Causal Mediation Analysis

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Outline

- Introduction
- Overview of **mediate**
- Traditional mediation
- Causal inference
- Causal mediation analysis
- Examples

Introduction

Causal mediation analysis combines:

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- Causal inference

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- Mediation analysis

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- Causal inference—What is the effect of a treatment on an outcome?

- Mediation analysis—Can the total effect of a predictor on an outcome be decomposed into a direct effect and an indirect effect through a mediating variable?

Causal inference

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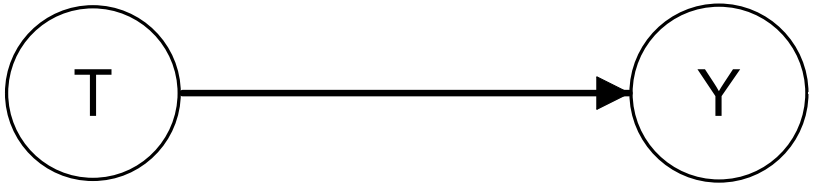

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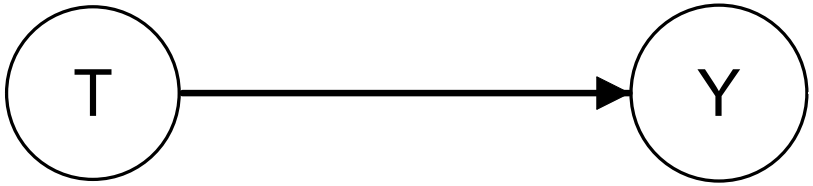
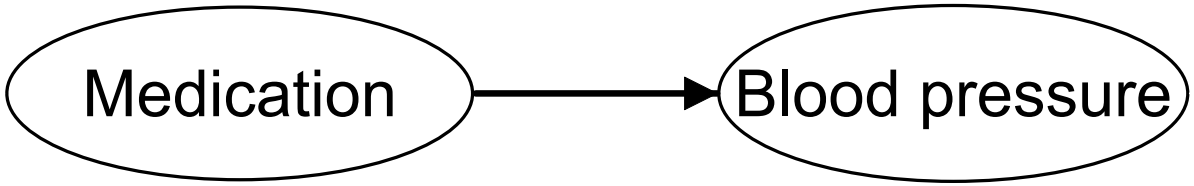


- What is the causal effect of **T** on **Y**?
- What is the expected difference in **Y** if the treatment **T** is applied versus if the treatment is not applied?

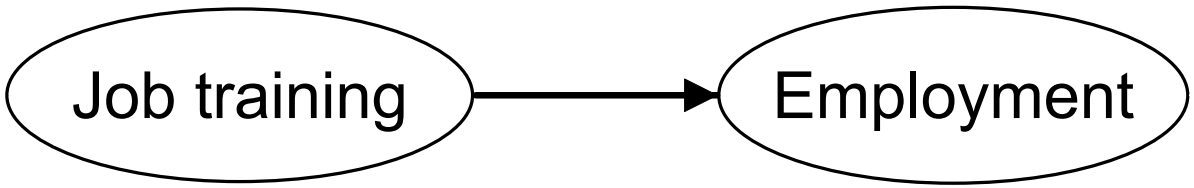
Causal inference

What is the effect of a medication on blood pressure?



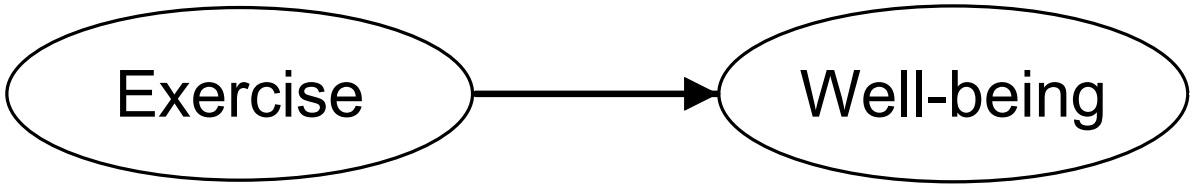
Causal inference

What is the effect of a job-training program on probability of employment?



Causal inference

What is the effect of exercise on self-perceived well-being?



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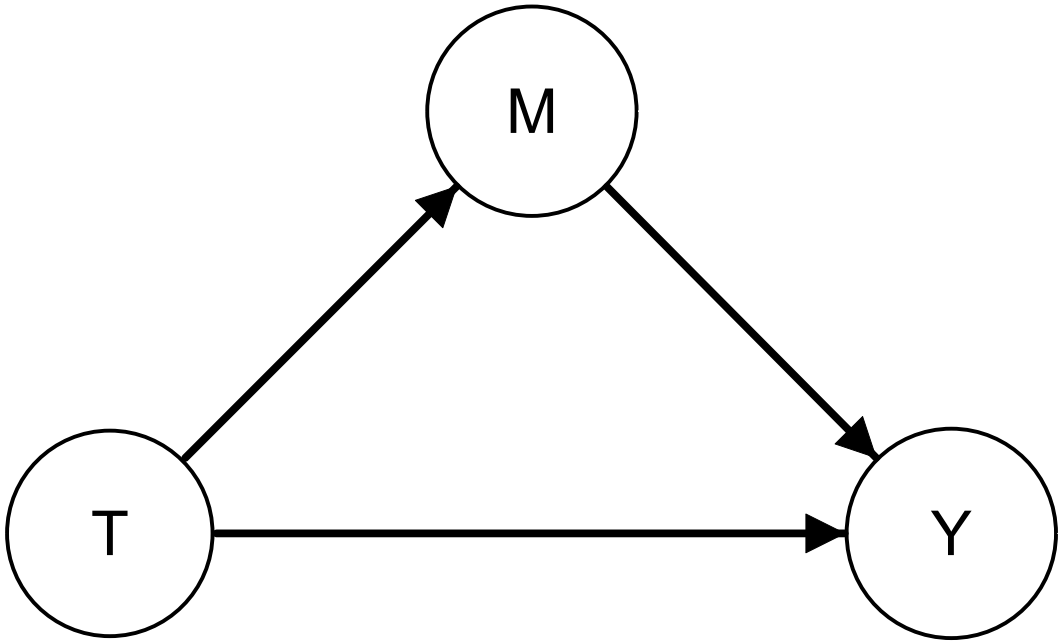

