Estimating Causal Mediation Effects from a Single Regression Model

Jeffrey D. Blume, PhD

Joint work with, and slides courtesy of,

Christina T. Saunders, PhD
Berry Consultants

VANDERBILT UNIVERSITY

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Slide Appendix

System congruency

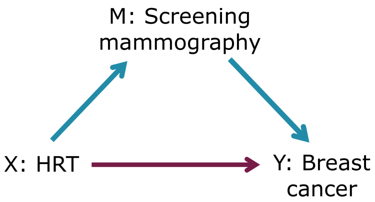
Suppose one believes M depends on X quadratically and writes the following system:

$$\mathbb{E}[Y|X,M] = \beta_0 + \beta_X X + \beta_M M$$
$$\mathbb{E}[M|X] = \alpha_0 + \alpha_X X + \alpha_{X^2} X^2$$
$$\mathbb{E}[Y|X] = \beta_0^* + \beta_X^* X$$

- This system is not congruous because marginalizing over the Full outcome model $\mathbb{E}_{M|X}[Y|X,M]$ does not yield the specified marginal model $\mathbb{E}[Y|X]$
- A properly specified system of equations would include an X^2 term in the third equation
- The difference and product approaches are not comparable because they are actually using *different systems* to estimate mediation effects

Usefulness of natural direct and indirect effects

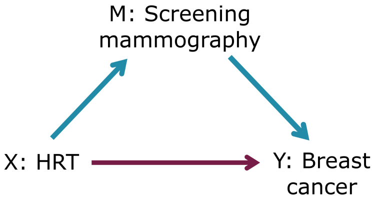
Suppose we are interested in estimating the mediating role of screening mammography in the relation between HRT and breast cancer.



- More breast cancer is observed among women taking hormone replacement therapy (HRT).
- Some portion of the excess cases is due to increased detection.

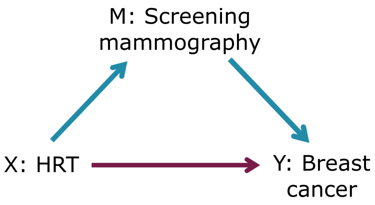
  But how much?

Usefulness of natural direct and indirect effects



The NIE tells us the breast cancer risk for a woman receiving HRT under the mammographic screening she received under HRT versus the risk under the screening *she would have had under no HRT*.

The controlled direct effect (CDE) and portion eliminated (PE)



- The CDE $= Y(x,m) - Y(x_\circ, m)$ corresponds to the effect of HRT on breast cancer that would remain after an intervention that sets mammography screening to a specific level m.
- The PE corresponds to the effect of HRT on breast cancer that would be eliminated after an intervention that sets mammography screening to a specific level.

The single-model approach

From the Full model,

$$\begin{bmatrix} \hat{\boldsymbol{\beta}}_{\boldsymbol{X}} \\ \hat{\boldsymbol{\beta}}_{\boldsymbol{M}} \end{bmatrix} \sim \mathsf{MVN}_k \left(\begin{bmatrix} \boldsymbol{\beta}_{\boldsymbol{X}} \\ \boldsymbol{\beta}_{\boldsymbol{M}} \end{bmatrix}, \begin{bmatrix} \boldsymbol{V}_{\boldsymbol{X}} & \boldsymbol{V}_{\boldsymbol{XM}} \\ \boldsymbol{V}_{\boldsymbol{MX}} & \boldsymbol{V}_{\boldsymbol{M}} \end{bmatrix} \right)$$

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From multivariate normal theory,

$$\begin{aligned}(\hat{\boldsymbol{\beta}}_{\boldsymbol{X}}|\hat{\boldsymbol{\beta}}_{\boldsymbol{M}} = 0) \sim \mathsf{MVN}_p(&\boldsymbol{\beta}^*_{\boldsymbol{X}}, \boldsymbol{V}^*_{\boldsymbol{X}})\\ \boldsymbol{\beta}^*_{\boldsymbol{X}} &= \boldsymbol{\beta}_{\boldsymbol{X}} - \boldsymbol{V}_{\boldsymbol{X}\boldsymbol{M}}\boldsymbol{V}_{\boldsymbol{M}}^{-\mathbf{1}}\boldsymbol{\beta}_{\boldsymbol{M}}\end{aligned}$$

