Karolinska Institutet

Studying Mediation in Intervention Evaluation

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Acknowledgement

Based on the Workshop by A. Bellavia (Harvard T.H. Chan School of Public Health):

Mediation and interaction analysis for health disparities research (October 3, 2016).

More material available at http://www.stats4life.se/workshop/

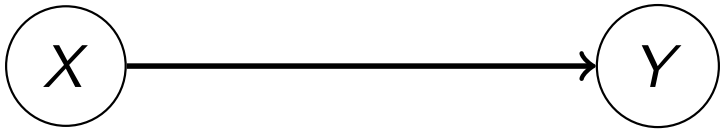
Introduction

Mediation Analysis

- Methodology to assess the importance of various pathways and mechanisms
- Originally developed in the field of social sciences and psychology
- Recent methodological advances in biostatistics (causal inference)
- Increasing interest in epidemiology and public health

Rationale

Epidemiology, public health, and clinical research are largely about assessing and explaining exposure-outcome associations



Observing a statistical association only represents the starting point

Addressing additional questions is required before implementing public health intervention and recommendations.

These questions are particularly relevant when X is something we can't intervene on (i.e. non-modifiable exposures).

> *Health disparities are defined as differences in health status that are systematically affecting groups of people based on their racial or ethnic group; religion; socioeconomic status; gender; age; mental health; cognitive, sensory, or physical disability; sexual orientation or gender identity; geographic locations; historical characteristics. (Healthy People 2020).*

Addressing our additional questions may contribute to identify and implement public health intervention and recommendations to reduce/prevent health disparities.

Potential fields of application

- Contribution of lifestyle factors in social epidemiology (e.g. The Stockholm Public Health Cohort).
- Medical predecessors of common diseases (e.g. diabetes, hypertension, depression).
- Epigenetics (and genes-environment interactions).
- . . . many other.

Investigating this contribution of third variables in an X-Y association generally requires merging multiple research fields.

Motivating example

Race/ethnicity and diabetes

In the US, racial/ethnic disparities in the prevalence of diabetes have been consistently documented (from Jackson, 1971).

Recent studies show a link between high exposure to certain classes of environmental chemicals and diabetes (James-Todd et al., 2012).

Racial/ethnic differences in the exposure to these chemicals have also been observed (James-Todd et al., 2014).

Does the higher exposure to chemicals (partly) explain the higher prevalence of diabetes in specific racial/ethnic subgroups?

Moreover, many of these chemicals are found in fast-food (Zota et al., 2016), and fast-food consumption differs across race/ethnicity (James et al., 2014).

What is the contribution of regular fast-food consumption in the reported disparity?

We want to quantify the contribution of chemicals exposure in the racial/ethnic disparity in diabetes, and to identify the proportion of disparity that could be reduced by implementing specific nutritional programs.

Data for the example

We will simulated data that resemble the motivating example.

Using simulated data simplifies:

- Implementation and interpretation (i.e. no-unmeasured confounders; all assumptions are met).
- Reproducing the code to your own situation.
- Sharing the same data.

Have a look at how I simulated the data here.

Mediation Analysis

The biological question comes before the statistical one

Statistical methods to assess mediation (or even confounding), are generally simple (and often similar).

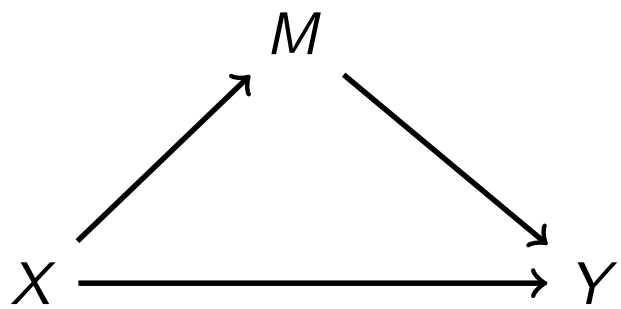
To correctly identify the potential role of each variable involved in the association is crucial. Methods to conceptualize the causal pathway are available and increasingly recommended (e.g. DAGs).

Failing to identify the correct DAG may lead to severe bias once we move to statistical analysis (i.e. the correct method is used to address a wrong question).

Concept of Mediation

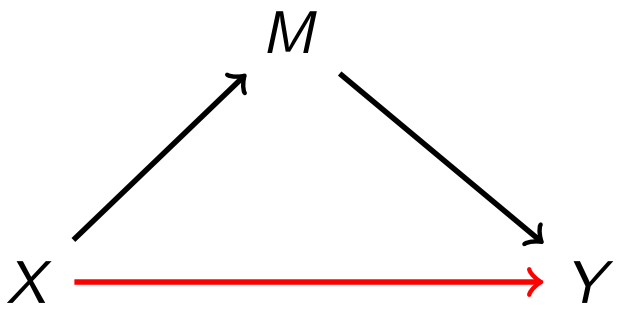
Mediation concerns the extent to which the effect of one variable on another is mediated by some intermediate variable(s).

A mediator is a covariate that mediates the association between X and Y.

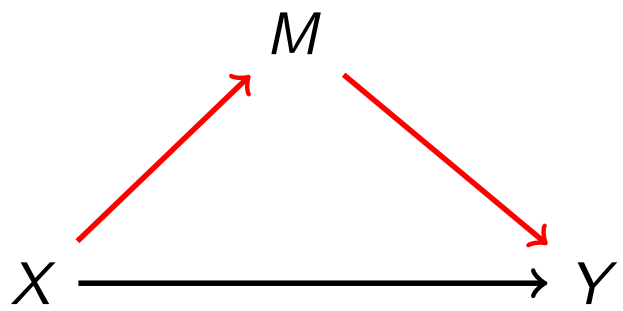


Part of the effect of X on Y is due to the fact that X causes M, which in turn causes Y.

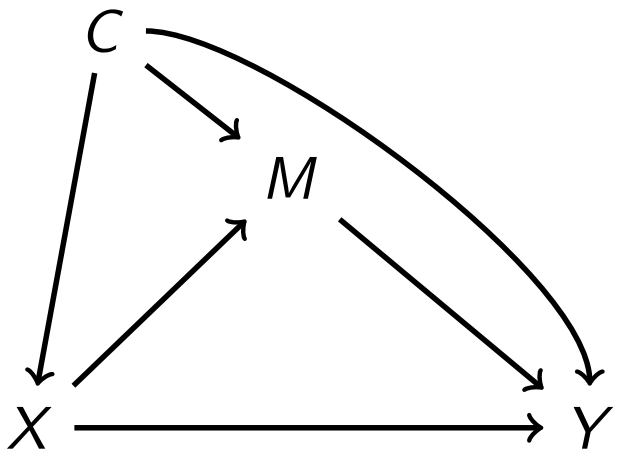
We aim to disentangle the total effect of X on Y into a **direct effect** (de) that goes through all possible pathways but M . . .