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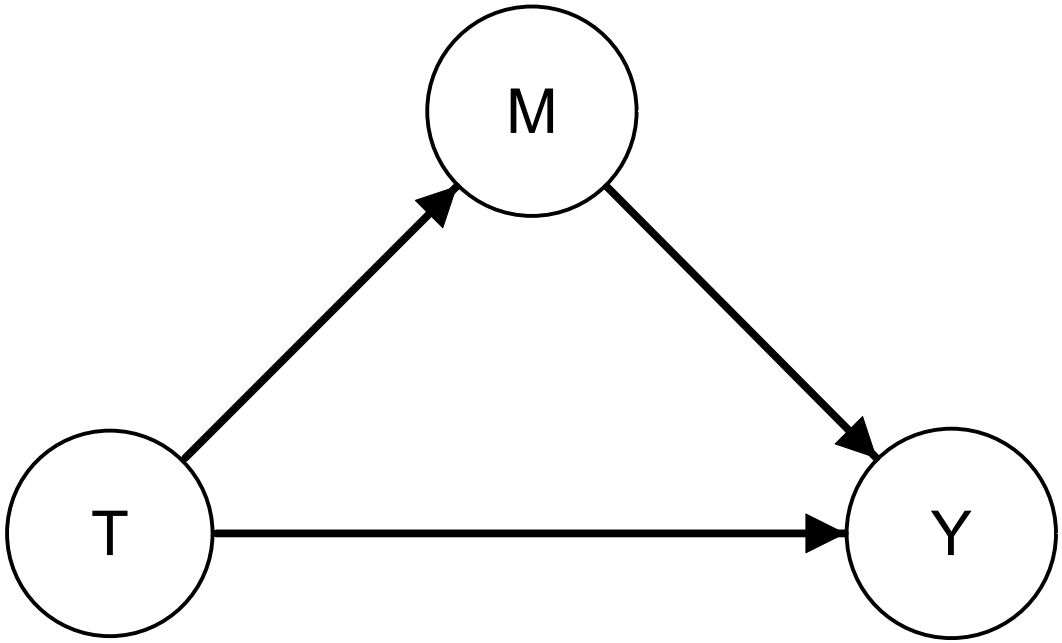
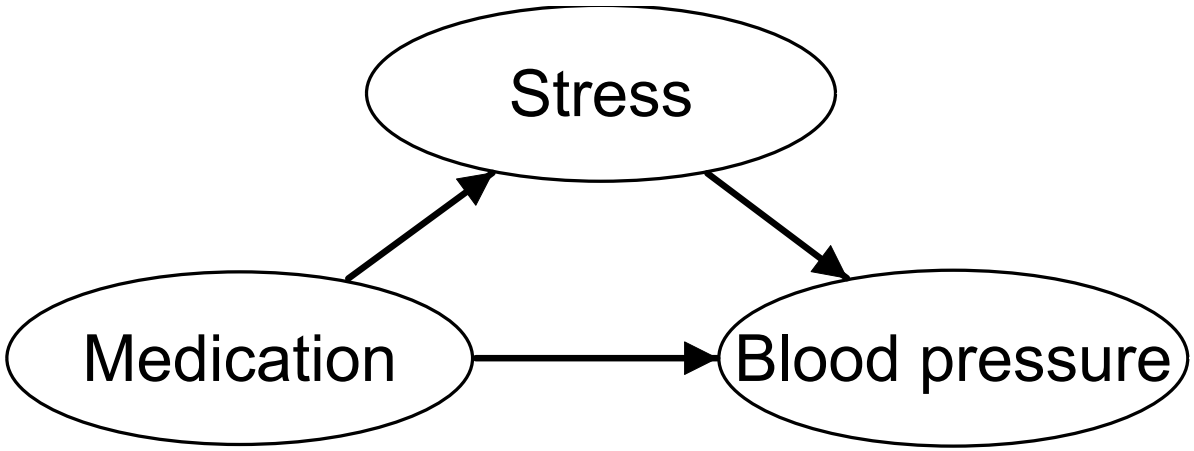


- Why does **T** affect **Y**?
- Can effect of **T** on **Y** be explained either completely or partially by a change in the mediator **M**?

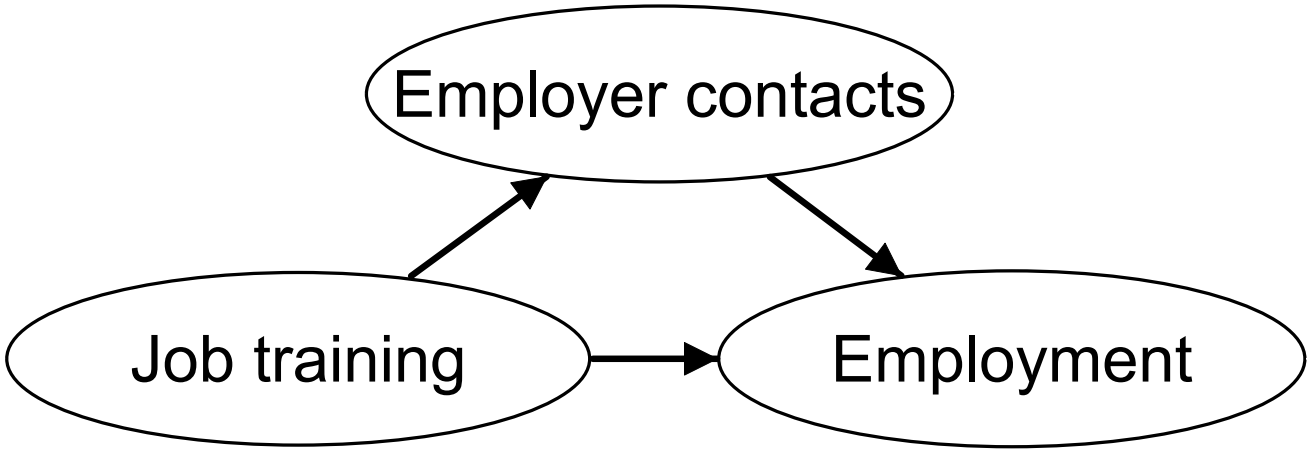
Mediation analysis

Does the medication result in lower stress levels, which in turn, results in lower blood pressure?



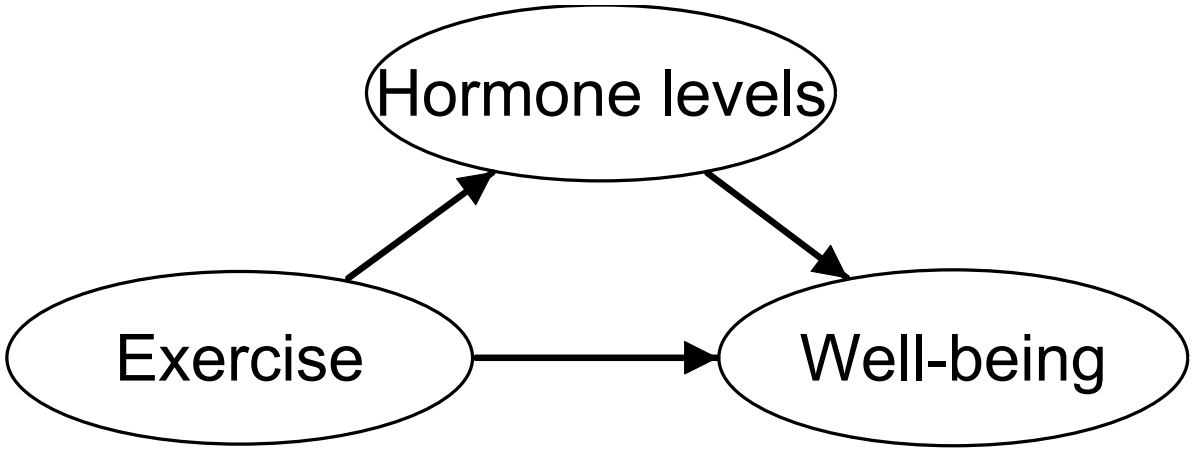
Mediation analysis

Does the job-training program put participants in contact with potential employers, which in turn, increases the probability of employment?



