# 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

Noevember, 2019

# Overview

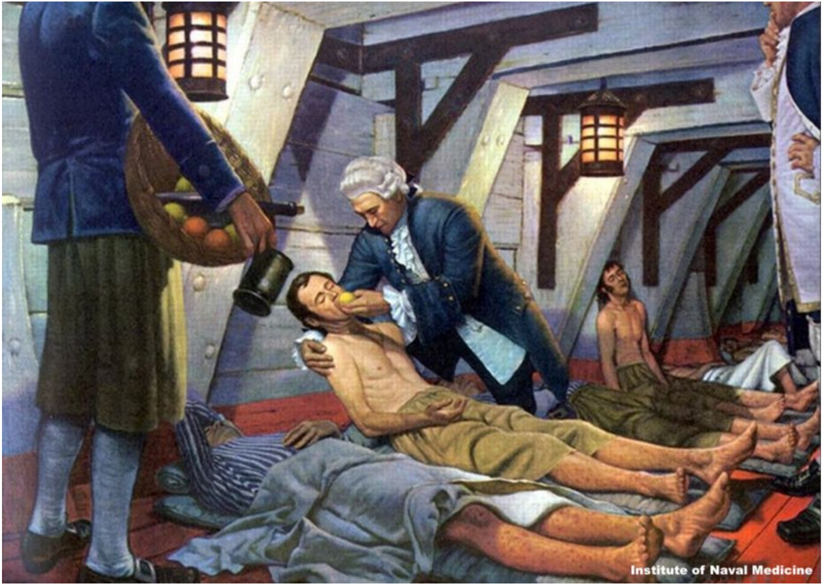
1. Introduction to mediation analysis
   - Motivation
   - Potential outcomes framework
   - Traditional approach
2. Proposed single-model approach
   - Estimate mediation effects from the fit of 1 model
   - Analytical expression for the variance
   - Beyond the simple mediation model: moderated mediation
   - Ongoing work

# Why do a mediation analysis?

## Why do a mediation analysis?

To understand causal mechanisms and
to answer questions like *"How?"* and *"Why?"*

# Scurvy



# Scurvy

- Dr. James Lind credited with the first clinical trial in 1747
- Administered 6 different treatments to 12 afflicted sailors:
  - 2 spoons of vinegar
  - 1 quart of cider
  - 1 cup of seawater
  - 2 oranges, 1 lemon
  - 25 drops elixir of vitriol
  - Paste of garlic, mustard seed, horseradish
- Sailors who were given the citrus fruits got better

Citrus $\longrightarrow$ Scurvy

# Scurvy

- Dr. James Lind credited with the first clinical trial in 1747

- Administered 6 different treatments to 12 afflicted sailors:
  - 2 spoons of vinegar
  - 1 quart of cider
  - 1 cup of seawater
  - 2 oranges, 1 lemon
  - 25 drops elixir of vitriol
  - Paste of garlic, mustard seed, horseradish

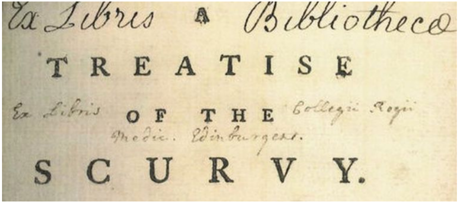
- Sailors who were given the citrus fruits got better. **But why?**

$$\text{Citrus} \xrightarrow{\quad ? \quad} \text{Scurvy}$$

# Scurvy

- Lind suggested lemons worked due to their acidity
- Published *Treatise of the Scurvy* in 1753

Citrus → Acidity → Scurvy


Ex Libris A Bibliotheca

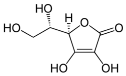
TREATISE

Ex Libris OF THE Collegii Regii
Medic. Edinburgens.

SCURVY.

# Scurvy

- Vitamin C discovered by Albert Szent-Gyorgyi in 1933
- Feeding the sailors citrus fruits increased their vitamin C levels, which in turn remedied their scurvy



Citrus $\longrightarrow$ Vitamin C $\longrightarrow$ Scurvy

Vitamin C is a **mediator** of the effect of citrus on scurvy.

# Motivation

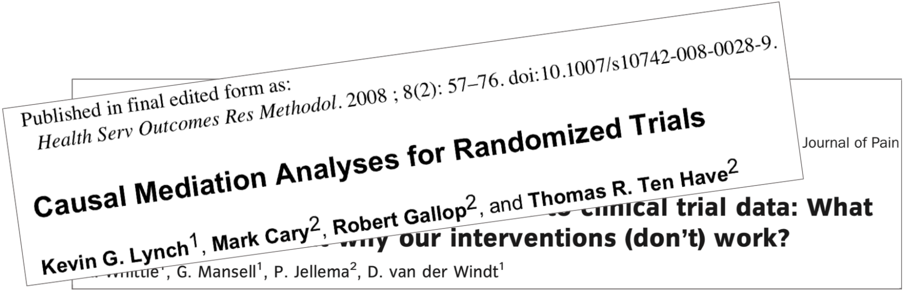
EJP
European Journal of Pain

ORIGINAL ARTICLE

**Applying causal mediation methods to clinical trial data: What can we learn about why our interventions (don't) work?**

R. Whittle[1], G. Mansell[1], P. Jellema[2], D. van der Windt[1]

# Motivation


Published in final edited form as:
*Health Serv Outcomes Res Methodol*. 2008 ; 8(2): 57–76. doi:10.1007/s10742-008-0028-9.

**Causal Mediation Analyses for Randomized Trials**

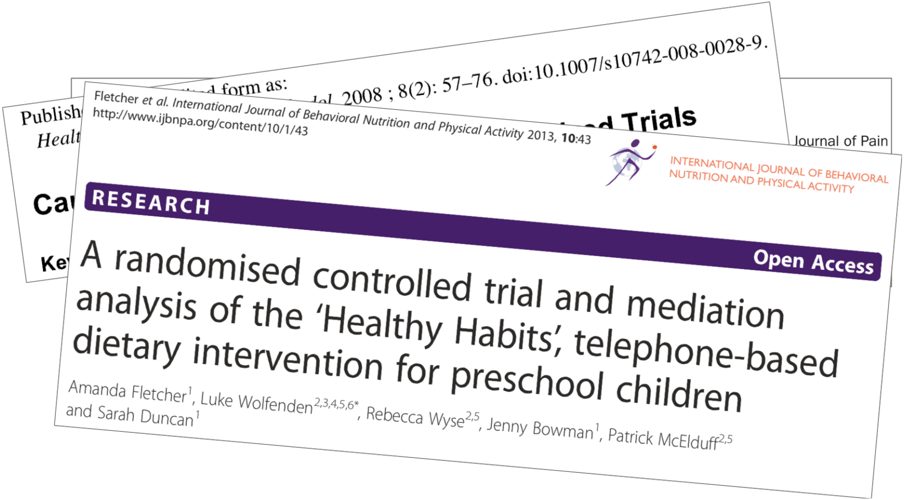
**Kevin G. Lynch**[1], **Mark Cary**[2], **Robert Gallop**[2], and **Thomas R. Ten Have**[2]

Journal of Pain

**clinical trial data: What**
**why our interventions (don't) work?**

G. Mansell[1], P. Jellema[2], D. van der Windt[1]

# Motivation



form as:
2008 ; 8(2): 57–76. doi:10.1007/s10742-008-0028-9.
Trials
Journal of Pain

Fletcher *et al. International Journal of Behavioral Nutrition and Physical Activity* 2013, **10**:43
http://www.ijbnpa.org/content/10/1/43

INTERNATIONAL JOURNAL OF BEHAVIORAL NUTRITION AND PHYSICAL ACTIVITY

RESEARCH

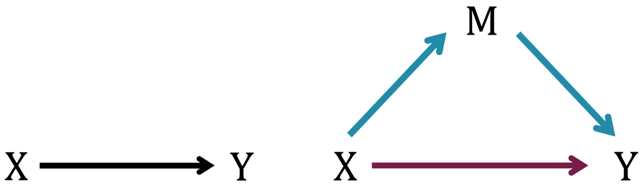
Open Access

A randomised controlled trial and mediation analysis of the 'Healthy Habits', telephone-based dietary intervention for preschool children

Amanda Fletcher[1], Luke Wolfenden[2,3,4,5,6*], Rebecca Wyse[2,5], Jenny Bowman[1], Patrick McElduff[2,5] and Sarah Duncan[1]

# Motivation

- Mediation analysis used frequently in scientific research (epidemiology, neuroscience, public health, social psychology)
- Goal is to gain scientific understanding of causal mechanisms
- Decompose the **total effect** of exposure $X$ on outcome $Y$ into the **direct effect** and the **mediated effect** transmitted through $M$

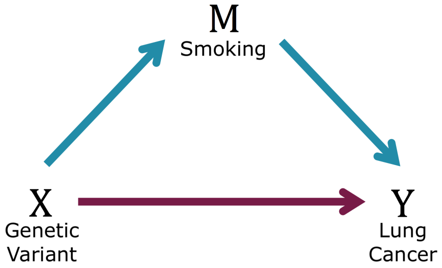


American Journal of Epidemiology
Vol. 175, No. 10
DOI: 10.1093/aje/kwr467
Advance Access publication: February 3, 2012



## Genetic Variants on 15q25.1, Smoking, and Lung Cancer: An Assessment of Mediation and Interaction

**Tyler J. VanderWeele*, Kofi Asomaning, Eric J. Tchetgen Tchetgen, Younghun Han, Margaret R. Spitz, Sanjay Shete, Xifeng Wu, Valerie Gaborieau, Ying Wang, John McLaughlin, Rayjean J. Hung, Paul Brennan, Christopher I. Amos, David C. Christiani, and Xihong Lin**