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From multivariate normal theory,

$$\begin{aligned} (\hat{\boldsymbol{\beta}}_{\boldsymbol{X}} | \hat{\boldsymbol{\beta}}_{\boldsymbol{M}} = 0) &\sim \mathsf{MVN}_p(\boldsymbol{\beta}^*_{\boldsymbol{X}}, \boldsymbol{V}^*_{\boldsymbol{X}}) \\ \boldsymbol{\beta}^*_{\boldsymbol{X}} &= \boldsymbol{\beta}_{\boldsymbol{X}} - \boldsymbol{V}_{\boldsymbol{X}M} \boldsymbol{V}_M^{-\mathbf{1}} \boldsymbol{\beta}_{\boldsymbol{M}} \\ \Delta = \boldsymbol{\beta}^*_{\boldsymbol{X}} - \boldsymbol{\beta}_{\boldsymbol{X}} &= -\boldsymbol{V}_{\boldsymbol{X}M} \boldsymbol{V}_M^{-\mathbf{1}} \boldsymbol{\beta}_{\boldsymbol{M}} \end{aligned}$$

The single-model approach

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Using properties of the sampling distribution, we see that the difference of coefficients Δ equals some product of coefficients.

Empiric vs implied total effect

Once the Full outcome model and the Mediator model are specified, there is one theoretical Reduced model; however, there can be several mediator models that imply *the same form* for the Reduced model.

(F)	$\mathbb{E}[Y\|X,M,W]$	$= \beta_0 + \beta_X X + \beta_M M + \beta_W W + \beta_{XW} XW$
(M)	(a) $\mathbb{E}[M\|X,W]$	$= \alpha_0 + \alpha_X X + \alpha_W W$
	(b) $\mathbb{E}[M\|X,W]$	$= \delta_0 + \delta_X X + \delta_W W + \delta_{XW} XW$
(R)	$\mathbb{E}[Y\|X,W]$	$= \gamma_0 + \gamma_X X + \gamma_W W + \gamma_{XW} XW$

Both marginal models have the same form. As a result, the *fitted* estimates of the marginal model effects $\hat{\gamma}$ will be the same.

The implied coefficients from the two marginal models are different:

(a): $(\beta_0 + \alpha_0\beta_M) + (\beta_X + \alpha_X\beta_M)X + (\beta_W + \alpha_W\beta_M)W + \beta_{XW}XW$
(b): $(\beta_0 + \delta_0\beta_M) + (\beta_X + \delta_X\beta_M)X + (\beta_W + \delta_W\beta_M)W + (\beta_{XW} + \delta_{XW}\beta_M)XW$

The mediation formula

$$\begin{aligned}\mathsf{NDE} &= \mathbb{E}[Y(x, M(x_\circ)) - Y(x_\circ, M(x_\circ))] \\ &= \Sigma_{c,m} \left(\mathbb{E}[Y|x, m, c] - \mathbb{E}[Y|x_\circ, m, c]\right) \mathsf{P}[m|x_\circ, c]\mathsf{P}[c]\end{aligned}$$

$$\begin{aligned}\mathsf{NIE} &= \mathbb{E}[Y(x, M(x)) - Y(x, M(x_\circ)] \\ &= \Sigma_{c,m}\mathbb{E}[Y|x, m, c] \left(\mathsf{P}[m|x, c] - \mathsf{P}[m|x_\circ, c]\right) \mathsf{P}[c]\end{aligned}$$

$$\begin{aligned}\mathsf{TE} &= \mathbb{E}[Y(x) - Y(x_\circ)] \\ &= \Sigma_c \left(\mathbb{E}[Y|x, c] - \mathbb{E}[Y|x_\circ, c]\right) \mathsf{P}[c]\end{aligned}$$

