$

Extras: The product method and the difference method

$$E(Y|X, M, \boldsymbol{W}) = g^{-1}(\beta_0 + \beta_1 X + \beta_2 M + \boldsymbol{\beta}_3^T \boldsymbol{W})$$
$$E(Y|X, \boldsymbol{W}) = g^{-1}(\beta_0^\star + \beta_1^\star X + \boldsymbol{\beta}_3^{\star T} \boldsymbol{W})$$
$$E(M|X, \boldsymbol{W}) = \gamma_0 + \gamma_1 X + \boldsymbol{\gamma}_2^T \boldsymbol{W}$$

- The difference method estimates $\beta_1^\star - \beta_1$. The product method estimates $\beta_2\gamma_1$.
- The estimates coincide (algebraically) for the identity link, but not for other link functions.
- Variance estimation by bootstrap. Alternatives rely on the delta method ignoring the covariance term.
- If the conditional model is replaced with a model with exposure-mediator interaction,

$$E(Y|X, M, \boldsymbol{W}) = g^{-1}(\beta_0 + \beta_1 X + \beta_2 M + \beta_3 XM + \boldsymbol{\beta}_4^T \boldsymbol{W}),$$

there is an extension for the product method available but not for