. . . and an **indirect effect** (ie) that goes through M



Consider a structure with exposure X, mediator M, outcome Y and confounders C.



Traditionally, we have a choice between

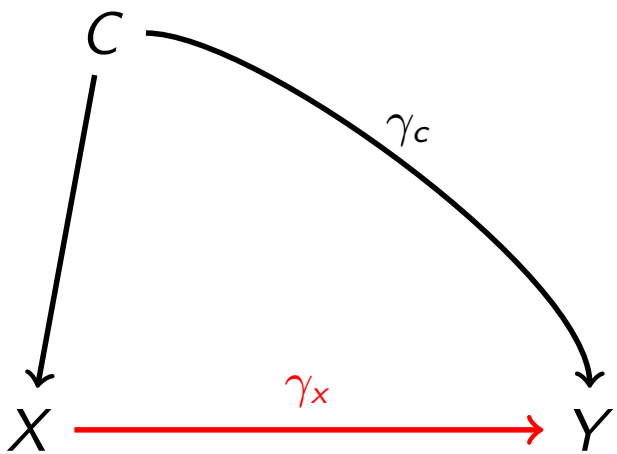
- the **difference in coefficients method** (epidemiology and the biomedical sciences)
- the **multiplication of coefficients method** (Baron & Kenny in social sciences)

The difference in coefficients method

Consider a setting with *continuous* Y and M.

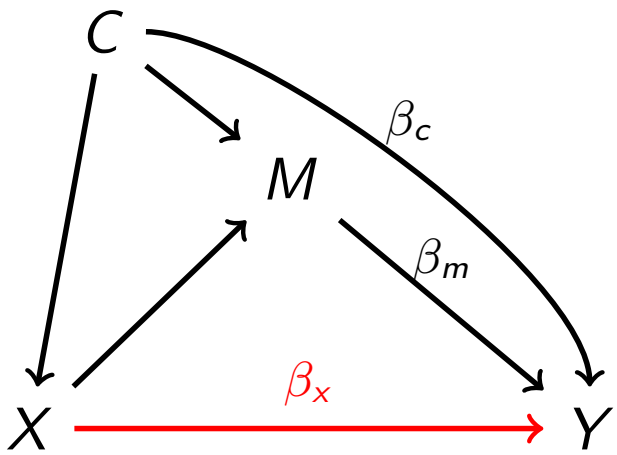
$$E[Y|X, C] = \gamma_0 + \gamma_x X + \gamma_c C$$

$\text{te} = \gamma_x$ is interpreted as the **total effect** of X on Y.



$$E[Y|X, M, C] = \beta_0 + \beta_x X + \beta_m M + \beta_c C$$

$\text{de} = \beta_x$ is interpreted as the **direct effect** of X on Y (not via M).



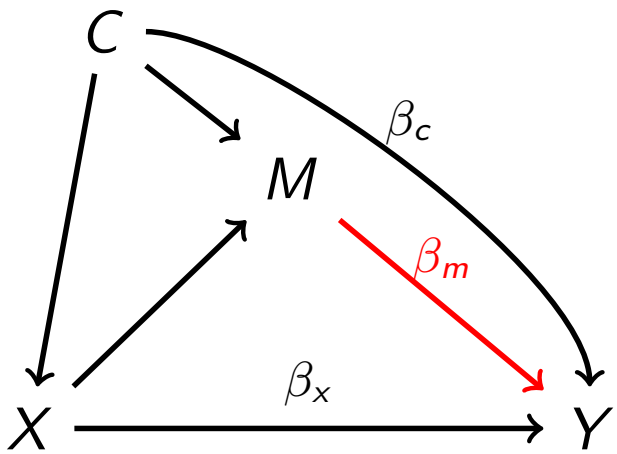
$\text{ie} = \gamma_x - \beta_x$ is interpreted as the **indirect effect** of X on Y (via M).

The product of coefficients method

Again, fit two regression models.

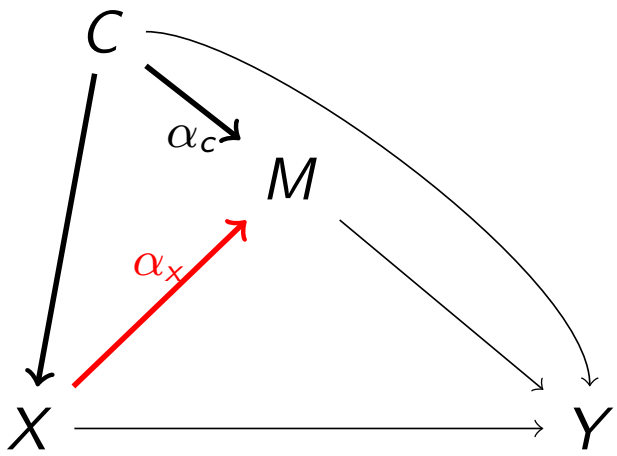
$$E[Y|X, M, C] = \beta_0 + \beta_x X + \beta_m M + \beta_c C$$

β_m is interpreted as the effect of M on Y.



$$E[M|X, C] = \alpha_0 + \alpha_x X + \alpha_c C$$

α_x is interpreted as the effect of X on M.



We can derive the **indirect effect** of X on Y as ie $= \alpha_x \beta_m$.

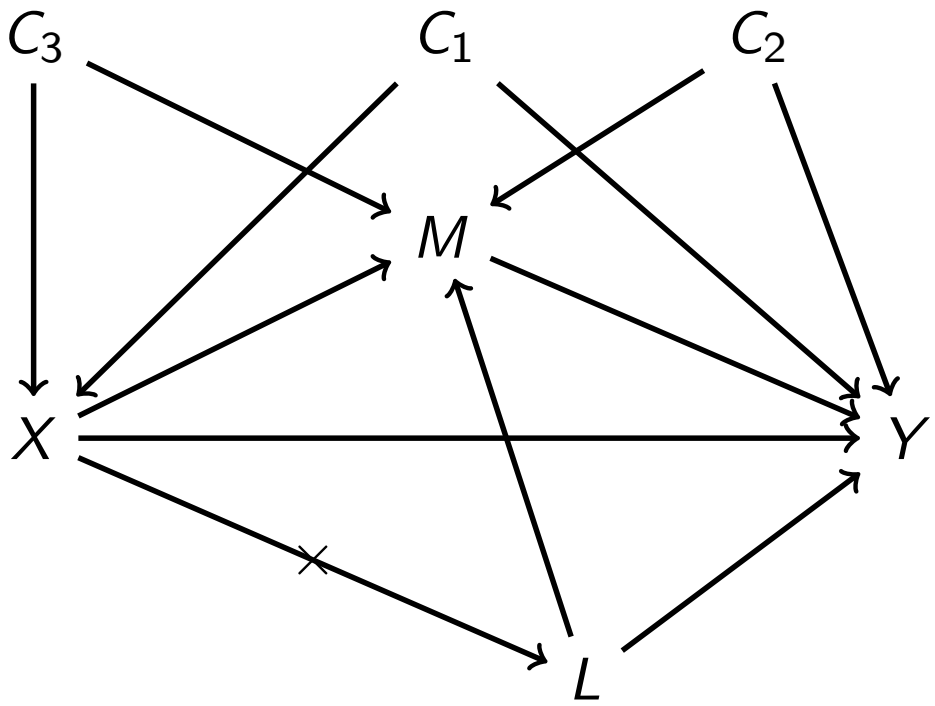
For a continuous outcome and mediator, $\alpha_x \beta_m = \gamma_x - \beta_x$