Nomenclature

SEM Name	PO Name(s)	PO Definition
Direct Effect of X	$(\beta_X + \beta_{XM} M)(x - x_\circ)$	
a) set $M = m$	Controlled direct effect	$Y(x, m) - Y(x_\circ, m)$
b) set $M = E[M \mid x_\circ, c]$	Natural direct effect †	$Y(x, M(x_\circ)) - Y(x_\circ, M(x_\circ))$
	Pure direct effect §	
	Average direct effect (control) ⋆	
c) set $M = E[M \mid x, c]$	Total direct effect §	$Y(x, M(x)) - Y(x_\circ, M(x))$
	Average direct effect (treatment) ⋆	
Indirect Effect of X		
a) set $X = x_\circ$	Pure indirect effect §	$Y(x_\circ, M(x)) - Y(x_\circ, M(x_\circ))$
	Average causal mediation effect (control) ⋆	
b) set $X = x$	Natural indirect effect †	$Y(x, M(x)) - Y(x, M(x_\circ))$
	Total indirect effect §	
	Average causal mediation effect (treat) ⋆	

†VanderWeele

§Robins and Greenland

⋆Imai et al.

Causal Mediation Models*
$\mathbf{E}[\boldsymbol{Y}\|\boldsymbol{X},\boldsymbol{M}] = \boldsymbol{\beta_0} + \boldsymbol{\beta_X X} + \boldsymbol{\beta_M M}$ $\mathrm{E}[M\|X] = \alpha_0 + \alpha_X X$
$\mathbf{E}[\boldsymbol{Y}\|\boldsymbol{X},\boldsymbol{M},\boldsymbol{C}] = \boldsymbol{\beta_0} + \boldsymbol{\beta_X X} + \boldsymbol{\beta_M M} + \boldsymbol{\beta_C C}$ $\mathrm{E}[M\|X,C] = \alpha_0 + \alpha_X X + \alpha_C C$
$\mathbf{E}[\boldsymbol{Y}\|\boldsymbol{X},\boldsymbol{M},\boldsymbol{C}] = \boldsymbol{\beta_0} + \boldsymbol{\beta_X X} + \boldsymbol{\beta_M M} + \boldsymbol{\beta_C C} + \boldsymbol{\beta_{XC} XC}$ $\mathrm{E}[M\|X,C] = \alpha_0 + \alpha_X X + \alpha_C C + \alpha_{XC} XC$
$\mathbf{E}[\boldsymbol{Y}\|\boldsymbol{X},\boldsymbol{M_1},\boldsymbol{M_2}] = \boldsymbol{\beta_0} + \boldsymbol{\beta_X X} + \boldsymbol{\beta_{M_1} M_1} + \boldsymbol{\beta_{M_2} M_2}$ $\mathrm{E}[M_1\|X] = \alpha_{01} + \alpha_1 X$ $\mathrm{E}[M_2\|X] = \alpha_{02} + \alpha_2 X$
$\mathbf{E}[\boldsymbol{Y}\|\boldsymbol{X},\boldsymbol{M_1},\boldsymbol{M_2},\boldsymbol{C}] = \boldsymbol{\beta_0} + \boldsymbol{\beta_X X} + \boldsymbol{\beta_{M_1} M_1} + \boldsymbol{\beta_{M_2} M_2} + \boldsymbol{\beta_C C}$ $\mathrm{E}[M_1\|X,C] = \alpha_{01} + \alpha_1 X + \alpha_{C1} C$ $\mathrm{E}[M_2\|X,C] = \alpha_{02} + \alpha_2 X + \alpha_{C2} C$
$\mathbf{E}[\boldsymbol{Y}\|\boldsymbol{X},\boldsymbol{M_1},\boldsymbol{M_2}] = \boldsymbol{\beta_0} + \boldsymbol{\beta_X X} + \boldsymbol{\beta_{M_1} M_1} + \boldsymbol{\beta_{M_2} M_2} + \boldsymbol{\beta_{M_1 M_2} M_1 M_2}$ $\mathrm{E}[M_1\|X] = \alpha_{01} + \alpha_1 X$ $\mathrm{E}[M_2\|X] = \alpha_{02} + \alpha_2 X$ $\mathrm{E}[M_1 M_2\|X] = \alpha_{03} + \alpha_3 X$