Mediation analysis

Does exercise change levels of some hormones, which in turn, change self-perceived well-being?



Causal mediation analysis

- With causal mediation analysis, we aim to draw causal inferences about the effect of a treatment on an outcome and to understand why the effect arises.

- To understand the why, we decompose the total effect into indirect effects through a mediator and direct effects.

Stata's **mediate** command

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```
mediate (ovar [omvarlist] [, omodel noconstant])
        (mvar [mmvarlist] [, mmodel noconsant])
        (tvar [, continuous(numlist)])
        [if] [in] [, stat options]
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        [if] [in] [, stat options]
```

- *ovar* is a continuous, binary, or count outcome of interest.
- *mvar* is the mediator variable and may be continuous, binary, or count.
- *tvar* is the treatment variable and may be binary, multivalued, or continuous.

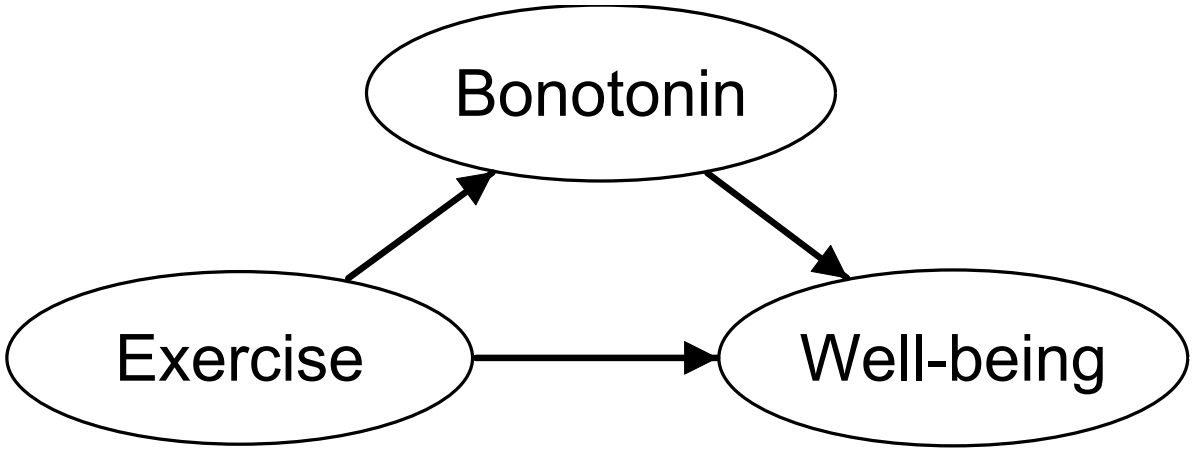
Stata's **mediate** command

Mediator / *Outcome*	linear	logit	probit	Poisson	exp. mean
linear	X	X	X	X	X
logit		X	X	X	
probit	X	X	X	X	X
Poisson	X	X	X	X	X
exp. mean	X	X	X	X	X

Note: X indicates a supported model combination

A first example

For a simple example using the **mediate** command, we continue with our hypothesis that exercise affects well-being and that this may, at least in part, be because of a change in hormone levels. We will consider a fictional hormone **bonotonin**.



A first example

```
. webuse wellbeing
(Fictional well-being data)
. list wellbeing bonotonin exercise in 1/5, abbreviate(10)
```

	wellbeing	bonotonin	exercise
1.	71.73816	196.5467	Control
2.	68.66573	195.8572	Exercise
3.	71.05155	228.6035	Exercise
4.	69.44469	206.6651	Exercise
5.	75.62035	261.6855	Exercise

- Both **wellbeing** and **bonotonin** are continuous, so we use the default linear model for the outcome and the mediator.
- **exercise** is a binary treatment variable with 0 representing the control group and 1 representing exercise group.

A first example

```
. mediate (wellbeing) (bonotonin) (exercise)

Iteration 0:  EE criterion =  5.104e-27
Iteration 1:  EE criterion =  2.031e-28

Causal mediation analysis                          Number of obs = 2,000

Outcome model:     Linear
Mediator model:    Linear
Mediator variable: bonotonin
Treatment type:    Binary
```

wellbeing	Coefficient	Robust std. err.	z	P>|z|	[95% conf.	interval]
NIE						
exercise (Exercise vs Control)	9.799821	.3943251	24.85	0.000	9.026958	10.57268
NDE						
exercise (Exercise vs Control)	2.891453	.2304278	12.55	0.000	2.439823	3.343083
TE						
exercise (Exercise vs Control)	12.69127	.4005941	31.68	0.000	11.90612	13.47642

Note: Outcome equation includes treatment-mediator interaction.

- We estimate the total effect of exercise on well-being is 12.7, with an indirect effect of 9.8 and a direct effect of 2.9.

A first example

- What proportion of the total effect exercise on well-being is mediated through bonotonin levels?

```
. estat proportion

Proportion mediated                                   Number of obs = 2,000
```

wellbeing	Proportion	Robust std. err.	z	P>|z|	[95% conf.	interval]
exercise (Exercise vs Control)	.77217	.0172979	44.64	0.000	.7382668	.8060732

Traditional mediation analysis: The formulation

- In traditional mediation analysis, we write models for the outcome and the mediator.

$$Y = \beta_0 + \beta_1 M + \beta_2 T + \epsilon$$
$$M = \alpha_0 + \alpha_1 T + \nu$$

- Then we define direct, indirect, and total effects as

$$\textit{Direct} = \beta_2$$
$$\textit{Indirect} = \alpha_1 * \beta_1$$
$$\textit{Total} = \beta_2 + \alpha_1 * \beta_1$$

Traditional mediation analysis: Estimation

- We can fit the linear regression models using **regress** and then manually compute direct, indirect, and total effects and the corresponding standard errors.
- Alternatively, we can fit models simultaneously using the **sem** command. Then we can use **estat teffects** to compute direct, indirect, and total effects and the corresponding standard errors.