Confounding assumptions

- **A1**: control for exposure-outcome confounding (C_1)
- **A2**: control for mediator-outcome confounding (direct and indirect effects) (C_2)
- **A3**: control for exposure-mediator confounding (C_3)
- **A4**: no mediator-outcome confounder that is itself affected by the exposure (no L) (little time between exposure and mediator)

Sensitivity analysis to assess possible violation in the assumptions.

Graphical assumptions



- Adjusting a model for a mediator gives an estimate of the direct effect rather than the total effect. **Crucial to distinguish confounders and mediators**.
- All models can be adjusted for potential confounders.
- The *product = difference statement* is not valid under some scenarios (binary and survival outcomes, exposure-mediator interaction, missing values on mediators).
- A common measure to summaries results from a mediation model is the proportion mediated.

$$\text{PM} = \frac{\text{Indirect Effect}}{\text{Total Effect}}$$

Exposure-mediator interaction

$$E[Y|X, M, C] = \beta_0 + \beta_x X + \beta_m M + \beta_{xm} XM + \beta_c C$$

$$E[M|X, C] = \alpha_0 + \alpha_x X + \alpha_c C$$

If the confounding assumptions A1-A4 hold, the effect estimates for a change in the exposure from level x_1 to x_2

$$\text{de} = \{\beta_x + \beta_{xm}(\alpha_0 + \alpha_x x_2 + \alpha_c C)\}(x_1 - x_2)$$

$$\text{ie} = (\alpha_x \beta_m + \alpha_x \beta_{xm} x_1)(x_1 - x_2)$$

Binary outcome

$$\text{logit}(Y|X, M, C) = \beta_0 + \beta_x X + \beta_m M + \beta_{xm} XM + \beta_c C$$

$$E[M|X, C] = \alpha_0 + \alpha_x X + \alpha_c C$$

Provided the *outcome is relatively rare* and the confounding assumptions *A1-A4 hold*

$$\log(\text{OR}^{\text{de}}) \approx \{\beta_x + \beta_{xm}(\alpha_0 + \alpha_x x_2 + \alpha_c C + \beta_m \sigma^2)(x_1 - x_2)\} + 0.5\beta_{xm}^2 \sigma^2 (x_1^2 - x_2^2)$$

$$\log(\text{OR}^{\text{ie}}) \approx (\alpha_x \beta_m + \alpha_x \beta_{xm} x_1)(x_1 - x_2)$$

σ^2 is the variance of the error term in the regression for the mediator

For rare outcomes, the proportion-mediated is

$$\text{PM} = \frac{\text{OR}^{\text{de}}(\text{OR}^{\text{ie}} - 1)}{\text{OR}^{\text{de}}\text{OR}^{\text{ie}} - 1}$$

When there is no exposure-mediator interaction:

$$\text{de} = \exp(\beta_x)$$

$$\text{ie} = \exp(\alpha_x \beta_m)$$

If the outcome is rare and there is no interaction, the product method and difference method approximate each other.

Notes:

- The *total* and *direct* effect are better interpreted on the exponential scale (i.e. OR).
- The *indirect effect* is computed using the coefficients of the model on the original scale (log OR), and is then exponentiated for ease of interpretation.
- The previous expressions only hold when the outcome is rare. If not, none of the expressions are valid.
- If the outcome is common, replace logistic regression with *log-binomial model*.

Binary mediator

$$E[Y|X, M, C] = \beta_0 + \beta_x X + \beta_m M + \beta_{xm} XM + \beta_c C$$

$$\text{logit}(M|X, C) = \alpha_0 + \alpha_x X + \alpha_c C$$

$$\text{de} = \beta_x(x_1 - x_2) + \beta_{xm}(x_1 - x_2)\frac{\exp(\alpha_0 + \alpha_x x_2 + \alpha_c C)}{1 + \exp(\alpha_0 + \alpha_x x_2 + \alpha_c C)}$$

$$\text{ie} = (\beta_m M + \beta_{xm} x_1)\{\frac{\exp(\alpha_0 + \alpha_x x_1 + \alpha_c C)}{1 + \exp(\alpha_0 + \alpha_x x_1 + \alpha_c C)} - \frac{\exp(\alpha_0 + \alpha_x x_2 + \alpha_c C)}{1 + \exp(\alpha_0 + \alpha_x x_2 + \alpha_c C)}\}$$

Binary mediator and binary outcome

$$\text{logit}(Y|X, M, C) = \beta_0 + \beta_x X + \beta_m M + \beta_{xm} XM + \beta_c C$$