* Bolded equation represents the fitted model used in the proposed framework

Illustration: $h(X) = [X, X^2]$

$$\mathbb{E}[Y|X,M,C] = \beta_0 + \beta_1 X + \beta_2 X^2 + \beta_M M + \beta_C C$$
$$\mathbb{E}[Y|X,C] = \beta_0^* + \beta_1^* X + \beta_2^* X^2 + \beta_C^* C$$

$$\text{TE} = \beta_1^*(x - x_\circ) + \beta_2^*(x^2 - x_\circ^2) = [\boldsymbol{h}(x) - \boldsymbol{h}(x_\circ)]\boldsymbol{\beta}^*_{\boldsymbol{X}}$$

$$\text{CDE} = \beta_1(x - x_\circ) + \beta_2(x^2 - x_\circ^2) = [\boldsymbol{h}(x) - \boldsymbol{h}(x_\circ)]\boldsymbol{\beta}_{\boldsymbol{X}}$$

$$\text{PE} = [x - x_\circ, x^2 - x_\circ^2]\begin{bmatrix}\beta_1^* - \beta_1 \\ \beta_2^* - \beta_2\end{bmatrix} = [\boldsymbol{h}(x) - \boldsymbol{h}(x_\circ)]\Delta$$

$$\text{EMCs } \Delta = -V_{\boldsymbol{X}M}V_M^{-1}\beta_M = -\begin{bmatrix}\text{cov}(\beta_1, \beta_M) \\ \text{cov}(\beta_2, \beta_M)\end{bmatrix}\text{var}(\beta_M)^{-1}\beta_M$$

What if there is moderated mediation?

Exposure-moderator interaction

$$\mathbb{E}[Y|X,M,W] = \beta_0 + \beta_X X + \beta_M M + \beta_W W + \beta_{XW} XW \qquad \text{(F)}$$

$$\mathbb{E}[Y|X,W] = \beta_0^* + \beta_X^* X + \beta_W^* W + \beta_{XW}^* XW \qquad \text{(R)}$$

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- $h(X) = [X, XW]$

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- $h(X) = [X, XW]$
- $\Delta = \begin{bmatrix} \beta_X^* - \beta_X \\ \beta_{XW}^* - \beta_{XW} \end{bmatrix} = -V_{XM} V_M^{-1} \beta_M$

$$= -\begin{bmatrix} \mathsf{cov}(\beta_X, \beta_M) \\ \mathsf{cov}(\beta_{XW}, \beta_M) \end{bmatrix} \mathsf{var}(\beta_M)^{-1} \beta_M$$

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- PE $= [h(x) - h(x_\circ)]\Delta$

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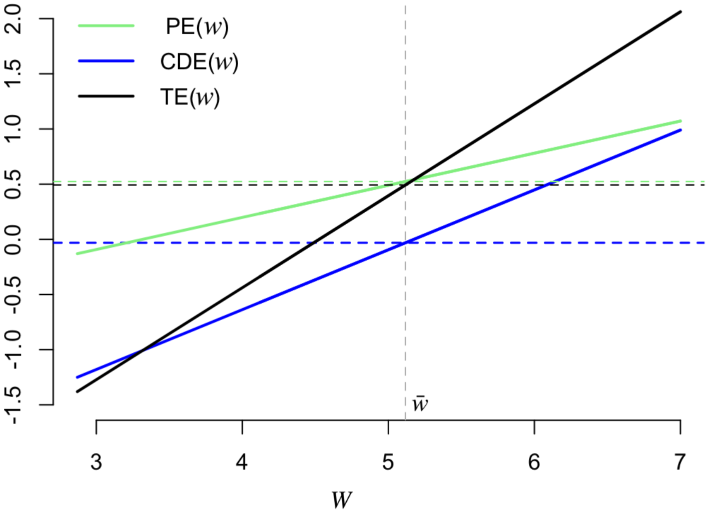
- PE $= [h(x) - h(x_\circ)]\Delta = [1, w]\Delta$
- The TE, CDE, and PE are *functions* of w