```
. sem (wellbeing <- bonotonin exercise)
       (bonotonin <- exercise)
. estat teffects
```

Notes on traditional mediation analysis

- Traditional mediation analysis began with linear models for both the outcome and the mediator.
- The model for the outcome did not include a mediator by treatment interaction term.
- What can a causal inference approach add?

Causal inference workflow

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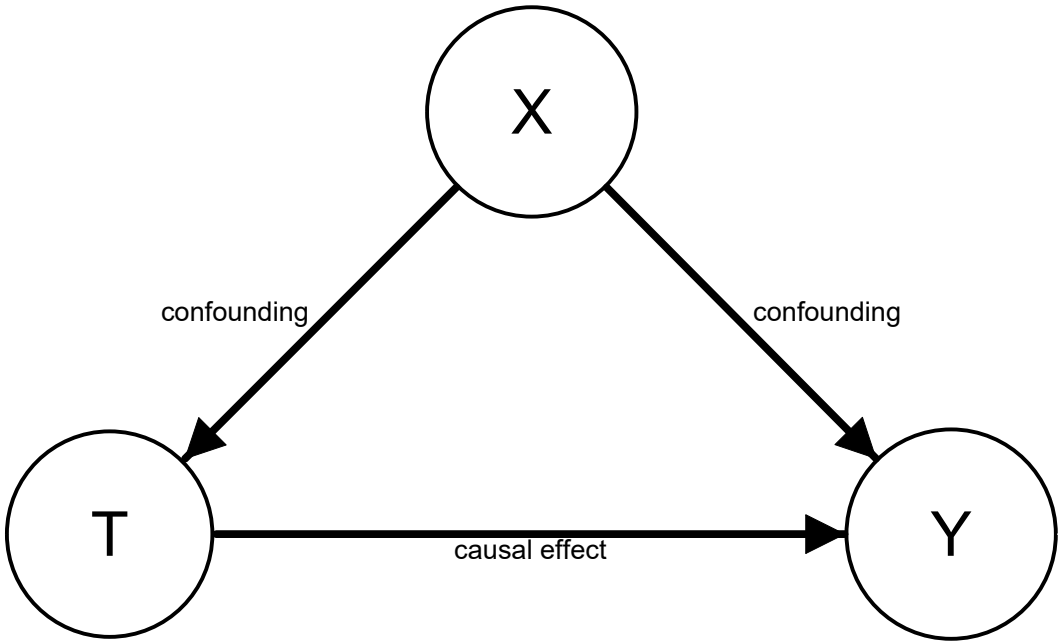
2. **Causal effect identification.** Based on the assumptions made in the first phase, the researcher tries to determine whether the causal effect can be identified.
3. **Parameter estimation.** If the answer to the second phase is positive, the researcher can then to estimate the causal effect.

Causal diagram



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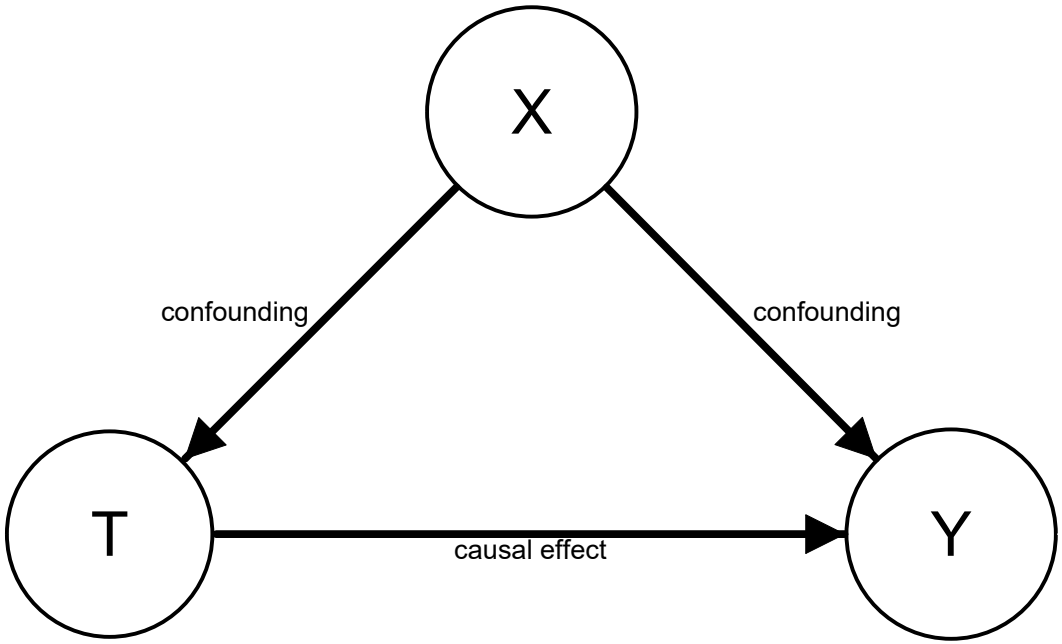

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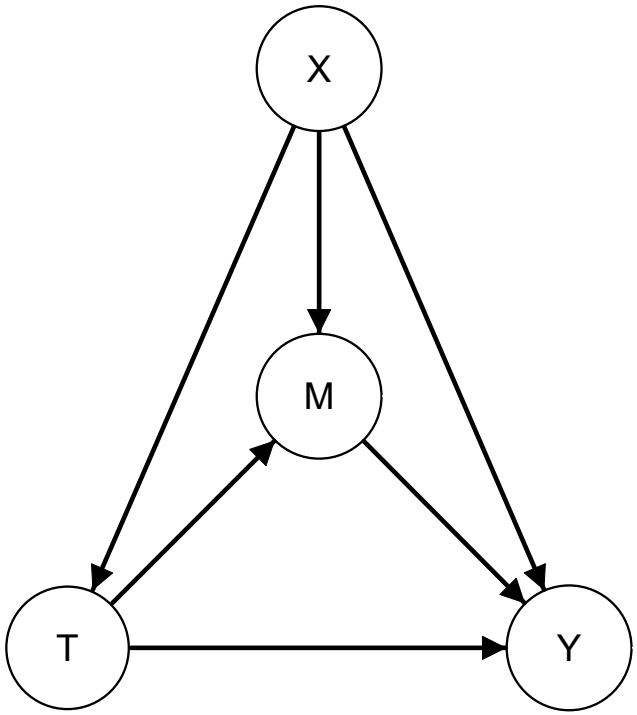
- **X** is a counfounder, and we must somehow control for confounding to obtain an unbiased estimate of the causal effect.

Causal diagram for mediation analysis

- We now include a mediator in the causal diagram.



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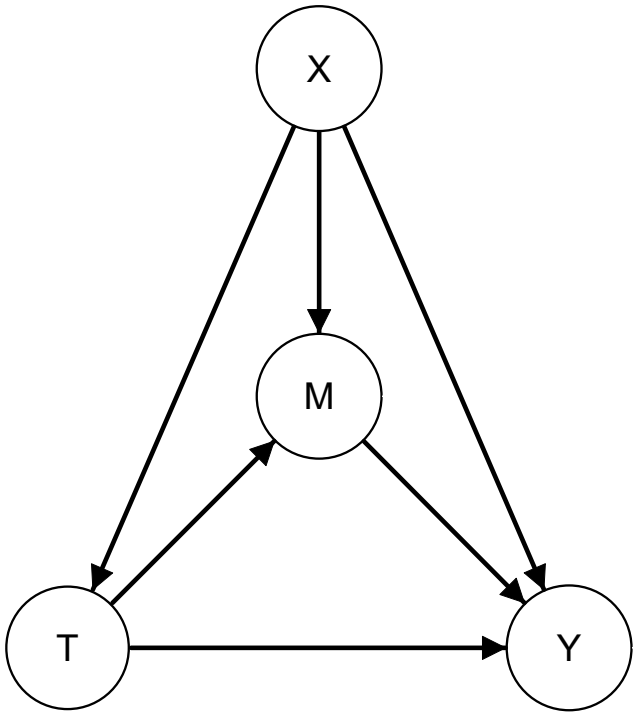

- In this example, **X** not only confounds the relationship between **T** and **Y** but also the relationships between **T** and **M** and between **M** and **Y**.

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- The average treatment effect (ATE) is $E[Y(1) - Y(0)]$.

Fundamental problem of causal inference

Subject	T	Y	Y(1)	Y(0)	Y(1) – Y(0)
1	0	2.1	?	2.1	?
2	1	3.7	3.7	?	?
3	1	4.2	4.2	?	?
4	0	6.2	?	6.2	?
...	...	...	...	...	...

For each individual, we can observe only one of $Y(1)$ or $Y(0)$.

Identifying a causal effect

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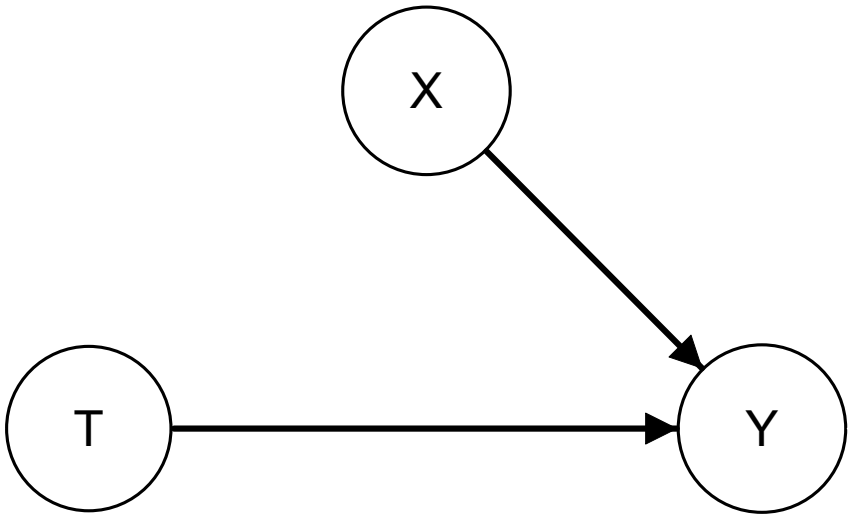

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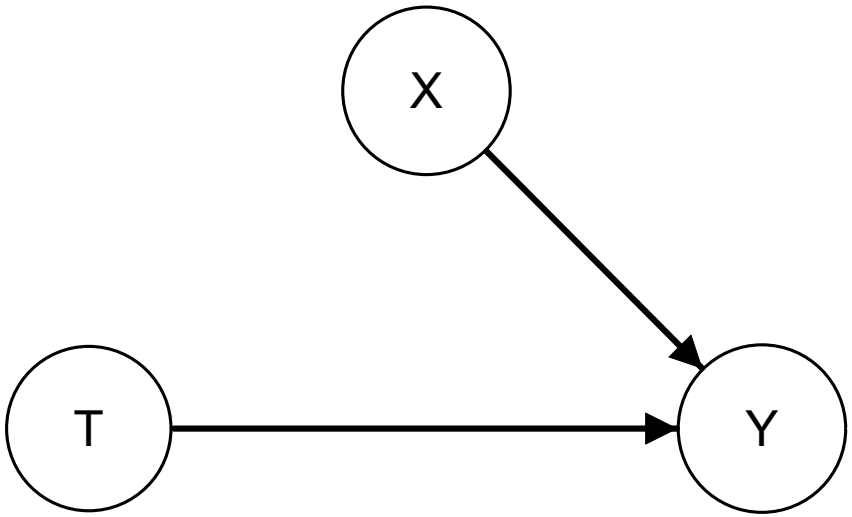

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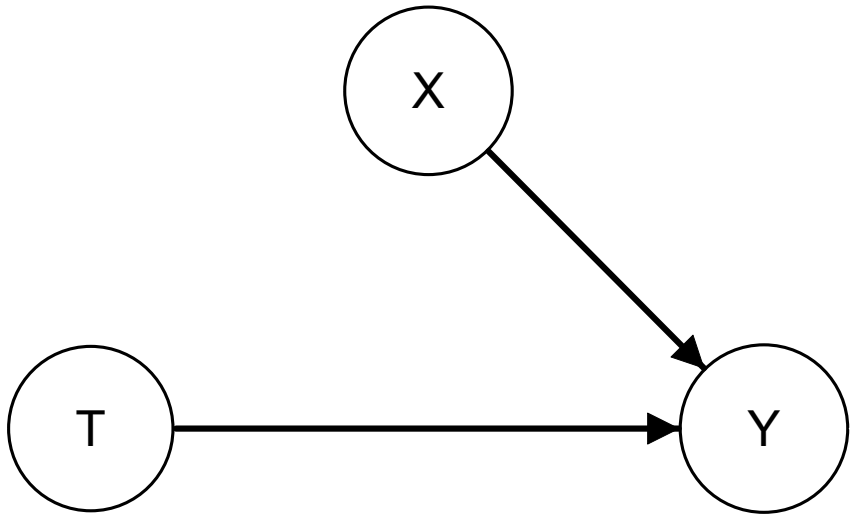

- In this case $E[Y(0)] = E[Y|T = 0]$ and $E[Y(1)] = E[Y|T = 1]$.
- We can estimate the ATE as $E[Y|T = 1] - E[Y|T = 0]$.

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- Now, the causal effect is identified:

$$E[Y(1)] - E[Y(0)] = E_x[E[Y|T = 1, X] - E[Y|T = 0, X]]$$

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  $$E[Y(1)] - E[Y(0)] = E_x[E[Y|T = 1, X] - E[Y|T = 0, X]]$$
- We can use commands such as **teffects** to estimate the ATE.

Estimating the causal effect