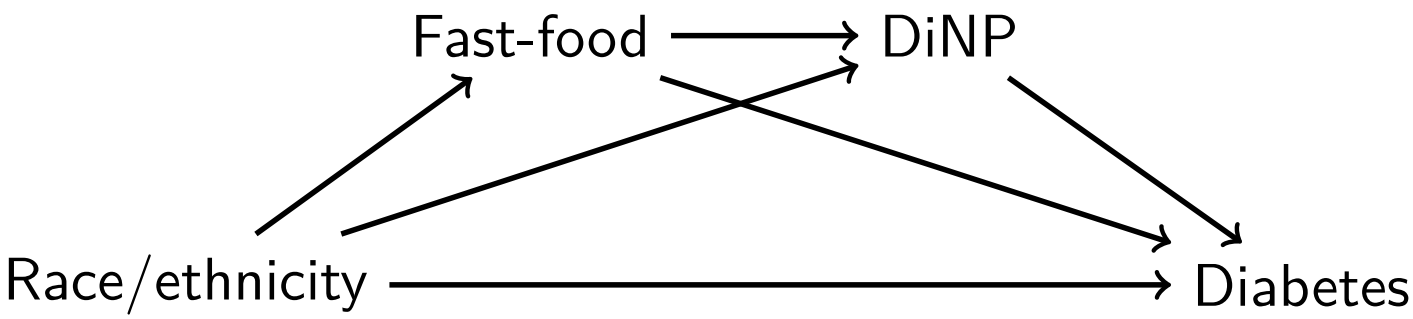
$$\text{logit}(M|X, C) = \alpha_0 + \alpha_x X + \alpha_c C$$

$$\text{OR}^{\text{de}} \approx \frac{\exp(\beta_x x_1)\{1 + \exp(\beta_m + \beta_{xm} x_1 + \alpha_0 + \alpha_x x_2 + \alpha_c C)\}}{\exp(\beta_x x_2)\{1 + \exp(\beta_m + \beta_{xm} x_2 + \alpha_0 + \alpha_x x_2 + \alpha_c C)\}}$$

$$\text{OR}^{\text{ie}} \approx \frac{\{1 + \exp(\alpha_0 + \alpha_x x_2 + \alpha_c C)\}}{\{1 + \exp(\alpha_0 + \alpha_x x_1 + \alpha_c C)\}} \cdot \frac{\{1 + \exp(\beta_m + \beta_{xm} x_1 + \alpha_0 + \alpha_x x_1 + \alpha_c C))\}}{\{1 + \exp(\beta_m + \beta_{xm} x_1 + \alpha_0 + \alpha_x x_2 + \alpha_c C))\}}$$

Practical Example

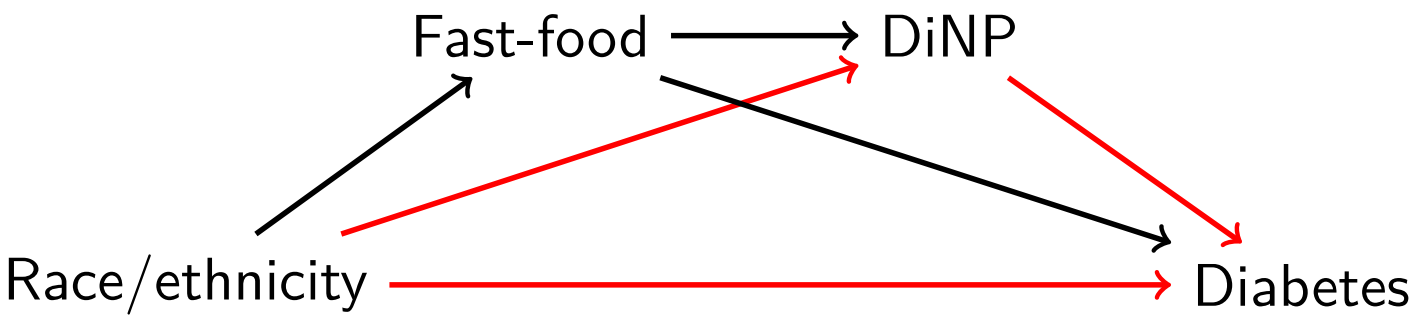
Race/ethnicity and diabetes



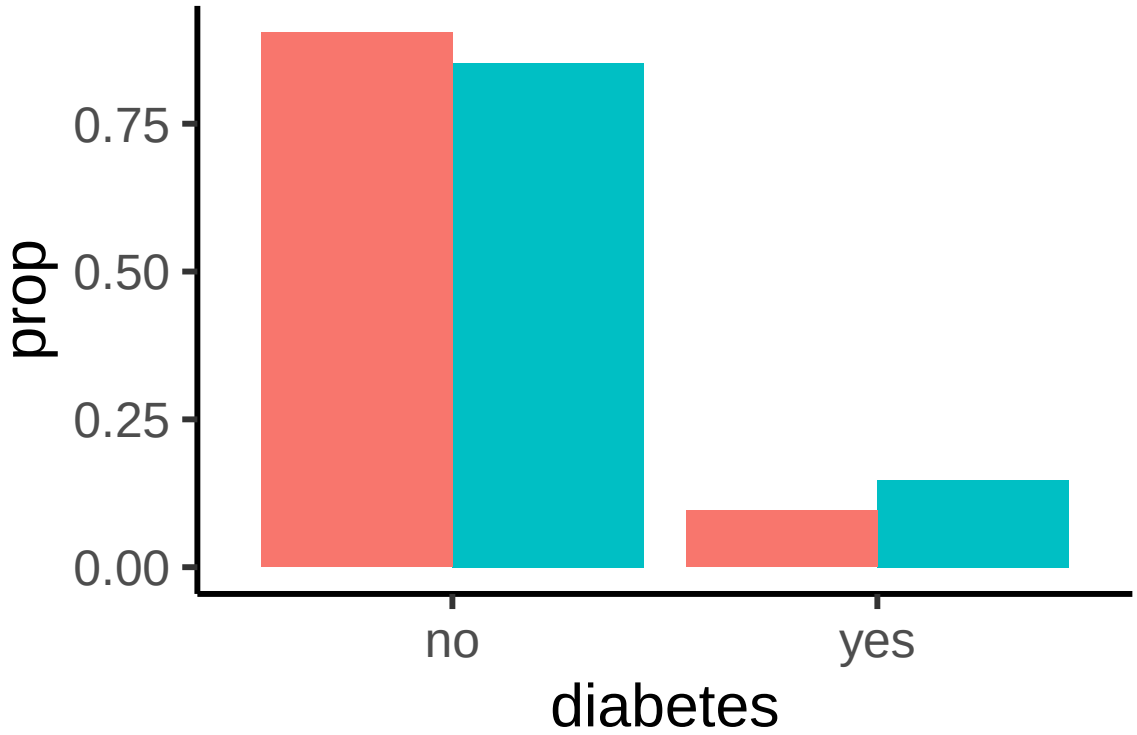
Description of simulated population

	Stratified by diabetes	
	no	yes
n	8944	1056
race = Black-American (%)	1594 (17.8)	276 (26.1)
fastfood = yes (%)	3107 (34.7)	461 (43.7)
dinp (mean (SD))	11.09 (1.30)	11.52 (1.45)