# How do we estimate mediation effects?

# The potential outcomes framework

(Robins and Greenland, 1992; VanderWeele, 2015)

# Notation

| | |
|---|---|
| $X$ | exposure(s) |
| $M$ | mediator(s) |
| $Y$ | outcome |
| $C$ | confounder(s) |

# Notation

| | |
|---|---|
| $X$ | exposure(s) |
| $M$ | mediator(s) |
| $Y$ | outcome |
| $C$ | confounder(s) |

$(x, x_\circ)$ a pair of exposure values, with $x_\circ$ being the referent level

# Notation

| | |
|---|---|
| $X$ | exposure(s) |
| $M$ | mediator(s) |
| $Y$ | outcome |
| $C$ | confounder(s) |

| | |
|---|---|
| $(x, x_\circ)$ | a pair of exposure values, with $x_\circ$ being the referent level |
| $Y(x)$ | the potential outcome given $X = x$ |

# Notation

| | |
|---|---|
| $X$ | exposure(s) |
| $M$ | mediator(s) |
| $Y$ | outcome |
| $C$ | confounder(s) |

| | |
|---|---|
| $(x, x_\circ)$ | a pair of exposure values, with $x_\circ$ being the referent level |
| $Y(x)$ | the potential outcome given $X = x$ |
| $M(x)$ | the potential mediator given $X = x$ |

# Notation

| | |
|---|---|
| $X$ | exposure(s) |
| $M$ | mediator(s) |
| $Y$ | outcome |
| $C$ | confounder(s) |

| | |
|---|---|
| $(x, x_\circ)$ | a pair of exposure values, with $x_\circ$ being the referent level |
| $Y(x)$ | the potential outcome given $X = x$ |
| $M(x)$ | the potential mediator given $X = x$ |
| $Y(x, m)$ | the potential outcome given $X = x$ and $M = m$ |

# Definitions of causal mediation effects

| | Causal Mediation Effects |
|---|---|
| Total Effect (TE) | $Y(x) - Y(x_\circ)$ |

# Definitions of causal mediation effects

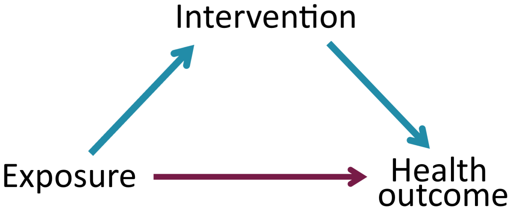
| | Causal Mediation Effects |
|---|---|
| Total Effect (TE) | $Y(x) - Y(x_\circ)$ |
| Controlled Direct Effect (CDE) | $Y(x, m) - Y(x_\circ, m)$ |

# Definitions of causal mediation effects

| | Causal Mediation Effects |
|---|---|
| Total Effect (TE) | $Y(x) - Y(x_\circ)$ |
| Controlled Direct Effect (CDE) | $Y(x,m) - Y(x_\circ,m)$ |
| Portion Eliminated (PE) | $Y(x) - Y(x_\circ) - (Y(x,m) - Y(x_\circ,m))$ |

# The portion eliminated (PE)

**The PE is the amount of the total exposure effect that would be eliminated if we were to intervene on the mediator.**



# Definitions of causal mediation effects

| | Causal Mediation Effects |
|---|---|
| Total Effect (TE) | $Y(x) - Y(x_\circ)$ |
| Controlled Direct Effect (CDE) | $Y(x, m) - Y(x_\circ, m)$ |
| Portion Eliminated (PE) | $Y(x) - Y(x_\circ) - (Y(x, m) - Y(x_\circ, m))$ |
| Natural Direct Effect (NDE) | $Y(x, M(x_\circ)) - Y(x_\circ, M(x_\circ))$ |

- Distinguish between *controlled* and *natural* direct effects

# Definitions of causal mediation effects

| | Causal Mediation Effects |
|---|---|
| Total Effect (TE) | $Y(x) - Y(x_\circ)$ |
| Controlled Direct Effect (CDE) | $Y(x, m) - Y(x_\circ, m)$ |
| Portion Eliminated (PE) | $Y(x) - Y(x_\circ) - (Y(x, m) - Y(x_\circ, m))$ |
| Natural Direct Effect (NDE) | $Y(x, M(x_\circ)) - Y(x_\circ, M(x_\circ))$ |
| Natural Indirect Effect (NIE) | $Y(x, M(x)) - Y(x, M(x_\circ))$ |

- Distinguish between *controlled* and *natural* direct effects
- Several ways to account for mediation:

  PE = TE − CDE and NIE = TE − NDE

# Definitions of causal mediation effects

| | Causal Mediation Effects |
|---|---|
| Total Effect (TE) | $Y(x) - Y(x_\circ)$ |
| Controlled Direct Effect (CDE) | $Y(x,m) - Y(x_\circ,m)$ |
| Portion Eliminated (PE) | $Y(x) - Y(x_\circ) - (Y(x,m) - Y(x_\circ,m))$ |
| Natural Direct Effect (NDE) | $Y(x,M(x_\circ)) - Y(x_\circ,M(x_\circ))$ |
| Natural Indirect Effect (NIE) | $Y(x,M(x)) - Y(x,M(x_\circ))$ |

- Distinguish between *controlled* and *natural* direct effects
- Several ways to account for mediation:

  PE = TE − CDE and NIE = TE − NDE
- $Y(x,M(x_\circ))$ and $Y(x_\circ,M(x))$ can't be observed

# Usefulness of natural direct and indirect effects

*International Journal of Epidemiology*, 2014, 1656–1661
doi: 10.1093/ije/dyu107
Advance Access Publication Date: 23 May 2014
Original article

## Mediation misgivings: ambiguous clinical and public health interpretations of natural direct and indirect effects

**Ashley I Naimi,[1]* Jay S Kaufman[2] and Richard F MacLehose[3]**

"**Natural direct and indirect effects** are becoming **effect estimates of choice** in applied mediation analyses. The merits of this choice have not been reconciled with the repeated calls for a more consequential epidemiology."

# Usefulness of natural direct and indirect effects

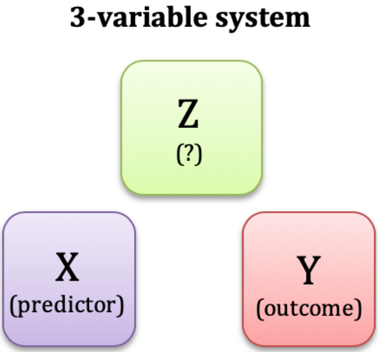
Natural direct and indirect effects:

- Involve the union of two logically incompatible exposure states $Y(x, M(x_\circ))$ and $Y(x_\circ, M(x))$
- Cannot be interpreted to inform individual, clinical, or public health interventions

"This last condition we believe markedly curtails the usefulness of natural direct and indirect effects, especially in light of the extensive history of calls for pragmatic epidemiological research." (Naimi et al.)

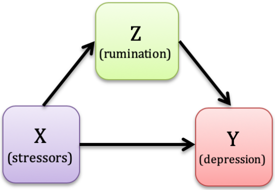
We need to make some assumptions in order to infer causality

# Three-variable systems

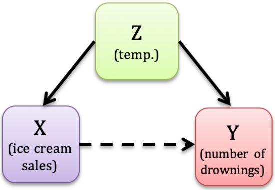


# Three-variable systems

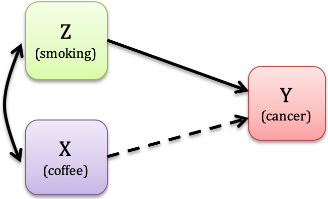
**Mediation**



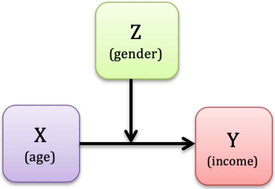

**Confounding**




**Spurious Association**

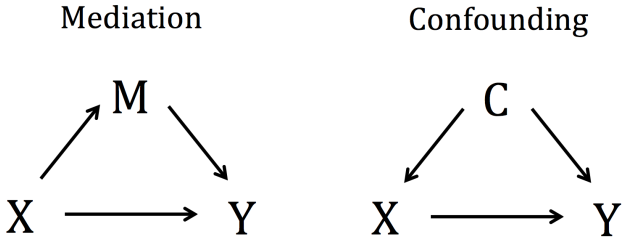



**Moderation (Interaction)**



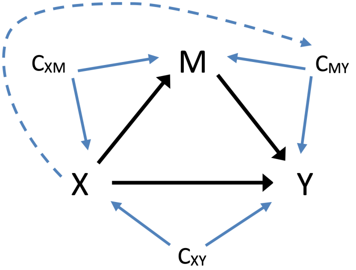
# Assumptions for causal inference

**Correctly specified causal structure:**




- The type of causal structure we believe exists should guide the type of analysis performed
- Draw a DAG!