Exposure-moderator interaction: example



Multiple mediators

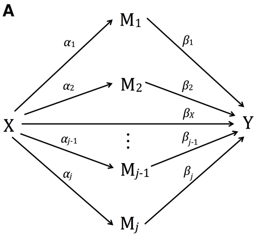
Consider the Full model that contains j mediators

$$\mathbb{E}[Y|X, M, C] = \beta_0 + h(X)\beta_X + \Sigma_{i=1}^{j}\beta_{M_i}M_i + \beta_C C$$

The total PE through $\boldsymbol{M} = [h(x) - h(x_\circ)][-V_{X\boldsymbol{M}}V_{\boldsymbol{M}}^{-1}\boldsymbol{\beta}_{\boldsymbol{M}}]$

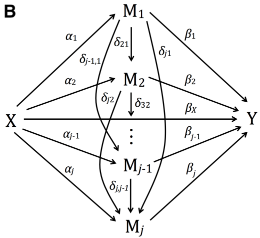
The mediator-specific PE $= [h(x) - h(x_\circ)][-V_{XM_i}V_{M_i}^{-1}\beta_{M_i}]$

Multiple mediators: parallel model



$$\mathrm{E}[Y|X, \boldsymbol{M}] = \beta_0 + \beta_X X + \beta_1 M_1 + \beta_2 M_2 + \cdots + \beta_j M_j$$
$$\mathrm{E}[M_i|X] = \alpha_{0i} + \alpha_i X, i = 1, \ldots, j$$
$$\mathrm{E}[Y|X] = \beta_0^* + \beta_X^* X$$

Multiple mediators: serial model



$$E[Y|X,\boldsymbol{M}] = \beta_0 + \beta_X X + \beta_1 M_1 + \beta_2 M_2 + \cdots + \beta_j M_j$$

$$E[M_i|X] = \alpha_{0i} + \alpha_i X + \Sigma_{k=1}^{i-1}\delta_{ik}M_k, i = 2, \ldots, j$$

$$E[M_1|X] = \alpha_{01} + \alpha_1 X$$

$$E[Y|X] = \beta_0^* + \beta_X^* X$$

Table of total effect decompositions 😱

<table>
<tr><td colspan="4">Total Effect</td></tr>
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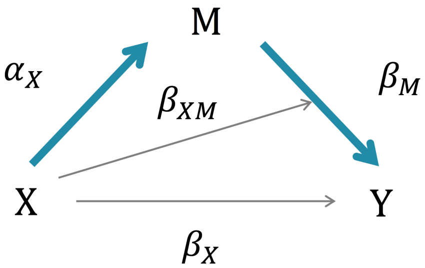
Exposure-mediator interaction



The **pure indirect effect** attributes the interaction effect to the direct effect of the exposure.

Non-nested mediation systems

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2. Use formula for $\hat{\Delta}$ to estimate Δ_{RG} between the Reduced model and the Global model
3. Use formula for $\hat{\Delta}$ to estimate Δ_{FG} between the Full model and the Global model
4. Subtract the corresponding Δs: $\Delta_{\mathsf{PE}} = \Delta_{\mathsf{RG}} - \Delta_{\mathsf{FG}}$.

Non-nested mediation systems

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Non-nested mediation systems

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Use formula for $\hat{\Delta}$

Non-nested mediation systems

$$\mathbb{E}[Y|X,M,C] = \gamma_0 + \gamma_X X + \gamma_M M + \gamma_{XM} XM + \gamma_C C + \gamma_{X^2} X^2 \qquad \text{(G)}$$

$$\mathbb{E}[Y|X,M,C] = \beta_0 + \beta_X X + \beta_M M + \beta_{XM} XM + \beta_C C \qquad \text{(F)}$$

$$\mathbb{E}[Y|X,C] = \beta_0^* + \beta_X^* X + \beta_{X^2}^* X^2 + \beta_C^* C \qquad \text{(R)}$$

$$\Delta_{\mathsf{RG}} = \begin{bmatrix} \beta_X^* - \gamma_X \\ \beta_{X^2}^* - \gamma_{X^2} \end{bmatrix} \text{ and } \Delta_{\mathsf{FG}} = \begin{bmatrix} \beta_X - \gamma_X \\ 0 - \gamma_{X^2} \end{bmatrix}$$

$$\Delta_{\mathsf{RG}} - \Delta_{\mathsf{FG}} = \begin{bmatrix} \beta_X^* - \gamma_X \\ \beta_{X^2}^* - \gamma_{X^2} \end{bmatrix} - \begin{bmatrix} \beta_X - \gamma_X \\ 0 - \gamma_{X^2} \end{bmatrix}$$