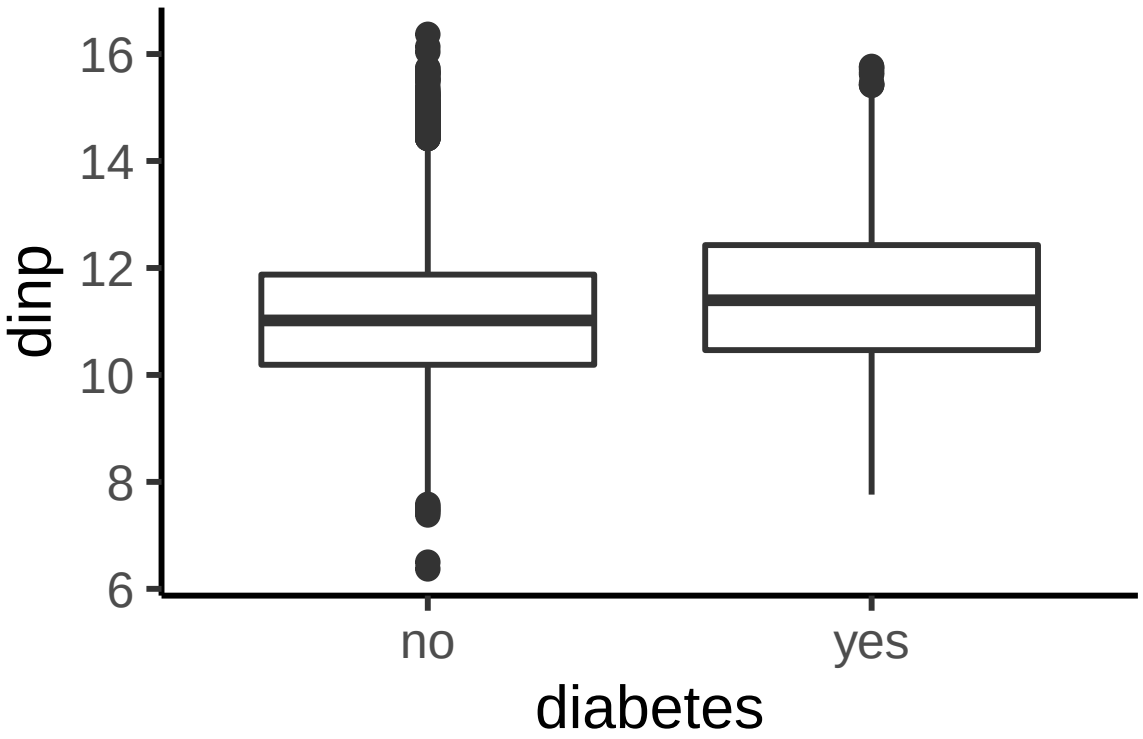
Binary Outcome



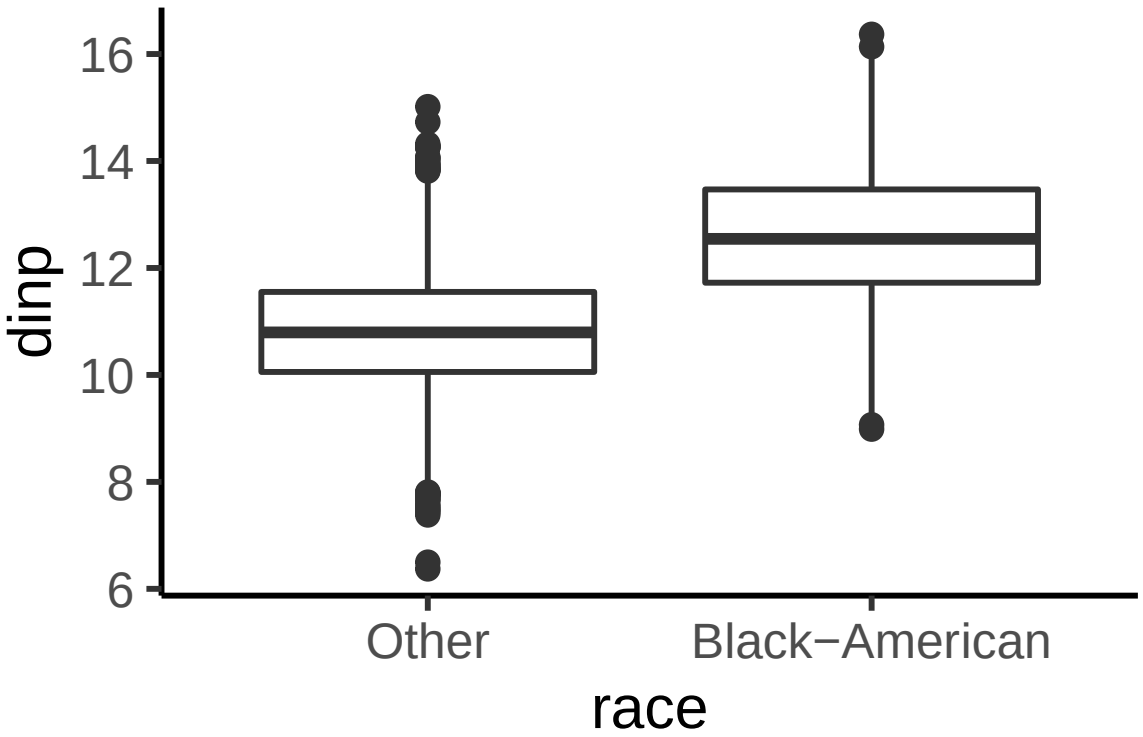
race	diabetes no	diabetes yes
Other	0.9041	0.0959
Black-American	0.8524	0.1476



diabetes	minimum	q1	median	mean	q3	maximum
no	6.37	10.2	11.0	11.1	11.9	16.4
yes	7.76	10.5	11.4	11.5	12.4	15.8



race	minimum	q1	median	mean	q3	maximum
Other	6.37	10.1	10.8	10.8	11.6	15.0
Black-American	8.99	11.7	12.5	12.6	13.5	16.4



Use a logistic regression model to estimate the racial/ethnic disparity in diabetes

$$\log\left(\text{odds}(\text{diabetes}|\text{race})\right) = \gamma_0 + \gamma_x \text{race}$$

	exp(Est.)	2.5%	97.5%
(Intercept)	0.106	0.099	0.114
raceBlack-American	1.632	1.408	1.891

Black-American have 63% higher odds of diabetes ($\text{te} = 1.63$; 95% CI: 1.40-1.89 - **total effect**) compared to other ethnicities.

Use a linear regression model to estimate the racial/ethnic disparity in DiNP exposure.

$$\mathrm{E}\left(\mathrm{DiNP}|\mathrm{race}\right) = \alpha_0 + \alpha_x \mathrm{race}$$

	Estimate	StdErr	z	P	2.5%	97.5%
(Intercept)	10.8	0.012	867.3	0	10.78	10.82
raceBlack-American	1.8	0.029	62.5	0	1.74	1.86

Black-American have higher DiNP urinary concentration ($\alpha_x = 1.8$; 95% CI: 1.74-1.86) compared to other ethnicities.