**No unmeasured confounding assumptions:**




i No unmeasured $X \rightarrow Y$ confounding

ii No unmeasured $M \rightarrow Y$ confounding

iii No unmeasured $X \rightarrow M$ confounding

iv No $M \rightarrow Y$ confounders caused by $X$

- Identifying the TE requires assumption (i)
- Identifying the CDE requires assumptions (i) and (ii)
- Identifying the PE requires assumptions (i) and (ii)
- Identifying the NDE and NIE requires all four assumptions

# Assumptions for causal inference

- **Consistency**

  If $X = x$, the observed outcomes $Y = Y(x)$ and $M = M(x)$
  If $X = x$ and $M = m$, the observed $Y = Y(x, m)$

- **Positivity**

  $0 < \mathsf{P}(X = x|C = c)$ and $0 < \mathsf{P}(M = m|X = x, C = c)$

- **Correctly specified causal structure**

- **Exchangeability** (aka no unmeasured confounding)

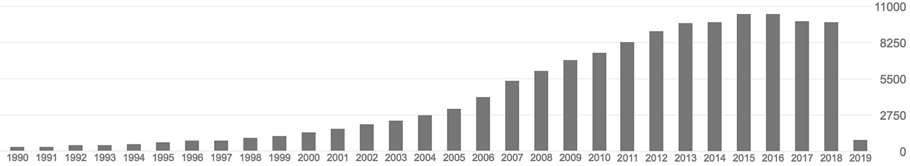
# The “traditional” approach
(Baron and Kenny, 1986)

# The traditional approach

Journal of Personality and Social Psychology
1986, Vol. 51, No. 6, 1173–1182

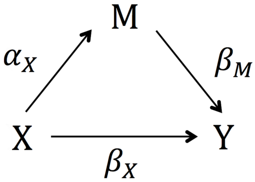
## The Moderator–Mediator Variable Distinction in Social Psychological Research: Conceptual, Strategic, and Statistical Considerations

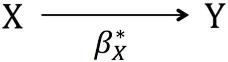
Reuben M. Baron and David A. Kenny
University of Connecticut




Cited over 80,000 times from 1990 - Present (Google Scholar)

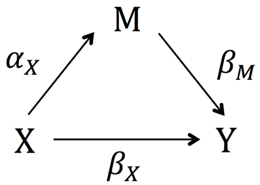
The "traditional" approach to mediation analysis uses a system of three equations (Baron and Kenny, 1986).



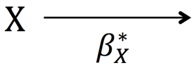

$$
\begin{aligned}
\mathbb{E}[Y|X,M] &= \beta_0 + \beta_X X + \beta_M M && \text{(F)}\\
\mathbb{E}[M|X] &= \alpha_0 + \alpha_X X && \text{(M)}\\
\mathbb{E}[Y|X] &= \beta_0^* + \beta_X^* X && \text{(R)}
\end{aligned}
$$

The "traditional" approach to mediation analysis uses a system of three equations (Baron and Kenny, 1986).



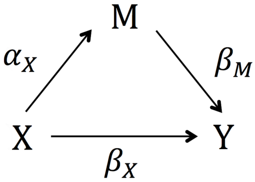

$$\begin{aligned}
\mathbb{E}[Y|X, M] &= \beta_0 + \beta_X X + \beta_M M && \text{(F)}\\
\mathbb{E}[M|X] &= \alpha_0 + \alpha_X X && \text{(M)}\\
\mathbb{E}[Y|X] &= \beta_0^* + \beta_X^* X && \text{(R)}
\end{aligned}$$

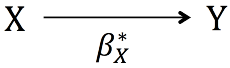
Direct effect: $\beta_X$



# The simple mediation model

The "traditional" approach to mediation analysis uses a system of three equations (Baron and Kenny, 1986).



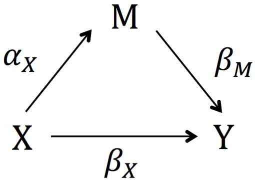

$$
\begin{aligned}
\mathbb{E}[Y|X,M] =& \beta_0 + \beta_X X + \beta_M M && \text{(F)}\\
\mathbb{E}[M|X] =& \alpha_0 + \alpha_X X && \text{(M)}\\
\mathbb{E}[Y|X] =& \beta_0^* + \beta_X^* X && \text{(R)}
\end{aligned}
$$

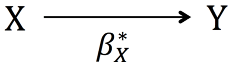
Direct effect: $\beta_X$

Total effect: $\beta_X^*$

# The simple mediation model

The "traditional" approach to mediation analysis uses a system of three equations (Baron and Kenny, 1986).




$$\begin{aligned}
\mathbb{E}[Y|X,M] =& \beta_0 + \beta_X X + \beta_M M && \text{(F)}\\
\mathbb{E}[M|X] =& \alpha_0 + \alpha_X X && \text{(M)}\\
\mathbb{E}[Y|X] =& \beta^*_0 + \beta^*_X X && \text{(R)}
\end{aligned}$$

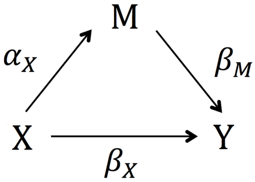
Direct effect: $\beta_X$

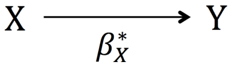
Total effect: $\beta^*_X$

Indirect effect: $\beta^*_X - \beta_X$

# The simple mediation model

The "traditional" approach to mediation analysis uses a system of three equations (Baron and Kenny, 1986).




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

$$\mathbb{E}[M|X] = \alpha_0 + \alpha_X X \qquad \text{(M)}$$

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

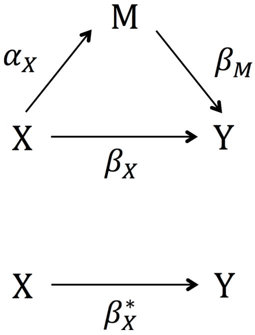
Direct effect: $\beta_X$

Total effect: $\beta_X^*$

Indirect effect: $\beta_X^* - \beta_X = \alpha_X \beta_M$

# The simple mediation model

The "traditional" approach to mediation analysis uses a system of three equations (Baron and Kenny, 1986).




$$
\begin{aligned}
\mathbb{E}[Y|X, M] =& \beta_0 + \beta_X X + \beta_M M && \text{(F)} \\
\mathbb{E}[M|X] =& \alpha_0 + \alpha_X X && \text{(M)} \\
\mathbb{E}[Y|X] =& \beta_0^* + \beta_X^* X && \text{(R)}
\end{aligned}
$$

Direct effect: $\beta_X$

Total effect: $\beta_X^*$

Indirect effect: $\beta_X^* - \beta_X = \alpha_X \beta_M$

Approximate Var$(\alpha_X \beta_M)$

# Do we need three equations?

$$\begin{cases} \text{(F)}\ \mathbb{E}[Y|X,M] & = \beta_0 + \beta_X X + \beta_M M \\ \text{(M)}\ \mathbb{E}[M|X] & = \alpha_0 + \alpha_X X \\ \text{(R)}\ \mathbb{E}[Y|X] & = \beta_0^* + \beta_X^* X \end{cases}$$

# Do we need three equations?

$$\begin{cases} \text{(F)}\ \mathbb{E}[Y|X,M] & = \beta_0 + \beta_X X + \beta_M M \\ \text{(M)}\ \mathbb{E}[M|X] & = \alpha_0 + \alpha_X X \\ \text{(R)}\ \mathbb{E}[Y|X] & = \beta_0^* + \beta_X^* X \end{cases}$$

If we marginalize over $M$:

$$\begin{aligned} \mathbb{E}[Y|X] &= \mathbb{E}_{M|X}\mathbb{E}[Y|X,M] \\ &= \beta_0 + \beta_X X + \beta_M \mathbb{E}[M|X] \\ &= (\beta_0 + \alpha\beta_M) + (\beta_X + \alpha_X \beta_M)X \\ &= \beta_0^* + \beta_X^* X \end{aligned}$$

# Do we need three equations?

$$\begin{cases} \text{(F)} \;\; \mathbb{E}[Y|X, M] & = \beta_0 + \beta_X X + \beta_M M \\ \text{(M)} \;\; \mathbb{E}[M|X] & = \alpha_0 + \alpha_X X \\ \text{(R)} \;\; \mathbb{E}[Y|X] & = \beta_0^* + \beta_X^* X \end{cases}$$

If we marginalize over $M$:

$$\begin{aligned} \mathbb{E}[Y|X] &= \mathbb{E}_{M|X}\mathbb{E}[Y|X, M] \\ &= \beta_0 + \beta_X X + \beta_M \mathbb{E}[M|X] \\ &= (\beta_0 + \alpha\beta_M) + (\beta_X + \alpha_X \beta_M)X \\ &= \beta_0^* + \beta_X^* X \end{aligned}$$

Equations (F) and (M) $\Rightarrow$ (R).

# Consider a different system...

$$\begin{cases} \text{(F)}\ \mathbb{E}[Y|X,M] & = \beta_0 + \beta_X X + \beta_M M \\ \text{(M)}\ \mathbb{E}[M|X] & = \alpha_0 + \alpha_1 X + \alpha_2 X^2 \\ \text{(R)}\ \mathbb{E}[Y|X] & = \beta_0^* + \beta_X^* X \end{cases}$$

# Consider a different system...

$$\begin{cases} \text{(F)} \ \mathbb{E}[Y|X,M] & = \beta_0 + \beta_X X + \beta_M M \\ \text{(M)} \ \mathbb{E}[M|X] & = \alpha_0 + \alpha_1 X + \alpha_2 X^2 \\ \text{(R)} \ \mathbb{E}[Y|X] & = \beta_0^* + \beta_X^* X \end{cases}$$

If we marginalize over $M$:

$$\begin{aligned} \mathbb{E}[Y|X] &= \beta_0 + \beta_X X + \beta_M \mathbb{E}[M|X] \\ &= \gamma_0 + \gamma_1 X + \gamma_2 X^2 \end{aligned}$$

# Consider a different system...

$$\begin{cases} \text{(F)} \;\; \mathbb{E}[Y|X,M] & = \beta_0 + \beta_X X + \beta_M M \\ \text{(M)} \; \mathbb{E}[M|X] & = \alpha_0 + \alpha_1 X + \alpha_2 X^2 \\ \text{(R)} \;\; \mathbb{E}[Y|X] & = \beta_0^* + \beta_X^* X \end{cases}$$

If we marginalize over $M$:

$$\begin{aligned} \mathbb{E}[Y|X] &= \beta_0 + \beta_X X + \beta_M \mathbb{E}[M|X] \\ &= \gamma_0 + \gamma_1 X + \gamma_2 X^2 \end{aligned}$$

Equations (F) and (M) $\not\Rightarrow$ (R).