```
. teffects ra (wellbeing age) (exercise)
Iteration 0:  EE criterion =  1.261e-27
Iteration 1:  EE criterion =  1.707e-29
Treatment-effects estimation                    Number of obs     =      2,000
Estimator      : regression adjustment
Outcome model  : linear
Treatment model: none
```

wellbeing	Coefficient	Robust std. err.	z	P>|z|	[95% conf.	interval]
ATE						
exercise (Exercise vs Control)	12.76801	.3961873	32.23	0.000	11.9915	13.54452
POmean						
exercise Control	57.06904	.2738341	208.41	0.000	56.53234	57.60575

Mediation analysis via potential outcomes

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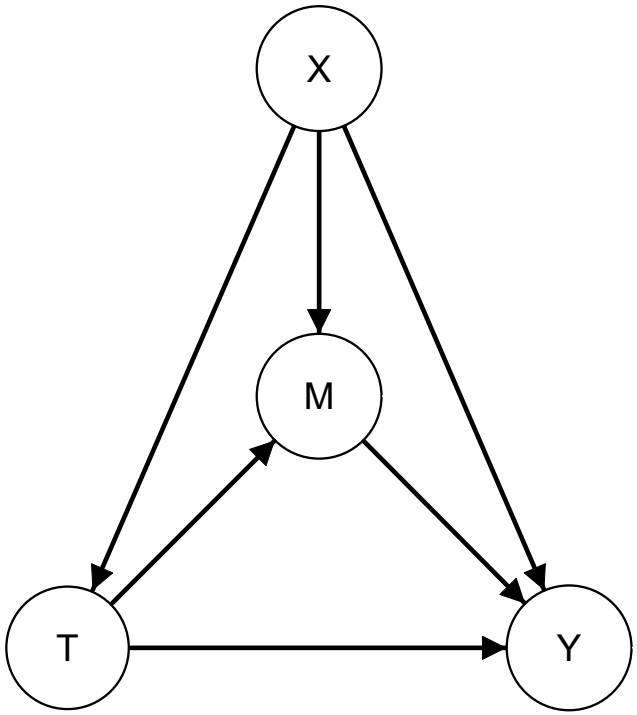
- We can extend the potential-outcomes framework to mediation analysis.

Mediation analysis via potential outcomes

- We can extend the potential-outcomes framework to mediation analysis.
- We can define a total average treatment effect as well as direct and indirect effects in terms of potential outcomes.

Mediation analysis: Causal inference workflow

- A causal diagram



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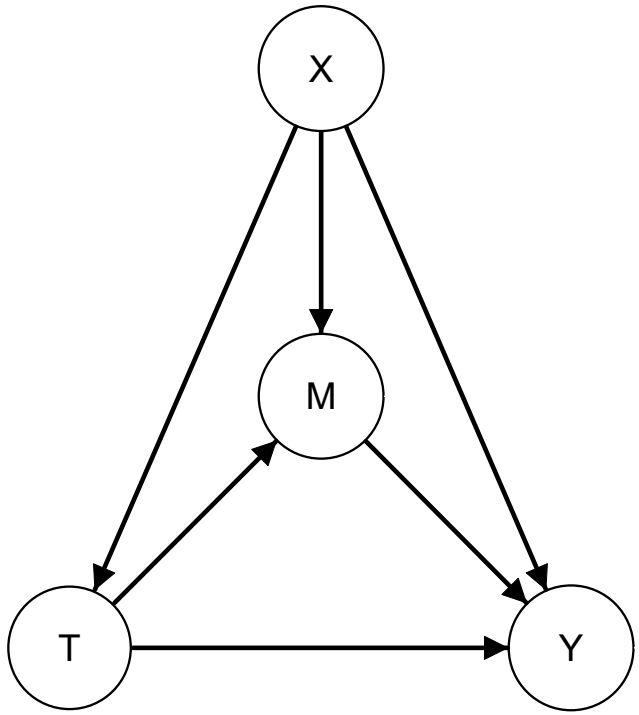

- As before, we will make assumptions that allow us to get unbiased estimates of the causal effects, even in the presence of confounders.

Potential outcomes

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- For the mediator, we have
  - $M(0)$ is the potential outcome of the mediator that would have been observed if treatment $T = 0$ was assigned.
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Potential outcomes

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  - $Y[1, M(0)]$ is the potential outcome that would be observed if treatment $T = 1$ was assigned, but the mediator is held at its value that would be observed if if $T = 0$ was assigned.

Potential outcomes

- Formally, let t be the treatment level with respect to the outcome, and let t' be the treatment level with respect to the mediator, the potential outcomes become $Y[t, M(t')]$.
- This leads to four types of potential outcomes:
  - $Y[0, M(0)]$ is the potential outcome that would be observed if treatment $T = 0$ was assigned.
  - $Y[1, M(1)]$ is the potential outcome that would be observed if treatment $T = 1$ was assigned.
  - $Y[1, M(0)]$ is the potential outcome that would be observed if treatment $T = 1$ was assigned, but the mediator is held at its value that would be observed if if $T = 0$ was assigned.
  - $Y[0, M(1)]$ is the potential outcome that would be observed if treatment $T = 0$ was assigned, but the mediator is held at its value that would be observed if if $T = 1$ was assigned.

Potential outcomes