Non-nested mediation systems

$$\mathbb{E}[Y|X,M,C] = \gamma_0 + \gamma_X X + \gamma_M M + \gamma_{XM} XM + \gamma_C C + \gamma_{X^2} X^2 \quad \text{(G)}$$

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$$\mathbb{E}[Y|X,C] = \beta_0^* + \beta_X^* X + \beta_{X^2}^* X^2 + \beta_C^* C \quad \text{(R)}$$

$$\Delta_{\mathsf{RG}} = \begin{bmatrix} \beta_X^* - \gamma_X \\ \beta_{X^2}^* - \gamma_{X^2} \end{bmatrix} \text{ and } \Delta_{\mathsf{FG}} = \begin{bmatrix} \beta_X - \gamma_X \\ 0 - \gamma_{X^2} \end{bmatrix}$$

$$\Delta_{\mathsf{RG}} - \Delta_{\mathsf{FG}} = \begin{bmatrix} \beta_X^* - \gamma_X \\ \beta_{X^2}^* - \gamma_{X^2} \end{bmatrix} - \begin{bmatrix} \beta_X - \gamma_X \\ 0 - \gamma_{X^2} \end{bmatrix} = \begin{bmatrix} \beta_X^* - \beta_X \\ \beta_{X^2}^* - 0 \end{bmatrix} \longleftarrow \Delta_{\mathsf{PE}}$$

Non-nested mediation systems

$$\mathbb{E}[Y|X,M,C] = \gamma_0 + \gamma_X X + \gamma_M M + \gamma_{XM} XM + \gamma_C C + \gamma_{X^2} X^2 \quad \text{(G)}$$

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Even for non-nested mediation systems, we can estimate the PE from the fit of one (Global) outcome model.

PE on link scale

Let g=logit link.

$$
\begin{aligned}
(\beta_X^* - \beta_X)(x - x_\circ) &= \text{logit } \mathsf{E}[Y|x,c] - \text{logit } \mathsf{E}[Y|x_\circ,c] \\
&\quad - (\text{logit } \mathsf{E}[Y|x,m,c] - \text{logit } \mathsf{E}[Y|x_\circ,m,c]) \\
&= \log \frac{\text{odds } \mathsf{E}[Y|x,c]}{\text{odds } \mathsf{E}[Y|x_\circ,c]} - \log \frac{\text{odds } \mathsf{E}[Y|x,m,c]}{\text{odds } \mathsf{E}[Y|x_\circ,m,c]} \\
&= \log \frac{\text{odds } \mathsf{E}[Y|x,c]/\text{odds } \mathsf{E}[Y|x_\circ,c]}{\text{odds } \mathsf{E}[Y|x,m,c]/\text{odds } \mathsf{E}[Y|x_\circ,m,c]} \\
&= \log \frac{\text{OR}^{\text{TE}}}{\text{OR}^{\text{CDE}}}
\end{aligned}
$$

$$
\Rightarrow e^{(\beta_X^* - \beta_X)(x - x_\circ)} = \frac{\text{OR}^{\text{TE}}}{\text{OR}^{\text{CDE}}} = \text{OR}^{\text{PE}}
$$