# Consider a different system...

$$
\begin{cases}
\text{(F)} \; \mathbb{E}[Y|X,M] & = \beta_0 + \beta_X X + \beta_M M \\
\text{(M)} \; \mathbb{E}[M|X] & = \alpha_0 + \alpha_1 X + \alpha_2 X^2 \\
\text{(R)} \; \mathbb{E}[Y|X] & = \beta_0^* + \beta_X^* X
\end{cases}
$$

If we marginalize over $M$:

$$
\begin{aligned}
\mathbb{E}[Y|X] &= \beta_0 + \beta_X X + \beta_M \mathbb{E}[M|X] \\
&= \gamma_0 + \gamma_1 X + \gamma_2 X^2
\end{aligned}
$$

Equations (F) and (M) $\not\Rightarrow$ (R).

In general, to allow $M = h(X)$ for some nonlinear function $h$, one should specify the Full model flexibly...

# How are these two frameworks related?

**Under the simple mediation model, the regression-based estimands from the potential outcomes approach reduce to those from the traditional framework.**

# The simple mediation model

| | Causal Mediation Effects | Simple Mediation Model* |
|---|---|---|
| TE | $\mathbb{E}[Y(x) - Y(x_\circ)]$ | $\beta^*_X$ |

*For a unit change in $X$ so $(x - x_0) = 1$

$$\mathbb{E}[Y|X, M] = \beta_0 + \beta_X X + \beta_M M$$
$$\mathbb{E}[M|X] = \alpha_0 + \alpha_X X$$
$$\mathbb{E}[Y|X] = \beta^*_0 + \beta^*_X X$$

# The simple mediation model

| | Causal Mediation Effects | Simple Mediation Model* |
|---|---|---|
| TE | $\mathbb{E}[Y(x) - Y(x_\circ)]$ | $\beta_X^*$ |
| CDE | $\mathbb{E}[Y(x,m) - Y(x_\circ,m)]$ | $\beta_X$ |
| NDE | $\mathbb{E}[Y(x,M(x_\circ)) - Y(x_\circ,M(x_\circ))]$ | $\beta_X$ |

$^\star$For a unit change in $X$ so $(x - x_0) = 1$

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

# The simple mediation model

| | Causal Mediation Effects | Simple Mediation Model* |
|---|---|---|
| TE | $\mathbb{E}[Y(x) - Y(x_\circ)]$ | $\beta_X^*$ |
| CDE | $\mathbb{E}[Y(x,m) - Y(x_\circ,m)]$ | $\beta_X$ |
| PE | $\mathbb{E}[Y(x) - Y(x_\circ) - (Y(x,m) - Y(x_\circ,m))]$ | $\beta_X^* - \beta_X = \alpha_X\beta_M$ |
| NDE | $\mathbb{E}[Y(x,M(x_\circ)) - Y(x_\circ,M(x_\circ))]$ | $\beta_X$ |
| NIE | $\mathbb{E}[Y(x,M(x)) - Y(x,M(x_\circ))]$ | $\beta_X^* - \beta_X = \alpha_X\beta_M$ |

*For a unit change in $X$ so $(x - x_0) = 1$

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

# The traditional approach

**Benefits:**

- ✓ Simple to understand
- ✓ Easy for non-statisticians to implement (>80,000 citations)

# The traditional approach

**Benefits:**

- ✓ Simple to understand
- ✓ Easy for non-statisticians to implement ($>$80,000 citations)

**Limitations:**

- x Does not generalize to complex models
  - Nonlinearities (e.g., splined $X$)
  - Multiple mediators
  - Interactions
  - Generalized linear models

# The traditional approach

**Benefits:**

- ✓ Simple to understand
- ✓ Easy for non-statisticians to implement ($>$80,000 citations)

**Limitations:**

- × Does not generalize to complex models
    - Nonlinearities (e.g., splined $X$)
    - Multiple mediators
    - Interactions
    - Generalized linear models
- × Requires fitting a system of equations
    - Risk of specifying incongruent system
    - Computational burden with big data

# The traditional approach

**Benefits:**

- ✓ Simple to understand
- ✓ Easy for non-statisticians to implement ($>$80,000 citations)

**Limitations:**

- × Does not generalize to complex models
  - Nonlinearities (e.g., splined $X$)
  - Multiple mediators
  - Interactions
  - Generalized linear models
- × Requires fitting a system of equations
  - Risk of specifying incongruent system
  - Computational burden with big data
- × Approximation to estimate variance (delta method, bootstrap)

# The potential outcomes framework

**Benefits:**

- ✓ Generalizes traditional approach to complex models
- ✓ Formalizes definitions of causal mediation effects
- ✓ Emphasizes the assumptions required for causal inference

# The potential outcomes framework

**Benefits:**

- ✓ Generalizes traditional approach to complex models
- ✓ Formalizes definitions of causal mediation effects
- ✓ Emphasizes the assumptions required for causal inference

**Limitations:**

- × Metaphysical definitions of NDE and NIE can be hard to interpret or irrelevant to real-world applications
- × Fitting a system of equations
  - Risk of specifying incongruent system
  - Computational burden with big data
- × Approximation to estimate variance

# The single-model approach

(Saunders and Blume, 2017)

*Biostatistics* (2018) **19**, 4, *pp.* 514–528
doi:10.1093/biostatistics/kxx054
Advance Access publication on October 26, 2017

## A classical regression framework for mediation analysis: fitting one model to estimate mediation effects

CHRISTINA T. SAUNDERS*, JEFFREY D. BLUME

# The single-model approach

**Benefits:**

- ✓ Generalizes traditional approach to complex models
- ✓ Formalizes definitions of causal mediation effects
- ✓ Emphasizes the assumptions required for causal inference

**~~Limitations:~~** **More Benefits:**

- × Metaphysical definitions of NDE and NIE can be hard to interpret or irrelevant to real-world applications
- × Fitting a system of equations
  - Risk of specifying incongruent system
  - Computational burden with big data
- × Approximation to estimate variance

# The single-model approach

**Benefits:**

- ✓ Generalizes traditional approach to complex models
- ✓ Formalizes definitions of causal mediation effects
- ✓ Emphasizes the assumptions required for causal inference

**~~Limitations:~~ More Benefits:**

- ✓ ~~Metaphysical definitions of NDE and NIE can be hard to interpret or irrelevant to real-world applications~~ PE has practical relevance
- × Fitting a system of equations
  - Risk of specifying incongruent system
  - Computational burden with big data
- × Approximation to estimate variance

# The single-model approach

**Benefits:**

- ✓ Generalizes traditional approach to complex models
- ✓ Formalizes definitions of causal mediation effects
- ✓ Emphasizes the assumptions required for causal inference

~~**Limitations:**~~ **More Benefits:**

- ✓ ~~Metaphysical definitions of NDE and NIE can be hard to interpret or irrelevant to real-world applications~~ PE has practical relevance
- ✓ ~~Fitting a system of equations~~ Fit one equation
    - Risk of specifying incongruent system
    - Computational burden with big data
- × Approximation to estimate variance

# The single-model approach

**Benefits:**

- ✓ Generalizes traditional approach to complex models
- ✓ Formalizes definitions of causal mediation effects
- ✓ Emphasizes the assumptions required for causal inference

**~~Limitations:~~ More Benefits:**

- ✓ ~~Metaphysical definitions of NDE and NIE can be hard to interpret or irrelevant to real-world applications~~ PE has practical relevance
- ✓ ~~Fitting a system of equations~~ Fit one equation
  - ~~Risk of specifying incongruent system~~ Avoid errors
  - Computational burden with big data
- × Approximation to estimate variance

# The single-model approach

**Benefits:**

- ✓ Generalizes traditional approach to complex models
- ✓ Formalizes definitions of causal mediation effects
- ✓ Emphasizes the assumptions required for causal inference

**~~Limitations:~~ More Benefits:**

- ✓ ~~Metaphysical definitions of NDE and NIE can be hard to interpret or irrelevant to real-world applications~~ PE has practical relevance
- ✓ ~~Fitting a system of equations~~ Fit one equation
  - ~~Risk of specifying incongruent system~~ Avoid errors
  - ~~Computational burden with big data~~ Efficiency
- × Approximation to estimate variance

# The single-model approach

**Benefits:**

- ✓ Generalizes traditional approach to complex models
- ✓ Formalizes definitions of causal mediation effects
- ✓ Emphasizes the assumptions required for causal inference

**~~Limitations:~~** **More Benefits:**

- ✓ ~~Metaphysical definitions of NDE and NIE can be hard to interpret or irrelevant to real-world applications~~ PE has practical relevance
- ✓ ~~Fitting a system of equations~~ Fit one equation
  - ~~Risk of specifying incongruent system~~ Avoid errors
  - ~~Computational burden with big data~~ Efficiency
  - Simple to apply modeling tools that are not easily implemented on a system of equations
- × Approximation to estimate variance

# The single-model approach

**Benefits:**

- ✓ Generalizes traditional approach to complex models
- ✓ Formalizes definitions of causal mediation effects
- ✓ Emphasizes the assumptions required for causal inference

**~~Limitations:~~ More Benefits:**

- ✓ ~~Metaphysical definitions of NDE and NIE can be hard to interpret or irrelevant to real-world applications~~ PE has practical relevance
- ✓ ~~Fitting a system of equations~~ Fit one equation
  - ~~Risk of specifying incongruent system~~ Avoid errors
  - ~~Computational burden with big data~~ Efficiency
  - Simple to apply modeling tools that are not easily implemented on a system of equations
- ✓ ~~Approximation to estimate variance~~ Analytical formula

# The single-model approach

The Full model

$$\mathbb{E}[Y|\boldsymbol{X}, \boldsymbol{M}, \boldsymbol{C}] = \beta_0 + \boldsymbol{\beta_X} \boldsymbol{h}(\boldsymbol{X}) + \boldsymbol{\beta_M} \boldsymbol{M} + \boldsymbol{\beta_C} \boldsymbol{C} \tag{F}$$