```
. mediate (wellbeing) (bonotonin) (exercise), pomeans
Iteration 0:  EE criterion =  5.104e-27
Iteration 1:  EE criterion =  2.023e-28
Causal mediation analysis                          Number of obs = 2,000
Outcome model:     Linear
Mediator model:    Linear
Mediator variable: bonotonin
Treatment type:    Binary
```

wellbeing	Coefficient	Robust std. err.	z	P>|z|	[95% conf.	interval]
POmeans						
Y0M0	57.11317	.2753201	207.44	0.000	56.57355	57.65278
Y1M0	60.00462	.3157888	190.02	0.000	59.38569	60.62356
Y0M1	66.68199	.3258477	204.64	0.000	66.04334	67.32064
Y1M1	69.80444	.2898927	240.79	0.000	69.23626	70.37262

Note: Outcome equation includes treatment-mediator interaction.

Direct, indirect, and total treatment effects

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$$\delta(t) \equiv E[Y(t, M(1))] - E[Y(t, M(0))], \quad t \in \{0, 1\}$$

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- The direct effect of the treatment is:

$$\zeta(t) \equiv E[Y(1, M(t))] - E[Y(0, M(t))], \quad t \in \{0, 1\}$$

- Notice that the total effect is the sum of direct and indirect effects

$$\tau = \delta(0) + \zeta(1)$$
$$\tau = \delta(1) + \zeta(0)$$

Estimands

- Denoting $E[Y(t, M(t'))]$ as $Y_{tM_{t'}}$, we define the following treatment effects of interest

(Total) natural indirect effect (**NIE**)	$Y_{1M_1} - Y_{1M_0}$
(Pure) natural direct effect (**NDE**)	$Y_{1M_0} - Y_{0M_0}$
(Pure) natural indirect effect (**PNIE**)	$Y_{0M_1} - Y_{0M_0}$
(Total) natural direct effect (**TNDE**)	$Y_{1M_1} - Y_{0M_1}$
Total effect (**TE**)	$Y_{1M_1} - Y_{0M_0}$

Decomposition 1

```
. mediate (wellbeing) (bonotonin) (exercise)

Iteration 0:  EE criterion =  5.104e-27
Iteration 1:  EE criterion =  2.031e-28

Causal mediation analysis                          Number of obs = 2,000

Outcome model:     Linear
Mediator model:    Linear
Mediator variable: bonotonin
Treatment type:    Binary
```

wellbeing	Coefficient	Robust std. err.	z	P>|z|	[95% conf.	interval]
NIE						
exercise (Exercise vs Control)	9.799821	.3943251	24.85	0.000	9.026958	10.57268
NDE						
exercise (Exercise vs Control)	2.891453	.2304278	12.55	0.000	2.439823	3.343083
TE						
exercise (Exercise vs Control)	12.69127	.4005941	31.68	0.000	11.90612	13.47642

Note: Outcome equation includes treatment-mediator interaction.

Decomposition 2