Further adjusting the main model (i.e. diabetes as a function of race/ethnicity) for DiNP concentration

$$\log\left(\text{odds}(\text{diabetes}|\text{race}, \text{DiNP})\right) = \beta_0 + \beta_x \text{race} + \beta_m \text{DiNP}$$

	exp(Est.)	2.5%	97.5%
(Intercept)	0.01	0.005	0.018
raceBlack-American	1.09	0.913	1.311
dinp	1.25	1.178	1.319

The main effect goes down to 9% ($\text{de} = 1.09$; 95% CI: 0.91-1.31) - **direct effect**).

The **log indirect effect** can be calculated on the log scale, with the product method as: $\log(\text{ie}) = \log(1.25) \cdot 1.8 = 0.4$, and then exponentiated to $\text{ie} = \exp(0.4) = 1.49$.

Comments:

Indirect effect calculated with the difference method:

$\log(\text{ie}) = \log(\text{te}) - \log(\text{de}) = \log(1.63) - \log(1.09) = 0.49 - 0.09 = 0.4$, so that the indirect effect is obtained by $\exp(0.4) = 1.49$

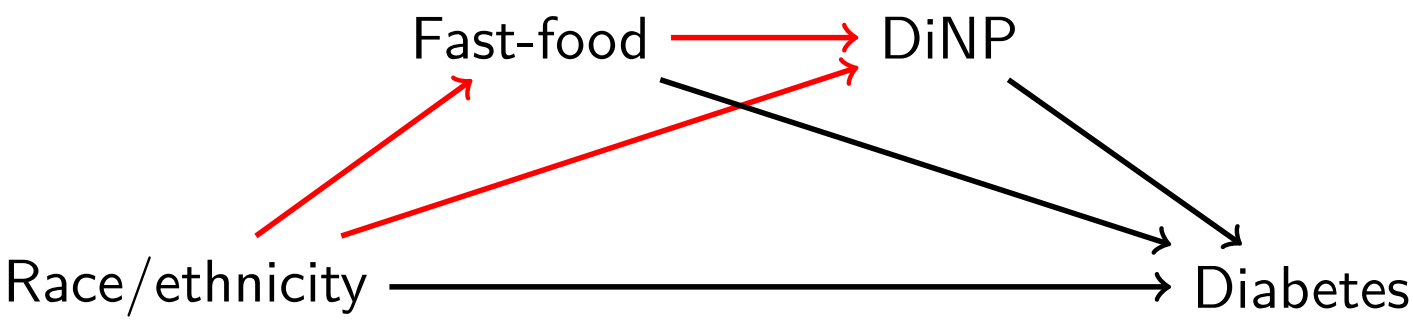
The proportion mediated is

$$\text{PM} = 100 \cdot \frac{\text{OR}^{\text{de}}(\text{OR}^{\text{ie}} - 1)}{\text{OR}^{\text{de}}\text{OR}^{\text{ie}} - 1} = 100 \cdot \frac{1.09(1.49-1)}{1.09 \cdot 1.49 - 1} = 85\%$$

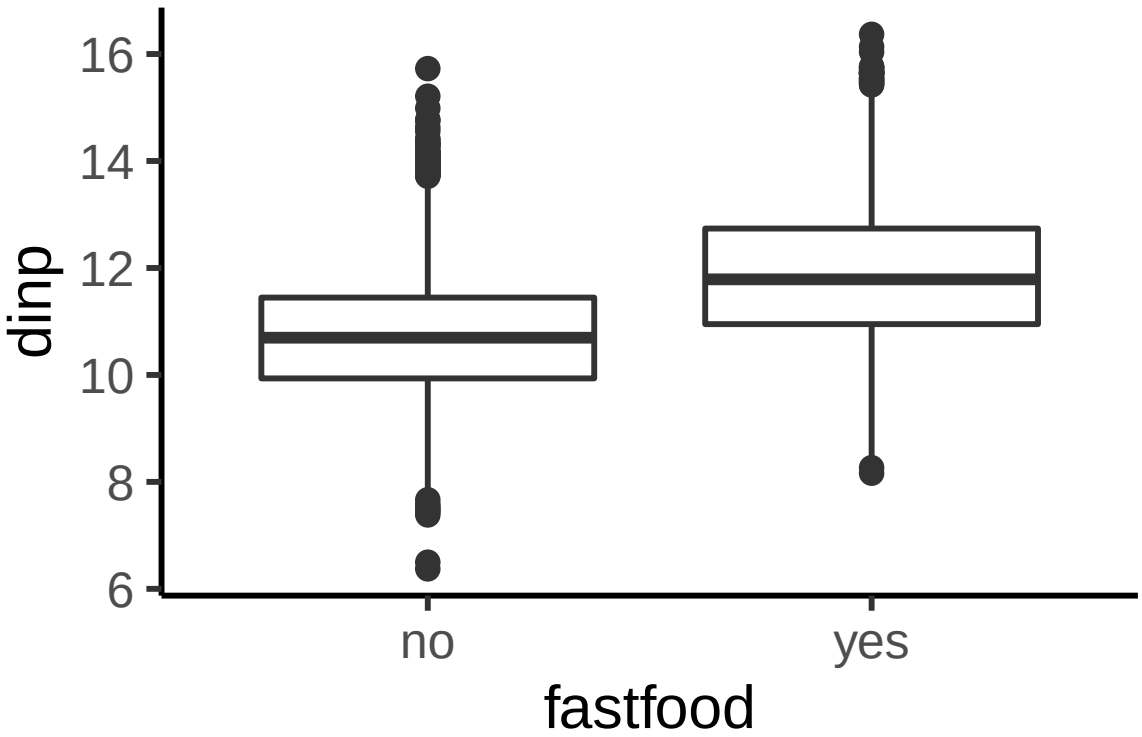
Assuming that there are no unmeasured confounders we can conclude that higher DiNP is responsible for the 85% of the racial/ethnic disparity in diabetes.

How can we reduce DiNP? One source of this chemicals is fast-food consumption.
How much of the difference in DiNP exposure between black-Americans and other race/ethnicities would be reduced by eliminating fast-food consumption?