$\boldsymbol{h}(\boldsymbol{X})$ allows for non-linear trends (e.g., splined $X$)
$\boldsymbol{M}$ and $\boldsymbol{C}$ can be vectors

# The single-model approach

The Full model and its implied Reduced model are

$$\mathbb{E}[Y|\boldsymbol{X},\boldsymbol{M},\boldsymbol{C}] = \beta_0 + \boldsymbol{\beta_X} \boldsymbol{h}(\boldsymbol{X}) + \boldsymbol{\beta_M} \boldsymbol{M} + \boldsymbol{\beta_C} \boldsymbol{C} \tag{F}$$

$$\mathbb{E}[Y|\boldsymbol{X},\boldsymbol{C}] = \beta_0^* + \boldsymbol{\beta^*_X} \boldsymbol{h}(\boldsymbol{X}) + \boldsymbol{\beta^*_C} \boldsymbol{C} \tag{R}$$

# The single-model approach

The Full model and its implied Reduced model are

$$\mathbb{E}[Y|\boldsymbol{X},\boldsymbol{M},\boldsymbol{C}] = \beta_0 + \boldsymbol{\beta_X h(X)} + \boldsymbol{\beta_M M} + \boldsymbol{\beta_C C} \tag{F}$$

$$\mathbb{E}[Y|\boldsymbol{X},\boldsymbol{C}] = \beta_0^* + \boldsymbol{\beta_X^* h(X)} + \boldsymbol{\beta_C^* C} \tag{R}$$

$$\text{TE} = [\boldsymbol{h}(x) - \boldsymbol{h}(x_\circ)]\boldsymbol{\beta_X^*}$$

# The single-model approach

The Full model and its implied Reduced model are

$$\mathbb{E}[Y|\boldsymbol{X}, \boldsymbol{M}, \boldsymbol{C}] = \beta_0 + \boldsymbol{\beta_X} \boldsymbol{h}(\boldsymbol{X}) + \boldsymbol{\beta_M} \boldsymbol{M} + \boldsymbol{\beta_C} \boldsymbol{C} \tag{F}$$

$$\mathbb{E}[Y|\boldsymbol{X}, \boldsymbol{C}] = \beta_0^* + \boldsymbol{\beta_X^*} \boldsymbol{h}(\boldsymbol{X}) + \boldsymbol{\beta_C^*} \boldsymbol{C} \tag{R}$$

$$\mathsf{TE} = [\boldsymbol{h}(x) - \boldsymbol{h}(x_\circ)]\boldsymbol{\beta_X^*}$$

$$\mathsf{CDE} = [\boldsymbol{h}(x) - \boldsymbol{h}(x_\circ)]\boldsymbol{\beta_X}$$

# The single-model approach

The Full model and its implied Reduced model are

$$\mathbb{E}[Y|\boldsymbol{X},\boldsymbol{M},\boldsymbol{C}] = \beta_0 + \boldsymbol{\beta_X} \boldsymbol{h}(\boldsymbol{X}) + \boldsymbol{\beta_M}\boldsymbol{M} + \boldsymbol{\beta_C}\boldsymbol{C} \tag{F}$$

$$\mathbb{E}[Y|\boldsymbol{X},\boldsymbol{C}] = \beta_0^* + \boldsymbol{\beta^*_X} \boldsymbol{h}(\boldsymbol{X}) + \boldsymbol{\beta^*_C}\boldsymbol{C} \tag{R}$$

$$\begin{aligned}
\mathsf{TE} &= [\boldsymbol{h}(x) - \boldsymbol{h}(x_\circ)]\boldsymbol{\beta^*_X} \\
\mathsf{CDE} &= [\boldsymbol{h}(x) - \boldsymbol{h}(x_\circ)]\boldsymbol{\beta_X} \\
\mathsf{PE} &= \mathsf{TE} - \mathsf{CDE} = [\boldsymbol{h}(x) - \boldsymbol{h}(x_\circ)](\boldsymbol{\beta^*_X} - \boldsymbol{\beta_X})
\end{aligned}$$

# The single-model approach

The Full model and its implied Reduced model are

$$\mathbb{E}[Y|\boldsymbol{X},\boldsymbol{M},\boldsymbol{C}] = \beta_0 + \boldsymbol{\beta_X h(X)} + \boldsymbol{\beta_M M} + \boldsymbol{\beta_C C} \tag{F}$$

$$\mathbb{E}[Y|\boldsymbol{X},\boldsymbol{C}] = \beta_0^* + \boldsymbol{\beta_X^* h(X)} + \boldsymbol{\beta_C^* C} \tag{R}$$

$$\begin{aligned}
\mathsf{TE} &= [\boldsymbol{h}(x) - \boldsymbol{h}(x_\circ)]\boldsymbol{\beta_X^*} \\
\mathsf{CDE} &= [\boldsymbol{h}(x) - \boldsymbol{h}(x_\circ)]\boldsymbol{\beta_X} \\
\mathsf{PE} &= \mathsf{TE} - \mathsf{CDE} = [\boldsymbol{h}(x) - \boldsymbol{h}(x_\circ)](\boldsymbol{\beta_X^*} - \boldsymbol{\beta_X})
\end{aligned}$$

$$\Delta \equiv \boldsymbol{\beta_X^*} - \boldsymbol{\beta_X}$$

# The single-model approach

The Full model and its implied Reduced model are

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

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

$$\begin{aligned}
\text{TE} &= [\boldsymbol{h}(x) - \boldsymbol{h}(x_\circ)]\boldsymbol{\beta_X^*} \\
\text{CDE} &= [\boldsymbol{h}(x) - \boldsymbol{h}(x_\circ)]\boldsymbol{\beta_X} \\
\text{PE} &= \text{TE} - \text{CDE} = [\boldsymbol{h}(x) - \boldsymbol{h}(x_\circ)](\boldsymbol{\beta_X^*} - \boldsymbol{\beta_X})
\end{aligned}$$

$$\Delta \equiv \boldsymbol{\beta_X^*} - \boldsymbol{\beta_X}$$

**We derived a formula for $\Delta$ that allows us to estimate the PE and its variance from the fit of one model (F).**

# Single-model formula for the PE

The Full model and its implied Reduced model are

$$\mathbb{E}[Y|\boldsymbol{X}, \boldsymbol{M}, \boldsymbol{C}] = \beta_0 + \boldsymbol{\beta_X} \boldsymbol{h}(\boldsymbol{X}) + \boldsymbol{\beta_M} \boldsymbol{M} + \boldsymbol{\beta_C} \boldsymbol{C} \tag{F}$$

$$\mathbb{E}[Y|\boldsymbol{X}, \boldsymbol{C}] = \beta_0^* + \boldsymbol{\beta^*_X} \boldsymbol{h}(\boldsymbol{X}) + \boldsymbol{\beta^*_C} \boldsymbol{C} \tag{R}$$

Formula for $\Delta$:

$$\Delta \equiv \boldsymbol{\beta^*_X} - \boldsymbol{\beta_X} = -\boldsymbol{V_{XM}} \boldsymbol{V_M^{-1}} \boldsymbol{\beta_M}$$

# Single-model formula for the PE

The Full model and its implied Reduced model are

$$\mathbb{E}[Y|\boldsymbol{X},\boldsymbol{M},\boldsymbol{C}] = \beta_0 + \boldsymbol{\beta_X} \boldsymbol{h}(\boldsymbol{X}) + \boldsymbol{\beta_M} \boldsymbol{M} + \boldsymbol{\beta_C} \boldsymbol{C} \tag{F}$$

$$\mathbb{E}[Y|\boldsymbol{X},\boldsymbol{C}] = \beta_0^* + \boldsymbol{\beta_X^*} \boldsymbol{h}(\boldsymbol{X}) + \boldsymbol{\beta_C^*} \boldsymbol{C} \tag{R}$$

Formula for $\Delta$:

$$\begin{aligned}\Delta \equiv \boldsymbol{\beta_X^*} - \boldsymbol{\beta_X} &= -\boldsymbol{V_{XM}} \boldsymbol{V_M^{-1}} \boldsymbol{\beta_M} \\ &= -\mathrm{cov}(\boldsymbol{\beta_X}, \boldsymbol{\beta_M}) \mathrm{var}(\boldsymbol{\beta_M})^{-1} \boldsymbol{\beta_M}\end{aligned}$$

# Single-model formula for the PE

The Full model and its implied Reduced model are

$$\mathbb{E}[Y|\boldsymbol{X},\boldsymbol{M},\boldsymbol{C}] = \beta_0 + \boldsymbol{\beta_X}\boldsymbol{h}(\boldsymbol{X}) + \boldsymbol{\beta_M}\boldsymbol{M} + \boldsymbol{\beta_C}\boldsymbol{C} \tag{F}$$

$$\mathbb{E}[Y|\boldsymbol{X},\boldsymbol{C}] = \beta_0^* + \boldsymbol{\beta_X^*}\boldsymbol{h}(\boldsymbol{X}) + \boldsymbol{\beta_C^*}\boldsymbol{C} \tag{R}$$

Formula for $\Delta$:

$$\begin{aligned}\Delta \equiv \boldsymbol{\beta_X^*} - \boldsymbol{\beta_X} &= -\boldsymbol{V_{XM}}\boldsymbol{V_M^{-1}}\boldsymbol{\beta_M} \\ &= -\mathsf{cov}(\boldsymbol{\beta_X},\boldsymbol{\beta_M})\mathsf{var}(\boldsymbol{\beta_M})^{-1}\boldsymbol{\beta_M}\end{aligned}$$