```
. mediate (wellbeing) (bonotonin) (exercise), pnie tnde te

Iteration 0:  EE criterion =  5.104e-27
Iteration 1:  EE criterion =  3.672e-28

Causal mediation analysis                          Number of obs = 2,000

Outcome model:     Linear
Mediator model:    Linear
Mediator variable: bonotonin
Treatment type:    Binary
```

wellbeing	Coefficient	Robust std. err.	z	P>|z|	[95% conf.	interval]
PNIE						
exercise (Exercise vs Control)	9.568827	.3884522	24.63	0.000	8.807475	10.33018
TNDE						
exercise (Exercise vs Control)	3.122447	.2418591	12.91	0.000	2.648412	3.596482
TE						
exercise (Exercise vs Control)	12.69127	.4005941	31.68	0.000	11.90612	13.47642

Note: Outcome equation includes treatment-mediator interaction.

Chosing a decomposition

Which decomposition do we want?

Nguyen, Schmid, and Stuart (2021) give suggestions for three scenarios:

Chosing a decomposition

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2. Want to know whether any direct effect exists in addition to a mediation effect? Use PNIE and TNDE.

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3. Have no prior assumption about whether direct or indirect effects exist? Use both decompositions.

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   We are assuming that some mediating effect exists and want to know whether there is an affect through any other mechanisms.

3. Have no prior assumption about whether direct or indirect effects exist? Use both decompositions.

   We describe try to learn all we can from all decompositions.

Behind the scenes

- **mediate** estimates all effects parameters, auxiliary parameters, and their variance–covariance matrix via generalized method of moments.
- We can specify **aequations** option to see estimated auxiliary parameters—the parameters estimated for the outcome and treatment models.

Auxiliary parameter estimates

```
. mediate (wellbeing) (bonotonin) (exercise), aequations

Iteration 0:  EE criterion =  5.104e-27
Iteration 1:  EE criterion =  2.031e-28

Causal mediation analysis                       Number of obs = 2,000

Outcome model:     Linear
Mediator model:    Linear
Mediator variable: bonotonin
Treatment type:    Binary
```

wellbeing	Coefficient	Robust std. err.	z	P>|z|	[95% conf.	interval]
NIE						
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TE						
exercise (Exercise vs Control)	12.69127	.4005941	31.68	0.000	11.90612	13.47642

Auxiliary parameter estimates

wellbeing						
exercise						
Exercise	2.065871	.8723559	2.37	0.018	.3560846	3.775657
bonotonin	.2130222	.0034547	61.66	0.000	.2062512	.2197932
exercise# c.bonotonin						
Exercise	.0051424	.0046954	1.10	0.273	-.0040604	.0143452
_cons	22.91374	.5633648	40.67	0.000	21.80956	24.01791
bonotonin						
exercise						
Exercise	44.91939	1.641668	27.36	0.000	41.70178	48.137
_cons	160.544	1.142508	140.52	0.000	158.3047	162.7832

Note: Outcome equation includes treatment-mediator interaction.

Causal identification and assumptions

- We defined our effects of interest in terms of potential-outcome means.

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- The potential-outcome means are the result of an integral of the conditional expectation of the outcome with respect to the conditional distribution of the mediator:

$$f[Y(t, M(t'))|\boldsymbol{X} = \boldsymbol{x}] = \int f[Y|M = m, T = t, \boldsymbol{X} = \boldsymbol{x}]\, dF[m|T = t', \boldsymbol{X} = \boldsymbol{x}]$$

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- This is sometimes referred to as the "mediation formula".
- Notice that this is a nonparametric identification result.

Causal identification and assumptions

- In addition to assumptions for standard SUTVA and overlap assumptions, we need to make an assumption of sequential ignorability.

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Causal identification and assumptions

- In addition to assumptions for standard SUTVA and overlap assumptions, we need to make an assumption of sequential ignorability.
- Sequential ignorability essentially means
  - No unobserved confounding in the treatment-outcome relationship.
  - No unobserved confounding in the mediator-outcome relationship.
  - No unmeasured confounding in the treatment-mediator relationship.
  - There are no (observed) confounders in the mediator-outcome relationship that are caused by the treatment.

Causal identification and assumptions

- To meet these assumptions, we may need to add covariates to the model for the outcome, the model for the mediator, or both.
- Here, we adjust for **age** in both models before estimating potential-outcome means and the effects.

Including covariates

```
. mediate (wellbeing age) (bonotonin age) (exercise)

Iteration 0:  EE criterion =  6.163e-27
Iteration 1:  EE criterion =  4.924e-29

Causal mediation analysis                          Number of obs = 2,000

Outcome model:     Linear
Mediator model:    Linear
Mediator variable: bonotonin
Treatment type:    Binary
```

wellbeing	Coefficient	Robust std. err.	z	P>|z|	[95% conf.	interval]
NIE						
exercise (Exercise vs Control)	9.851525	.3905733	25.22	0.000	9.086015	10.61703
NDE						
exercise (Exercise vs Control)	2.915712	.2327821	12.53	0.000	2.459468	3.371957
TE						
exercise (Exercise vs Control)	12.76724	.3964534	32.20	0.000	11.9902	13.54427

Note: Outcome equation includes treatment-mediator interaction.

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- For binary treatment, CDE(m) is defined as $Y(1|M = m) - Y(0|M = m)$.

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- CDE(m) is then the average of the differences between potential outcomes.
- For binary treatment, CDE(m) is defined as $Y(1|M = m) - Y(0|M = m)$.
- Perhaps we want to know the effect of exercise on well-being if we had a medication that stabilized bonotonin levels at 200 for everyone in the population.

Controlled direct effects

```
. estat cde, mvalue(200)
Controlled direct effect                        Number of obs = 2,000
Mediator variable: bonotonin
Mediator value = 200
```

	Delta-method CDE	std. err.	z	P>|z|	[95% conf.	interval]
exercise (Exercise vs Control)	3.121577	.2315869	13.48	0.000	2.667675	3.575479

Modifying outcome and mediator models

What if we have a different type of outcome, mediator, or treatment?

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- **mediate** allows a binary, multivalued, a continuous treatment.

Modifying outcome and mediator models

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- **mediate** allows a continuous, binary, or count mediator. You can specify a linear, logit, probit, Poisson, or exponential mean model for the mediator.
- **mediate** allows a binary, multivalued, a continuous treatment.

Logit models

- To demonstrate, we model a binary mediator, **bbonotonin**, which is an indicator for at least 10% increase in bonotonin over the baseline level.
- We also have a binary outcome, **bwellbeing**, which is an indicator for at least 10% improvement in well-being over the baseline value.
- We will fit a logit model for both the outcome and mediator and estimate the effects of interest using the same definitions based on potential-outcome means.

Logit models

```
. mediate (bwellbeing basewell age, logit)
>         (bbonotonin basebono age, logit)
>         (exercise), nointeraction

Iteration 0:  EE criterion =  4.840e-18
Iteration 1:  EE criterion =  1.836e-33

Causal mediation analysis                          Number of obs = 2,000

Outcome model:     Logit
Mediator model:    Logit
Mediator variable: bbonotonin
Treatment type:    Binary
```

bwellbeing	Coefficient	Robust std. err.	z	P>|z|	[95% conf.	interval]
NIE						
exercise (Exercise vs Control)	.1110896	.0142334	7.80	0.000	.0831926	.1389866
NDE						
exercise (Exercise vs Control)	.146092	.0189224	7.72	0.000	.1090047	.1831792
TE						
exercise (Exercise vs Control)	.2571816	.0143876	17.88	0.000	.2289824	.2853807