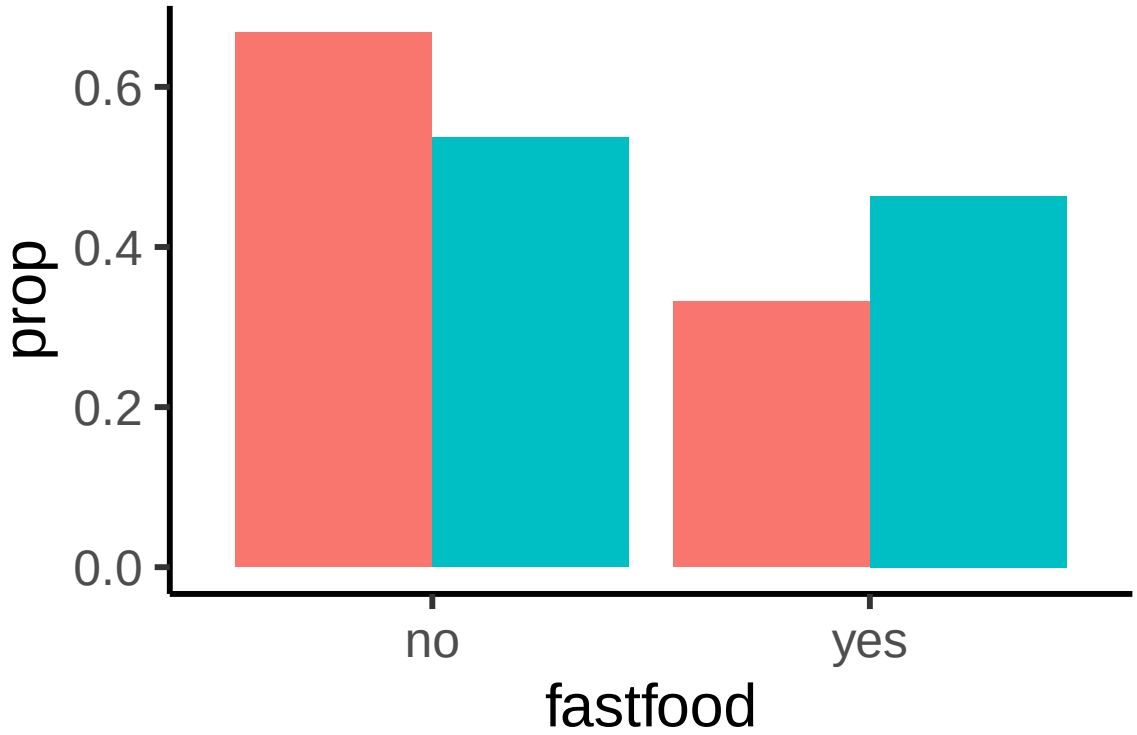
Continuous outcome



fastfood	minimum	q1	median	mean	q3	maximum
no	6.37	9.94	10.7	10.7	11.4	15.7
yes	8.16	10.95	11.8	11.9	12.7	16.4



race	fastfood	
	no	yes
Other	0.668	0.332
Black-American	0.536	0.464



Use a linear regression model to estimate the racial/ethnic disparity in DiNP

$$\mathrm{E}\left(\mathrm{DiNP}|\mathrm{race}\right) = \gamma_0 + \gamma_x \mathrm{race}$$

	Estimate	StdErr	z	P	2.5%	97.5%
(Intercept)	10.8	0.0125	867.3	0	10.78	10.82
raceBlack-American	1.8	0.0288	62.5	0	1.74	1.86

Black-American have higher DiNP urinary concentration ($\gamma_x = 1.80$; 95% CI: 1.74-1.86 - **total effect**)

$$\mathrm{E}\left(\mathrm{DiNP}|\mathrm{race}, \mathrm{fastfood}\right) = \beta_0 + \beta_x \mathrm{race} + \beta_m \mathrm{fastfood}$$

	Estimate	StdErr	z	P	2.5%	97.5%
(Intercept)	10.46	0.0132	789.7	0	10.434	10.49
raceBlack-American	1.67	0.0261	63.9	0	1.615	1.72
fastfoodyes	1.03	0.0212	48.3	0	0.984	1.07

Further adjusting the main model for fast-food consumption the main effect goes down to 1.67 ug/l ($\beta_x = 1.67$; 95% CI: 1.61-1.72 - **direct effect**).

and a logistic regression model to estimate the racial/ethnic difference in fast-food consumption.

$$\log(\text{odds}\,(\text{fastfood}|\text{race})) = \alpha_0 + \alpha_x \text{race}$$

	exp(Est.)	2.5%	97.5%
(Intercept)	0.498	0.475	0.521
raceBlack-American	1.737	1.569	1.924

Black-Americans have a 73% higher odds of fast-food consumption ($\alpha_x = 0.55$; 95% CI: 0.45-0.65).

The **indirect effect** can be calculated as

$$\text{ie} = 1.03\left(\frac{\exp(-0.7+0.55)}{1+\exp(-0.7+0.55)} - \frac{\exp(-0.7\text{`})}{1+\exp(-0.7\text{`})}\right) = 0.13$$

Thus, $\text{PM} = 100 \cdot \frac{0.13}{1.8} = 7.5\%$

We can conclude that fast-food consumption is responsible for only 8% of the higher DiNP level among black-American. Other sources of exposure must be identified.

Exposure-mediator interaction

$$\mathsf{E}\left(\mathrm{DiNP}|\mathrm{race}, \mathrm{fastfood}\right) = \beta_0 + \beta_x \mathrm{race} + \beta_m \mathrm{fastfood} + \beta_{xm} \mathrm{race} \cdot \mathrm{fastfood}$$

	Estimate	StdErr	z	P	2.5%	97.5%
(Intercept)	10.496	0.0137	768.8	0.00e+00	10.469	10.523
raceBlack-American	1.434	0.0346	41.5	0.00e+00	1.366	1.501
fastfoodyes	0.917	0.0237	38.7	0.00e+00	0.871	0.964
raceBlack-American:fastfoodyes	0.531	0.0523	10.2	3.31e-24	0.428	0.634

$$\text{de} = 1.43 + 0.53 \cdot (\exp(-0.7)/(1 + \exp(-0.7))) = 1.61$$

$$\text{ie} = (0.92+0.53)\cdot\left(\frac{\exp(-0.7 + 0.55)}{1 + \exp(-0.7 + 0.55)} - \frac{\exp(-0.7)}{1 + \exp(-0.7)}\right) = 0.19$$

$$\text{PM} = 100 \cdot \frac{0.19}{1.8} = 10.6\%$$

Remarks

Software

Both the approaches for mediation analysis consists of a set of regression models.

All statistical software that implement generalized linear models (in the examples covered linear and logistic models) can be used to perform a mediation analysis.

There are various options for obtaining the standard error (and thus confidence intervals) for the indirect effect: either using the *delta method* or by *bootstrapping*.