# Single-model formula for the PE

The Full model and its implied Reduced model are

$$\mathbb{E}[Y|\boldsymbol{X},\boldsymbol{M},\boldsymbol{C}] = \beta_0 + \boldsymbol{\beta_X}\boldsymbol{h}(\boldsymbol{X}) + \boldsymbol{\beta_M}\boldsymbol{M} + \boldsymbol{\beta_C}\boldsymbol{C} \tag{F}$$

$$\mathbb{E}[Y|\boldsymbol{X},\boldsymbol{C}] = \beta_0^* + \boldsymbol{\beta_X^*}\boldsymbol{h}(\boldsymbol{X}) + \boldsymbol{\beta_C^*}\boldsymbol{C} \tag{R}$$

Formula for $\Delta$:

$$\begin{aligned}\Delta \equiv \boldsymbol{\beta_X^*} - \boldsymbol{\beta_X} &= -\boldsymbol{V_{XM}}\boldsymbol{V_M^{-1}}\boldsymbol{\beta_M} \\ &= -\mathsf{cov}(\boldsymbol{\beta_X},\boldsymbol{\beta_M})\mathsf{var}(\boldsymbol{\beta_M})^{-1}\boldsymbol{\beta_M}\end{aligned}$$

# Single-model formula for the PE

The Full model and its implied Reduced model are

$$\mathbb{E}[Y|\boldsymbol{X},\boldsymbol{M},\boldsymbol{C}] = \beta_0 + \boldsymbol{\beta_X h(X)} + \boldsymbol{\beta_M M} + \boldsymbol{\beta_C C} \qquad \text{(F)}$$
$$\mathbb{E}[Y|\boldsymbol{X},\boldsymbol{C}] = \beta_0^* + \boldsymbol{\beta_X^* h(X)} + \boldsymbol{\beta_C^* C} \qquad \text{(R)}$$

Formula for $\Delta$ and its variance:

$$\begin{aligned}\Delta = \boldsymbol{\beta_X^*} - \boldsymbol{\beta_X} &= -\boldsymbol{V_{XM} V_M^{-1} \beta_M} \\ &= -\mathsf{cov}(\boldsymbol{\beta_X}, \boldsymbol{\beta_M})\mathsf{var}(\boldsymbol{\beta_M})^{-1}\boldsymbol{\beta_M} \\ \mathsf{Var}(\hat{\Delta}|X,M) &= V_{XM}V_M^{-1}V_{MX}\end{aligned}$$

# Single-model formula for the PE

The Full model and its implied Reduced model are

$$\mathbb{E}[Y|\boldsymbol{X}, \boldsymbol{M}, \boldsymbol{C}] = \beta_0 + \boldsymbol{\beta_X h(X)} + \boldsymbol{\beta_M M} + \boldsymbol{\beta_C C} \tag{F}$$

$$\mathbb{E}[Y|\boldsymbol{X}, \boldsymbol{C}] = \beta_0^* + \boldsymbol{\beta_X^* h(X)} + \boldsymbol{\beta_C^* C} \tag{R}$$

Formula for $\Delta$ and its variance:

$$\begin{aligned}\Delta = \boldsymbol{\beta_X^*} - \boldsymbol{\beta_X} &= -\boldsymbol{V_{XM} V_M^{-1}} \boldsymbol{\beta_M} \\ &= -\mathsf{cov}(\boldsymbol{\beta_X}, \boldsymbol{\beta_M})\mathsf{var}(\boldsymbol{\beta_M})^{-1}\boldsymbol{\beta_M} \\ \mathsf{Var}(\hat{\Delta}|X, M) &= V_{XM} V_M^{-1} V_{MX}\end{aligned}$$

To estimate the portion eliminated: $\widehat{\mathsf{PE}} = [\boldsymbol{h}(x) - \boldsymbol{h}(x_\circ)]\hat{\Delta}$

# Single-model formula for the PE

The Full model and its implied Reduced model are

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

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

Formula for $\Delta$ and its variance:

$$\begin{aligned} \Delta = \boldsymbol{\beta_X^*} - \boldsymbol{\beta_X} &= -\boldsymbol{V_{XM} V_M^{-1} \beta_M} \\ &= -\mathsf{cov}(\boldsymbol{\beta_X}, \boldsymbol{\beta_M})\mathsf{var}(\boldsymbol{\beta_M})^{-1}\boldsymbol{\beta_M} \\ \mathsf{Var}(\hat{\Delta}|X, M) &= V_{XM} V_M^{-1} V_{MX} \end{aligned}$$

To estimate the portion eliminated: $\widehat{\mathsf{PE}} = [\boldsymbol{h}(x) - \boldsymbol{h}(x_\circ)]\hat{\Delta}$

**Estimate $\widehat{\textbf{PE}}$ and its variance using functionals of (F).**

# What can we do with this?

- Estimate causal mediation effects from the fit of one model
- Analytical variance for the PE
- Multiple mediators
- Non-linear exposure effects (e.g., splined $X$)
- Moderated mediation (i.e., interactions)
- Visualizing mediation effects

# Beyond the simple mediation model

(Saunders and Blume, 2018)

MULTIVARIATE BEHAVIORAL RESEARCH
https://doi.org/10.1080/00273171.2018.1552109

Routledge
Taylor & Francis Group

**A Regression Framework for Causal Mediation Analysis with Applications to Behavioral Science**

IN PRESS

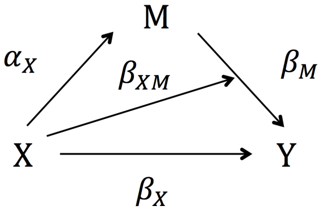
Christina T. Saunders and Jeffrey D. Blume

What about exposure-*mediator* interactions?

What about exposure-*mediator* interactions?

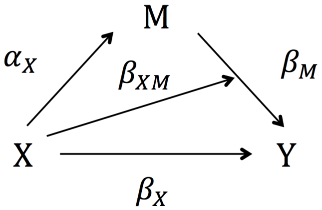
not as straightforward ...

# Exposure-mediator interaction



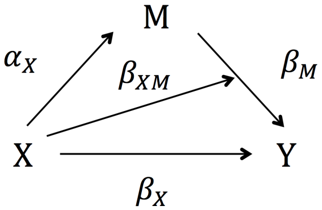

$$\mathbb{E}[Y|X, M, C] = \beta_0 + \beta_X X + \beta_M M + \beta_C C + \beta_{XM} XM$$

# Exposure-mediator interaction



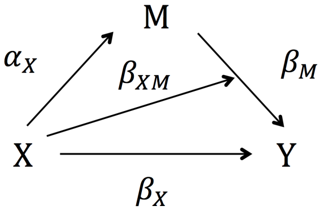

$$\begin{aligned}\mathbb{E}[Y|X,M,C] &= \beta_0 + \beta_X X + \beta_M M + \beta_C C + \beta_{XM} XM \\ &= \beta_0 + (\beta_X X + \beta_{XM} M)X + \beta_M M + \beta_C C\end{aligned}$$

# Exposure-mediator interaction




$$
\begin{aligned}
\mathbb{E}[Y|X, M, C] &= \beta_0 + \beta_X X + \beta_M M + \beta_C C + \beta_{XM} XM \\
&= \beta_0 + (\beta_X X + \beta_{XM} M)X + \beta_M M + \beta_C C \\
&= \beta_0 + \beta_X X + (\beta_M + \beta_{XM} X)M + \beta_C C
\end{aligned}
$$

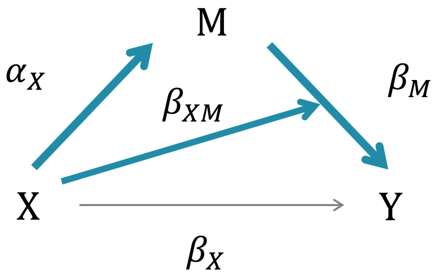
# Exposure-mediator interaction




**How do we account for the interaction effect $\beta_{XM}$?**

$$
\begin{aligned}
\mathbb{E}[Y|X,M,C] &= \beta_0 + \beta_X X + \beta_M M + \beta_C C + \beta_{XM} XM \\
&= \beta_0 + (\beta_X X + \beta_{XM} M)X + \beta_M M + \beta_C C \\
&= \beta_0 + \beta_X X + (\beta_M + \beta_{XM} X)M + \beta_C C
\end{aligned}
$$

# Exposure-mediator interaction




The **portion eliminated** is the portion of the total effect attributed to **both** interaction and mediation.

# Exposure-mediator interaction

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

# Exposure-mediator interaction

$$\mathbb{E}[Y|X,M,C] = \beta_0 + \beta_X X + \beta_M M + \beta_C C + \beta_{XM} XM \qquad \text{(F)}$$
$$\mathbb{E}[M|X,C] = \alpha_0 + \alpha_X X + \alpha_C C \qquad \text{(M)}$$

# Exposure-mediator interaction

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

$$\mathbb{E}[M|X,C] = \alpha_0 + \alpha_X X + \alpha_C C \qquad \text{(M)}$$

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

# Exposure-mediator interaction

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

$$\mathbb{E}[M|X,C] = \alpha_0 + \alpha_X X + \alpha_C C \qquad \text{(M)}$$

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

# Exposure-mediator interaction

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

$$\mathbb{E}[M|X,C] = \alpha_0 + \alpha_X X + \alpha_C C \qquad \text{(M)}$$

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

$$\Delta = \begin{bmatrix} \beta_X^* - \beta_X \\ \beta_{X^2}^* - 0 \end{bmatrix}$$

$$\mathbb{E}[Y|X,M,C] = \beta_0 + \beta_X X + \beta_M M + \beta_C C + \beta_{XM} XM \tag{F}$$
$$\mathbb{E}[M|X,C] = \alpha_0 + \alpha_X X + \alpha_C C \tag{M}$$
$$\mathbb{E}[Y|X,C] = \beta_0^* + \beta_X^* X + \beta_{X^2}^* X^2 + \beta_C^* C \tag{R}$$

$$\Delta = \begin{bmatrix} \beta_X^* - \beta_X \\ \beta_{X^2}^* - 0 \end{bmatrix}$$

A direct application of the $\Delta$ formula is not applicable when the Reduced model (R) is not nested within the Full model (F).