```
Note: Outcome equation does not include treatment-mediator interaction.
```

Logit models

- With a binary outcome, the effects are interpreted on a probability scale or as risk differences.

Logit models

- With a binary outcome, the effects are interpreted on a probability scale or as risk differences.
- We expect the probability of better well-being to be 0.26 higher if everyone in the population exercises than if no one exercises. Of that, the probability of better well-being is 0.11 higher because of an increase in bonotonin levels which and 0.15 higher because of other factors.

Logit models

- With a binary outcome, the effects are interpreted on a probability scale or as risk differences.
- We expect the probability of better well-being to be 0.26 higher if everyone in the population exercises than if no one exercises. Of that, the probability of better well-being is 0.11 higher because of an increase in bonotonin levels which and 0.15 higher because of other factors.
- We can use **estat rr** to report risk ratios or **estat or** to report odds ratios.

Risk ratios

```
. estat rr
estat rr requires potential-outcome means; refitting model ...
Transformed treatment effects                          Number of obs = 2,000
```

bwellbeing	Risk ratio	Robust std. err.	z	P>|z|	[95% conf.	interval]
NIE						
exercise (Exercise vs Control)	1.245647	.0392724	6.97	0.000	1.171004	1.325047
NDE						
exercise (Exercise vs Control)	1.477205	.0708189	8.14	0.000	1.344724	1.622738
TE						
exercise (Exercise vs Control)	1.840076	.0706258	15.89	0.000	1.70673	1.983839

Odds ratios

```
. estat or
estat or requires potential-outcome means; refitting model ...
Transformed treatment effects                          Number of obs = 2,000
```

bwellbeing	Odds ratio	Robust std. err.	z	P>|z|	[95% conf.	interval]
NIE						
exercise (Exercise vs Control)	1.562536	.0898293	7.76	0.000	1.396031	1.748901
NDE						
exercise (Exercise vs Control)	1.871182	.1490494	7.87	0.000	1.600713	2.187352
TE						
exercise (Exercise vs Control)	2.92379	.1841129	17.04	0.000	2.584315	3.307858

Continuous treatment

- **mediate** supports binary, multivalued, and continuous treatments.
- When the treatment is continuous, we need to include the **continuous()** option in the treatment specification and define the values at which we want the potential-outcome means to be evaluated. The first value will be considered the control.

Continuous treatment

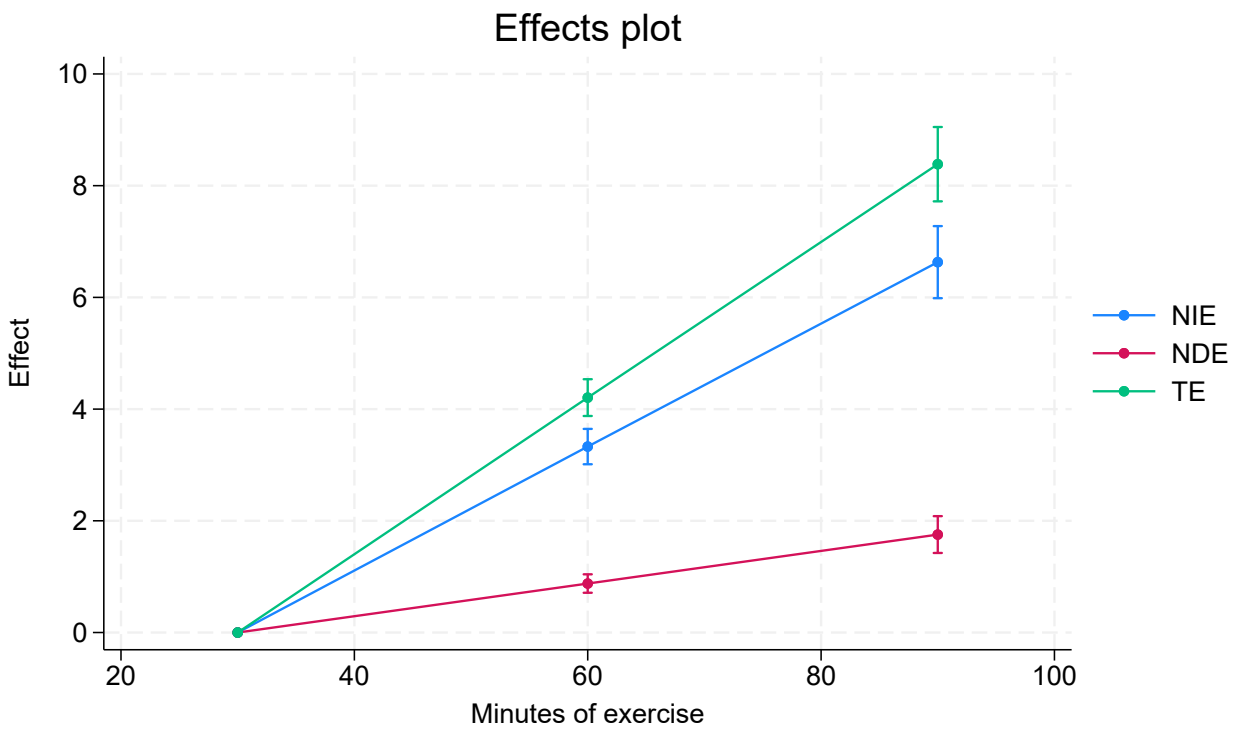
```
. mediate (wellbeing) (bonotonin) (cexercise, continuous (30 60 90))

Iteration 0:  EE criterion =  8.416e-28
Iteration 1:  EE criterion =  8.416e-28  (backed up)

Causal mediation analysis                          Number of obs = 2,000

Outcome model:     Linear
Mediator model:    Linear
Mediator variable: bonotonin
Treatment type:    Continuous

Continuous treatment levels:
  0: cexercise = 30 (control)
  1: cexercise = 60
  2: cexercise = 90
```

wellbeing	Coefficient	Robust std. err.	z	P>|z|	[95% conf.	interval]
NIE						
cexercise						
(1 vs 0)	3.329037	.1613581	20.63	0.000	3.012781	3.645293
(2 vs 0)	6.630837	.3292353	20.14	0.000	5.985548	7.276127
NDE						
cexercise						
(1 vs 0)	.8769353	.0841601	10.42	0.000	.7119845	1.041886
(2 vs 0)	1.753871	.1683203	10.42	0.000	1.423969	2.083772
TE						
cexercise						
(1 vs 0)	4.205972	.1679266	25.05	0.000	3.876842	4.535103
(2 vs 0)	8.384708	.3394717	24.70	0.000	7.719356	9.05006

Note: Outcome equation includes treatment-mediator interaction.

Graphing effects

- When we evaluate effects at multiple points, we can use **estat effectsplot** to easily compare the effects visually.



Final remarks

- Learn more:
  `https://www.stata.com/manuals/causalmediate.pdf`

Thank you!

References

Nguyen, T. Q., I. Schmid, and E. A. Stuart. 2021. Clarifying causal mediation analysis for the applied researcher: Defining effects based on what we want to learn. Psychological Methods 26: 255-271.