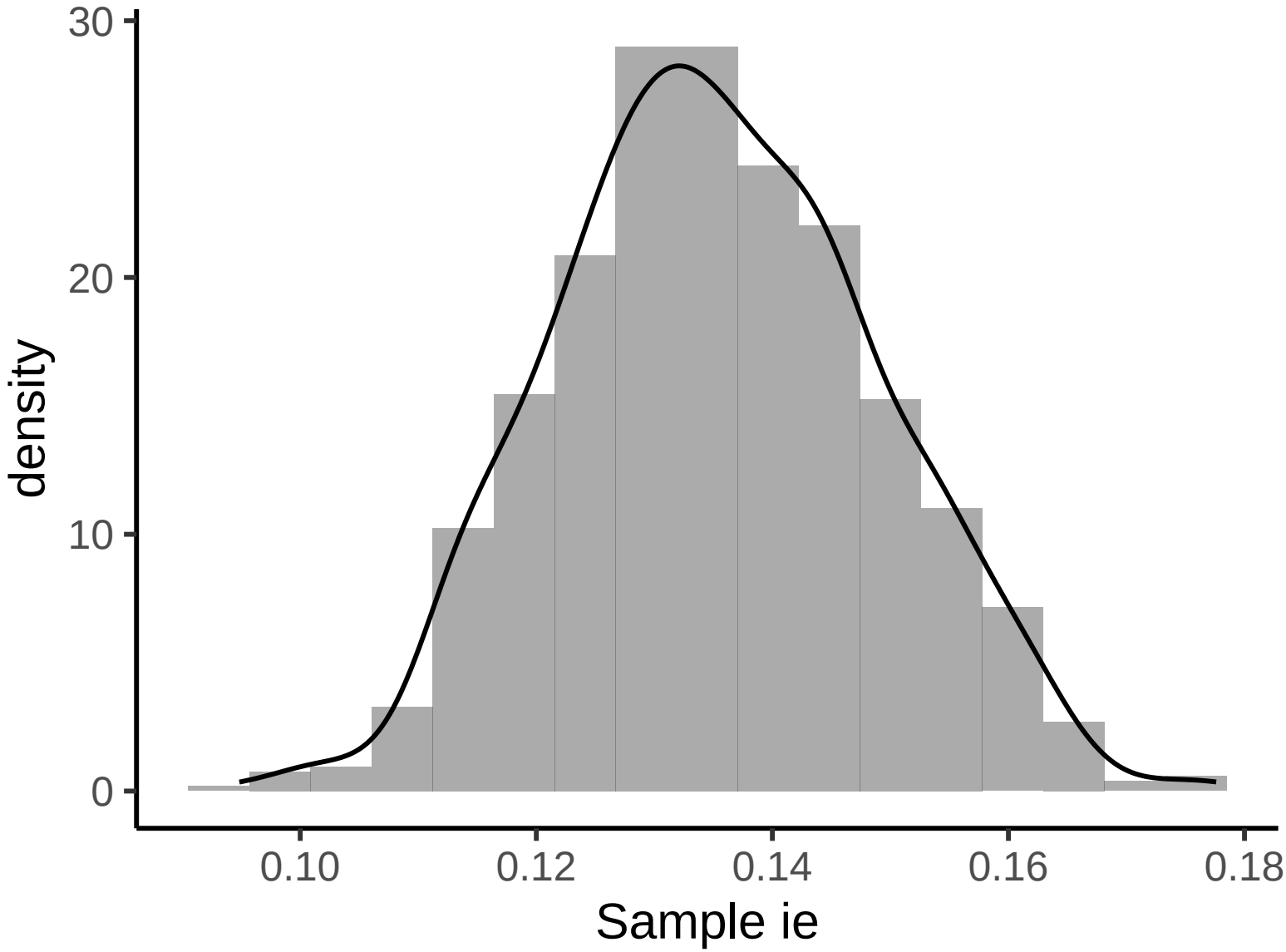
```
library(boot)
ind_eff <- function(data, indices) {
  d <- mediation[indices, ]
  fit_de2 <- lm(dinp ~ race + fastfood, data = d)
  beta2_m <- coef(fit_de2)[3]
  fit_m2 <- glm(fastfood ~ race, data = d, family = "binomial")
  alpha2 <- coef(fit_m2)

  return(beta2_m*((exp(alpha2[1] + alpha2[2]))/(1 + exp(alpha2[1] + alpha2[2])) -
                  (exp(alpha2[1]))/(1 + exp(alpha2[1]))))

}
results <- boot(data = mediation, ind_eff, R = 1000)
boot.ci(results, type = "norm")
BOOTSTRAP CONFIDENCE INTERVAL CALCULATIONS
Based on 1000 bootstrap replicates

CALL :
boot.ci(boot.out = results, type = "norm")

Intervals :
Level      Normal
95%   ( 0.108,  0.161 )
```


30
20
10
0
density
0.10
0.12
0.14
0.16
0.18
Sample ie

```
# For binary response models, the 'mediator' must be a numeric variable with val
mediation$ff <- as.double(mediation$fastfood) - 1
fit_xm1 <- glm(ff ~ race, data = mediation, family = "binomial")
fit_m1m2 <- lm(dinp ~ race + ff, data = mediation)
med_out <- mediate(fit_xm1, fit_m1m2, treat = "race", mediator = "ff",
                   robustSE = TRUE, sims = 1000)
summary(med_out)

Causal Mediation Analysis

Quasi-Bayesian Confidence Intervals

               Estimate 95% CI Lower 95% CI Upper p-value
ACME             0.1346       0.1062         0.17  <2e-16
ADE              1.6642       1.6131         1.72  <2e-16
Total Effect     1.7988       1.7395         1.86  <2e-16
Prop. Mediated   0.0746       0.0598         0.09  <2e-16

Sample Size Used: 10000


Simulations: 1000
```

Specific procedure have been written in:

- R: mediation
- Stata: paramed
- SAS and SPSS: macros from Valeri & Vanderweele
- SPSS

Code for the output in these slides available for R and Stata.

Further topics

- Sensitivity analysis
- Conterfactual approach
- Other extensions

Summary

- Mediation is about explaining mechanisms that underlie exposure-outcome associations, in particular providing insights on how an effect occurs.
- These methods can be applied with different data structures and to address different research questions, particularly those dealing when non-modifiable exposures.

A temporal sequence of exposure, mediator, and outcome, is generally recommended. In health disparities research, however, we can often assume a priori that the exposure precedes the mediator (e.g. gender, race/ethnicity)

Exposure-mediator, exposure-outcome, mediator-outcome, and mediator-mediator confounding must be all taken into account and are dealt in different ways. Studies are often designed without thinking of mediator-outcome confounders.