# Exposure-mediator interaction

$$\mathbb{E}[Y|X,M,C] = \beta_0 + \beta_X X + \beta_M M + \beta_C C + \beta_{XM} XM \qquad \text{(F)}$$
$$\mathbb{E}[M|X,C] = \alpha_0 + \alpha_X X + \alpha_C C \qquad \text{(M)}$$
$$\mathbb{E}[Y|X,C] = \beta_0^* + \beta_X^* X + \beta_{X^2}^* X^2 + \beta_C^* C \qquad \text{(R)}$$

$$\Delta = \begin{bmatrix} \beta_X^* - \beta_X \\ \beta_{X^2}^* - 0 \end{bmatrix}$$

A direct application of the $\Delta$ formula is not applicable when the Reduced model (R) is not nested within the Full model (F).

**How can we estimate $\Delta$ from a "non-nested" system?**

$$\mathbb{E}[Y|X,M,C] = \beta_0 + \beta_X X + \beta_M M + \beta_C C + \beta_{XM} XM \qquad \text{(F)}$$
$$\mathbb{E}[M|X,C] = \alpha_0 + \alpha_X X + \alpha_C C \qquad \text{(M)}$$
$$\mathbb{E}[Y|X,C] = \beta_0^* + \beta_X^* X + \beta_{X^2}^* X^2 + \beta_C^* C \qquad \text{(R)}$$

$$\Delta = \begin{bmatrix} \beta_X^* - \beta_X \\ \beta_{X^2}^* - 0 \end{bmatrix}$$

A direct application of the $\Delta$ formula is not applicable when the Reduced model (R) is not nested within the Full model (F).

**How can we estimate $\Delta$ from a "non-nested" system?**
Specify a *Global model* under which the (F) and (R) are nested.

# The single-model approach

**Benefits:**

- ✓ Generalizes traditional approach to complex models
- ✓ Emphasizes the assumptions required for causal inference
- ✓ Estimates PE, a mediation effect with practical relevance
- ✓ Fits one equation
  - Avoid non-congruent estimates from fitting a system
  - Computational efficiency
  - Apply routine modeling tools
- ✓ Analytical formula for variance

**Limitations:**

- Does not estimate natural direct and indirect effects
- Extension to GLMs under development 🚧

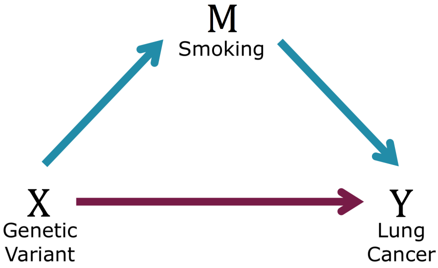
# Example from genetic epidemiology

American Journal of Epidemiology

Vol. 175, No. 10
DOI: 10.1093/aje/kwr467
Advance Access publication:
February 3, 2012

**Genetic Variants on 15q25.1, Smoking, and Lung Cancer: An Assessment of Mediation and Interaction**

**Tyler J. VanderWeele*, Kofi Asomaning, Eric J. Tchetgen Tchetgen, Younghun Han, Margaret R. Spitz, Sanjay Shete, Xifeng Wu, Valerie Gaborieau, Ying Wang, John McLaughlin, Rayjean J. Hung, Paul Brennan, Christopher I. Amos, David C. Christiani, and Xihong Lin**



# Example from genetic epidemiology

**Does smoking mediate the relationship between genetic variants on chr15q25 and lung cancer?** (VanderWeele et al. 2012)

- Case-control study at MGH (1836 cases, 1452 controls, all Caucasian)
- Exposure: increasing copies of minor allele at rs8034191
- Mediator: cigarettes smoked per day
- Confounders: age, sex, education, smoking duration

# Example from genetic epidemiology

**Does smoking mediate the relationship between genetic variants on chr15q25 and lung cancer?** (VanderWeele et al. 2012)

- Case-control study at MGH (1836 cases, 1452 controls, all Caucasian)
- Exposure: increasing copies of minor allele at rs8034191
- Mediator: cigarettes smoked per day
- Confounders: age, sex, education, smoking duration

$$\begin{aligned}\text{logit } \mathsf{P}[\texttt{LC}|X, M, C] =& \beta_0 + \beta_X \texttt{SNP} + \beta_M \texttt{cigs} + \beta_{XM} \texttt{SNP:cigs} + \\ & \beta_{C1} \texttt{age} + \beta_{C2} \texttt{sex} + \beta_{C3} \texttt{edu} + \beta_{C4} \texttt{dur}\end{aligned}$$

# Example from genetic epidemiology

**Does smoking mediate the relationship between genetic variants on chr15q25 and lung cancer?** (VanderWeele et al. 2012)

- Case-control study at MGH (1836 cases, 1452 controls, all Caucasian)
- Exposure: increasing copies of minor allele at rs8034191
- Mediator: cigarettes smoked per day
- Confounders: age, sex, education, smoking duration

$$\begin{aligned}\text{logit } \mathsf{P}[\texttt{LC}|X,M,C] =&\beta_0 + \beta_X \texttt{SNP} + \beta_M \texttt{cigs} + \beta_{XM} \texttt{SNP:cigs} + \\ &\beta_{C1}\texttt{age} + \beta_{C2}\texttt{sex} + \beta_{C3}\texttt{edu} + \beta_{C4}\texttt{dur}\end{aligned}$$

$$\begin{aligned}\mathsf{E}[\texttt{cigs}|X,C] =&\alpha_0 + \alpha_X \texttt{SNP} + \\ &\alpha_{C1}\texttt{age} + \alpha_{C2}\texttt{sex} + \alpha_{C3}\texttt{edu} + \alpha_{C4}\texttt{dur}\end{aligned}$$

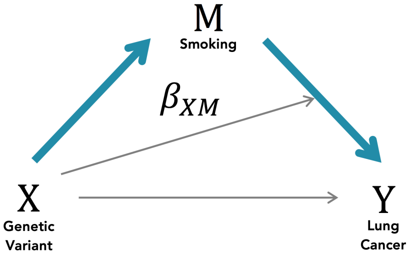
# Example from genetic epidemiology

The **total effect** is the odds ratio for lung cancer comparing those with and without an additional copy of the minor allele on rs8034191: $\text{OR}^{\text{TE}} = 1.26$ (1.19, 1.34).

# Example from genetic epidemiology

The **natural indirect effect** is the odds ratio for lung cancer for those with an additional copy of the minor allele *comparing smoking had the genetic variant been present to smoking had the genetic variant been absent*.

The natural indirect effect of the genetic variant through smoking is small because the variants do not substantially increase cigarettes per day: $\mathrm{OR}^{\mathrm{NIE}} = 1$ (1.00, 1.01).



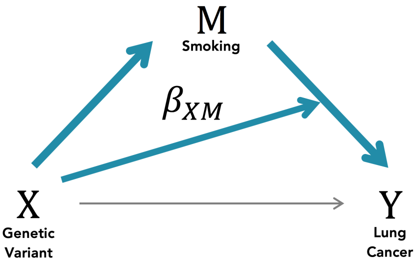
# Example from genetic epidemiology

- Evidence of strong interaction between genetic variant and smoking
- There may be a *pure interaction* such that the genetic variant has no effect on lung cancer for nonsmokers (Li et al. 2010)

# Example from genetic epidemiology

If there were a pure interaction and the genetic variant had no effect on smoking, then:
$\Rightarrow$ The CDE(smoke=0) = 0
$\Rightarrow$ The PE would be 100% of the total effect

By eliminating smoking, 100% of the genetic variant's effect on lung cancer would be eliminated.



# Application to genetic epidemiology

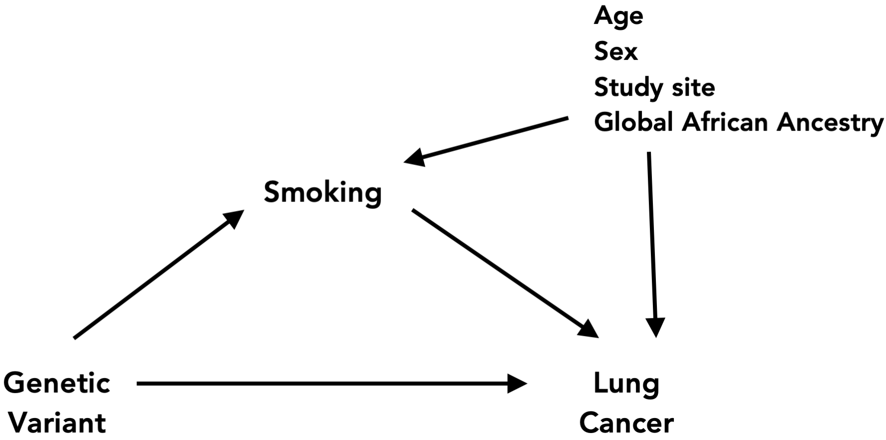
**Does smoking mediate the relationship between genetics and lung cancer in African Americans?**

# Application to genetic epidemiology

**Does smoking mediate the relationship between genetics and lung cancer in African Americans?**

- Genotyping data on over 4000 subjects from the African American Lung Cancer Consortium
- Exposure: genotype at a given SNP
- Mediator: smoking pack-years
- Outcome: lung cancer
- Confounders: age, sex, study site, global African Ancestry