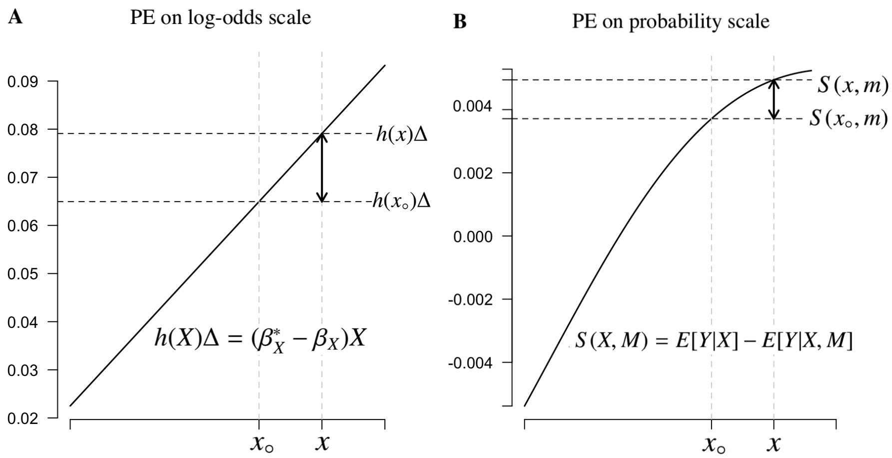
PE on expected value scale

$$g(\mathsf{E}[Y|X,M,C]) = \beta_0 + h(X)\beta_X + \beta_M M + \beta_C C$$
$$g(\mathsf{E}[Y|X,C]) = \beta_0^* + h(X)\beta_X^* + \beta_C^* C$$

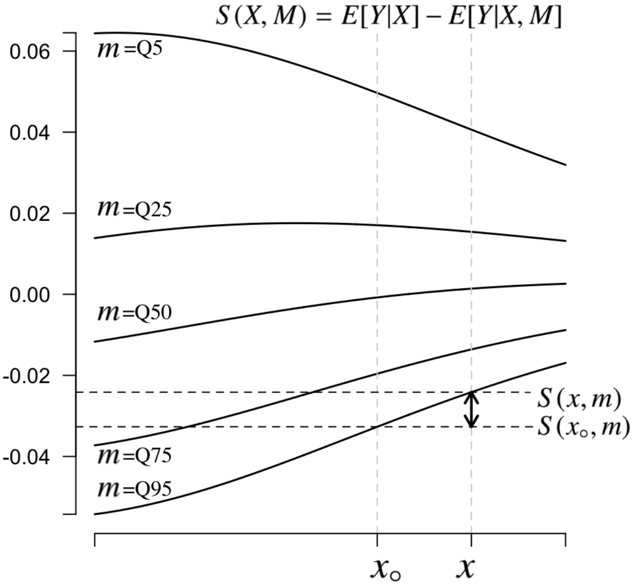
$$\mathsf{E}[Y|x,m,c] = g^{-1}(\eta_F(x,m,c))$$
$$\mathsf{E}[Y|x,c] = g^{-1}(\eta_R(x,c))$$

$$\begin{aligned}\mathsf{PE} &= \mathsf{E}[Y|x,c] - \mathsf{E}[Y|x_\circ,c] - (\mathsf{E}[Y|x,m,c] - \mathsf{E}[Y|x_\circ,m,c]) \\ &= \frac{e^{\eta_R(x,c)}}{1+e^{\eta_R(x,c)}} - \frac{e^{\eta_R(x_\circ,c)}}{1+e^{\eta_R(x_\circ,c)}} - \left(\frac{e^{\eta_F(x,m,c)}}{1+e^{\eta_F(x,m,c)}} - \frac{e^{\eta_F(x_\circ,m,c)}}{1+e^{\eta_F(x_\circ,m,c)}}\right)\end{aligned}$$

Visualizations for GLMs



PE on probability scale



Interpretation at a particular SNP

The exposure is increasing copies of the minor allele (i.e., $x - x_\circ = 1$).

The **total effect** $\text{OR}^{\text{TE}} = \frac{\text{odds E}[Y(1)|c]}{\text{odds E}[Y(1)|c]}$ is the odds ratio for lung cancer comparing those with and without an additional copy of the minor allele.

The **controlled direct effect** $\text{OR}^{\text{CDE}} = \frac{\text{odds E}[Y(1,m)|c]}{\text{odds E}[Y(0,m)|c]}$ is the odds ratio for lung cancer comparing those with and without an additional copy of the minor allele if pack-years were fixed at a certain level m.

The **portion eliminated** $\text{OR}^{\text{PE}} = \text{OR}^{\text{TE}}/\text{OR}^{\text{CDE}}$ is the portion of the total effect of increasing copy of the minor allele on lung cancer that would be eliminated if we were to fix pack-years to the same value m for all persons.