**Does smoking mediate the relationship between genetics and lung cancer in African Americans?**



# The data

| | N | No cancer $N = 2843$ | Cancer $N = 1410$ |
|---|---|---|---|
| Sex | 4253 | | |
| Male | | 42% (1202) | 50% ( 698) |
| Female | | 58% (1641) | 50% ( 712) |
| Patient age | 4253 | 49 57 66 (57 $\pm$13) | 54 61 69 (61 $\pm$11) |
| Lung cancer histology | 1410 | | |
| Adenocarcinoma | | | 45% (632) |
| Large cell | | | 2% ( 34) |
| Other | | | 22% (306) |
| Small Cell | | | 6% ( 81) |
| Squamous Cell | | | 24% (337) |
| Unknown/Missing | | | 1% ( 20) |
| Smoking category (never/former/current) | 4209 | | |
| Never | | 43% (1208) | 8% ( 110) |
| Former | | 30% ( 838) | 37% ( 520) |
| Current | | 27% ( 755) | 55% ( 778) |
| Pack years | 4051 | 0.0 0.4 15.5 (10.3 $\pm$17.4) | 3.5 22.0 42.0 (28.4 $\pm$29.3) |
| Heavy smoker (yes/no) | 4051 | | |
| Heavy smoker | | 19% ( 520) | 53% ( 729) |
| Non-heavy smoker | | 81% (2149) | 47% ( 653) |
| Study site | 4253 | | |
| MDA | | 35% (1001) | 26% ( 373) |
| NCI_UMD | | 13% ( 375) | 15% ( 208) |
| SCCS | | 12% ( 338) | 12% ( 168) |
| UCSF | | 23% ( 661) | 23% ( 325) |
| WayneState | | 16% ( 468) | 24% ( 336) |
| Estimated European global ancestry | 4253 | 0.11 0.17 0.25 (0.19 $\pm$0.12) | 0.10 0.16 0.25 (0.19 $\pm$0.13) |
| Estimated African global ancestry | 4253 | 0.75 0.83 0.89 (0.81 $\pm$0.12) | 0.75 0.84 0.90 (0.81 $\pm$0.13) |

# The data

| | N | No cancer $N = 2843$ | | Cancer $N = 1410$ | |
|---|---|---|---|---|---|
| Sex | 4253 | | | | |
| Male | | 42% | (1202) | 50% | ( 698) |
| Female | | 58% | (1641) | 50% | ( 712) |
| Patient age | 4253 | 49 57 66 | (57 ±13) | 54 61 69 | (61 ±11) |
| Lung cancer histology | 1410 | | | | |
| Adenocarcinoma | | | | 45% | (632) |
| Large cell | | | | 2% | ( 34) |
| Other | | | | 22% | (306) |
| Small Cell | | | | 6% | ( 81) |
| Squamous Cell | | | | 24% | (337) |
| Unknown/Missing | | | | 1% | ( 20) |
| Smoking category (never/former/current) | 4209 | | | | |
| Never | | 43% | (1208) | 8% | ( 110) |
| Former | | 30% | ( 838) | 37% | ( 520) |
| Current | | 27% | ( 755) | 55% | ( 778) |
| Pack years | 4051 | 0.0 0.4 15.5 | (10.3 ±17.4) | 3.5 22.0 42.0 | (28.4 ±29.3) |
| Heavy smoker (yes/no) | 4051 | | | | |
| Heavy smoker | | 19% | ( 520) | 53% | ( 729) |
| Non-heavy smoker | | 81% | (2149) | 47% | ( 653) |
| Study site | 4253 | | | | |
| MDA | | 35% | (1001) | 26% | ( 373) |
| NCI_UMD | | 13% | ( 375) | 15% | ( 208) |
| SCCS | | 12% | ( 338) | 12% | ( 168) |
| UCSF | | 23% | ( 661) | 23% | ( 325) |
| WayneState | | 16% | ( 468) | 24% | ( 336) |
| Estimated European global ancestry | 4253 | 0.11 0.17 0.25 | (0.19 ±0.12) | 0.10 0.16 0.25 | (0.19 ±0.13) |
| Estimated African global ancestry | 4253 | 0.75 0.83 0.89 | (0.81 ±0.12) | 0.75 0.84 0.90 | (0.81 ±0.13) |

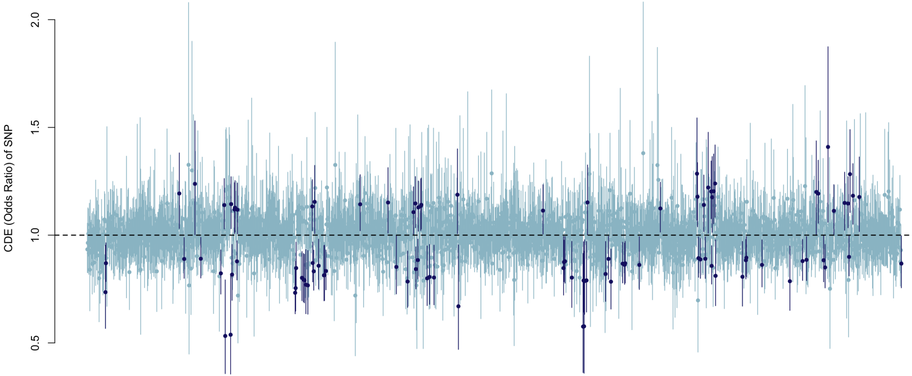
# The data

| | N | No cancer $N = 2843$ | | Cancer $N = 1410$ | |
|---|---|---|---|---|---|
| Sex | 4253 | | | | |
| Male | | 42% | (1202) | 50% | ( 698) |
| Female | | 58% | (1641) | 50% | ( 712) |
| Patient age | 4253 | 49 57 66 | (57 ±13) | 54 61 69 | (61 ±11) |
| Lung cancer histology | 1410 | | | | |
| Adenocarcinoma | | | | 45% | (632) |
| Large cell | | | | 2% | ( 34) |
| Other | | | | 22% | (306) |
| Small Cell | | | | 6% | ( 81) |
| Squamous Cell | | | | 24% | (337) |
| Unknown/Missing | | | | 1% | ( 20) |
| Smoking category (never/former/current) | 4209 | | | | |
| Never | | 43% | (1208) | 8% | ( 110) |
| Former | | 30% | ( 838) | 37% | ( 520) |
| Current | | 27% | ( 755) | 55% | ( 778) |
| Pack years | 4051 | 0.0 0.4 15.5 | (10.3 ±17.4) | 3.5 22.0 42.0 | (28.4 ±29.3) |
| Heavy smoker (yes/no) | 4051 | | | | |
| Heavy smoker | | 19% | ( 520) | 53% | ( 729) |
| Non-heavy smoker | | 81% | (2149) | 47% | ( 653) |
| Study site | 4253 | | | | |
| MDA | | 35% | (1001) | 26% | ( 373) |
| NCI_UMD | | 13% | ( 375) | 15% | ( 208) |
| SCCS | | 12% | ( 338) | 12% | ( 168) |
| UCSF | | 23% | ( 661) | 23% | ( 325) |
| WayneState | | 16% | ( 468) | 24% | ( 336) |
| Estimated European global ancestry | 4253 | 0.11 0.17 0.25 | (0.19 ±0.12) | 0.10 0.16 0.25 | (0.19 ±0.13) |
| Estimated African global ancestry | 4253 | 0.75 0.83 0.89 | (0.81 ±0.12) | 0.75 0.84 0.90 | (0.81 ±0.13) |

# The data

| | N | No cancer $N = 2843$ | | Cancer $N = 1410$ | |
|---|---|---|---|---|---|
| Sex | 4253 | | | | |
| Male | | 42% | (1202) | 50% | ( 698) |
| Female | | 58% | (1641) | 50% | ( 712) |
| Patient age | 4253 | 49 57 66 | (57 ±13) | 54 61 69 | (61 ±11) |
| Lung cancer histology | 1410 | | | | |
| Adenocarcinoma | | | | 45% | (632) |
| Large cell | | | | 2% | ( 34) |
| Other | | | | 22% | (306) |
| Small Cell | | | | 6% | ( 81) |
| Squamous Cell | | | | 24% | (337) |
| Unknown/Missing | | | | 1% | ( 20) |
| Smoking category (never/former/current) | 4209 | | | | |
| Never | | 43% | (1208) | 8% | ( 110) |
| Former | | 30% | ( 838) | 37% | ( 520) |
| Current | | 27% | ( 755) | 55% | ( 778) |
| Pack years | 4051 | 0.0 0.4 15.5 | (10.3 ±17.4) | 3.5 22.0 42.0 | (28.4 ±29.3) |
| Heavy smoker (yes/no) | 4051 | | | | |
| Heavy smoker | | 19% | ( 520) | 53% | ( 729) |
| Non-heavy smoker | | 81% | (2149) | 47% | ( 653) |
| Study site | 4253 | | | | |
| MDA | | 35% | (1001) | 26% | ( 373) |
| NCI_UMD | | 13% | ( 375) | 15% | ( 208) |
| SCCS | | 12% | ( 338) | 12% | ( 168) |
| UCSF | | 23% | ( 661) | 23% | ( 325) |
| WayneState | | 16% | ( 468) | 24% | ( 336) |
| Estimated European global ancestry | 4253 | 0.11 0.17 0.25 | (0.19 ±0.12) | 0.10 0.16 0.25 | (0.19 ±0.13) |
| Estimated African global ancestry | 4253 | 0.75 0.83 0.89 | (0.81 ±0.12) | 0.75 0.84 0.90 | (0.81 ±0.13) |

# Controlled direct effect odds ratios on chr15q25




$$\text{logit P}[\texttt{LC}|X, M, C] = \beta_0 + \beta_X \texttt{SNP} + \beta_M \texttt{packyears} + \beta_{C1}\texttt{age} + \beta_{C2}\texttt{sex} + \beta_{C3}\texttt{site} + \beta_{C4}\texttt{Afr}$$

Questions?