Interpretation at a particular SNP

The **natural direct effect** $\mathrm{OR}^{\mathsf{NDE}} = \frac{\text{odds } \mathsf{E}[Y(1,M(0))|c]}{\text{odds } \mathsf{E}[Y(0,M(0))|c]}$ is the odds ratio for lung cancer comparing those with and without an additional copy of the minor allele *if pack-years were what it would have been without an additional copy of the minor allele*.

The **natural indirect effect** $\mathrm{OR}^{\mathsf{NIE}} = \frac{\text{odds } \mathsf{E}[Y(1,M(1))|c]}{\text{odds } \mathsf{E}[Y(1,M(0))|c]}$ is the odds ratio for lung cancer for those with an additional copy of the minor allele *comparing what would happen if pack-years were set to what it would have been with and without the additional copy of the minor allele*.

Comparison of approaches for logistic regression

	Fitted Models	PE=TE-CDE
Diff. of coefs	$\text{logit } \mathrm{E}[Y\|X,M] = \beta_0 + \beta_X X + \beta_M M$ $\text{logit } \mathrm{E}[Y\|X] = \beta_0^* + \beta_X^* X$	$\beta_X^* - \beta_X$
KHB method	$\text{logit } \mathrm{E}[Y\|X,M] = \beta_0 + \beta_X X + \beta_M M$ $\mathrm{E}[M\|X] = \alpha_0 + \alpha_X X \to \varepsilon_{M\|X}$ $\text{logit } \mathrm{E}[Y\|X,M] = \tilde\beta_0 + \tilde\beta_X X + \tilde\beta_M \varepsilon_{M\|X}$	$\tilde\beta_X - \beta_X$ $= \alpha_X \beta_M$
Mediation formula	$\text{logit } \mathrm{E}[Y\|X,M] = \beta_0 + \beta_X X + \beta_M M$ $\mathrm{E}[M\|X] = \alpha_0 + \alpha_X X$	$\alpha_X \beta_M$
Our formula	$\text{logit } \mathrm{E}[Y\|X,M] = \beta_0 + \beta_X X + \beta_M M$ $\mathrm{E}[M\|X] = \alpha_0 + \alpha_X X, w = \hat p(1-\hat p)$	$-V_{XM} V_M^{-1} \beta_M$ $= \alpha_{X.WLS} \beta_M$

KHB and product approach

$$\tilde{\beta}_x - \beta_X = \frac{\tilde{\gamma}_x}{\tilde{\sigma}_F} - \frac{\gamma_X}{\sigma_F} = \frac{\gamma_X^*}{\sigma_F} - \frac{\gamma_X}{\sigma_F} = \frac{\gamma_X^* - \gamma_X}{\sigma_F}$$

$$\tilde{\beta}_x - \beta_X = \frac{\tilde{\gamma}_x - \gamma_X}{\sigma_F} = \frac{\alpha_X \gamma_M}{\sigma_F} = \alpha_X \beta_M$$

Extension to GLMs

$$g(\mathsf{E}[Y|X, M, C]) = \beta_0 + h(X)\beta_X + \beta_M M + \beta_C C$$
$$g(\mathsf{E}[Y|X, C]) = \beta_0^* + h(X)\beta_X^* + \beta_C^* C$$

- Interpretation of Δ changes
- $-\hat{V}_{XM}\hat{V}_M^{-1}\hat{\beta}_M \approx \hat{\beta}_X^* - \hat{\beta}_X$
- $\mathsf{E}[M|X, C] = \alpha_0 + h(X)\alpha_X + \alpha_C C$, $w = \hat{p}(1 - \hat{p})$

Extension to GLMs

$$g(\mathsf{E}[Y|X, M, C]) = \beta_0 + h(X)\beta_X + \beta_M M + \beta_C C$$

Things to consider:

- Mediation effects defined on link scale or expected value scale
- What is the true marginal model? Marginalizing over logistic doesn't necessarily yield another logistic
- Collapsibility

Working solution:

- Hold the error variance constant by splitting M into the amount that depends on X and the residuals $\varepsilon_{M|X}$ (generalization of the "KHB approach")
- Use Global model idea