Causal mediation analysis with multiple mediators

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Road map

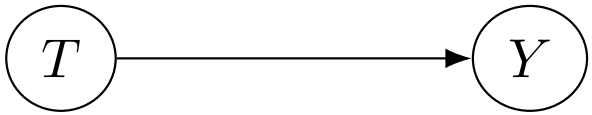
- Causal mediation and the potential outcomes framework
- Causal mediation with a single mediator
- Causal mediation with two mediators

Causal inference and mediation

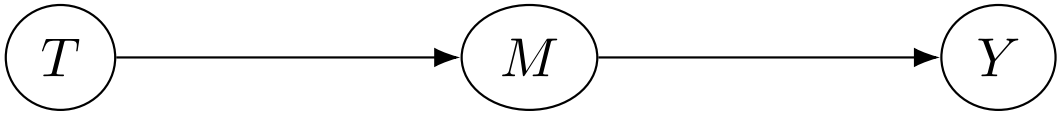
- The goal of causal inference is to identify and quantify the effect of some treatment (exposure) on some outcome.
- With causal mediation, we can disentangle causal effects into direct and indirect effects.
- By decomposing causal effects into direct and indirect effects, we are targeting the underlying mechanism of causal relations.
- In other words, we use causal mediation to learn about *why* certain causes have the effect they have.

Causal diagram illustration

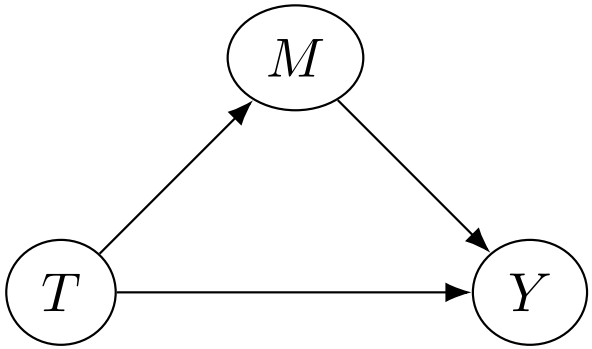
- Simple causal model for the effect of T on Y:



- Causal model for the effect of T on Y through M:



- Mediation model with a direct and an indirect effect:



Potential outcomes framework (1)

- Consider a simple randomized experiment with binary treatment T and outcome Y, with sample observations $i = 1...N$.
- We wish to identify two sets of potential outcomes, $Y_i(1)$ and $Y_i(0)$, where $Y_i(t)$ is the outcome that would be realized if the ith individual were exposed to treatment level t.
- If it were possible to observe an individual in both states at the same time, we would observe one outcome value under treatment, $Y_i(1)$, and one value under the control condition, $Y_i(0)$.
- The (individual-level) treatment effect would then be the difference $\tau_i = Y_i(1) - Y_i(0)$.
- Averaging the difference over all individuals in the sample would yield an estimate of the ATE
  $\tau = E[Y_i(1) - Y_i(0)] = E[Y_i(1)] - E[Y_i(0)]$.

Potential outcomes framework (2)

- As we know, it is not possible to observe the same individual under both conditions at the same time.
- We can only observe one of these while the other is missing.
- If an individual is treated, we observe $Y_i(1)$, and if not, we observe $Y_i(0)$.
- This has been coined the "fundamental problem of causal inference"
- Much of the treatment effects and causal inference literature deals with the question of how to estimate an ATE in the presence of this problem.
- In a simple experiment where treatment is randomly assigned, the potential outcomes are independent of treatment assignment and the missing potential outcomes are missing completely at random.
- With observational rather than experimental data the potential outcomes are not independent of the treatment assignment process, and the causal effect is not identifiable without imposing further assumptions such as conditional independence.

Potential outcome framework for causal mediation

- Now consider the case where we have a mediator M in addition to treatment T and outcome Y.
- We now have an additional set of potential outcomes, $M_i(1)$ and $M_i(0)$, because M is also causally related to the treatment.
- $M_i(1)$ are the potential outcomes of the mediator that would be observed had the ith individual been assigned to the group of active treatment.
- $M_i(0)$ are the potential outcomes of the mediator that would be observed had the ith individual been assigned to the control group.
- 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 $Y_i[t, M_i(t')]$.

Causal mediation potential outcomes (1)

- With binary treatment, we now have four sets of potential outcomes: $Y_i[0, M_i(0)]$, $Y_i[1, M_i(1)]$, $Y_i[1, M_i(0)]$ and $Y_i[0, M_i(1)]$.
- $\boldsymbol{Y_i[0, M_i(0)]}$ is observed if $T_i = 0$.
- $\boldsymbol{Y_i[1, M_i(1)]}$ is observed if $T_i = 1$.
- $\boldsymbol{Y_i[0, M_i(0)]}$ are the potential outcomes that we would observe if nobody in the population received treatment.
- $\boldsymbol{Y_i[1, M_i(1)]}$ are the potential outcomes that we would observe if everybody in the population received treatment.
- Notice that $Y_i[0, M_i(0)] = Y_i(0)$ and $Y_i[1, M_i(1)] = Y_i(1)$

Causal mediation potential outcomes (2)

- $\boldsymbol{Y_i}[\mathbf{1}, \boldsymbol{M_i}(\mathbf{0})]$ and $\boldsymbol{Y_i}[\mathbf{0}, \boldsymbol{M_i}(\mathbf{1})]$, sometimes referred to as cross-world potential outcomes, are never observed.
- $\boldsymbol{Y_i}[\mathbf{1}, \boldsymbol{M_i}(\mathbf{0})]$ are the potential outcomes that we would observe if everybody in the population received treatment, but where the mediator is held at a value that would be observed as though nobody in the population received treatment.
- $\boldsymbol{Y_i}[\mathbf{0}, \boldsymbol{M_i}(\mathbf{1})]$ are the potential outcomes that we would observe if nobody in the population received treatment, but where the mediator is held at a value that would be observed as though everybody in the population received treatment.

Direct, indirect, and total treatment effects

- Average direct, indirect, and total treatment effects are contrasts between potential outcome means.
- The total effect is:

$$\tau \equiv E[Y_i(1)] - E[Y_i(0)] = E[Y_i(1, M_i(1))] - E[Y_i(0, M_i(0))]$$

- The effect of the treatment on the outcome through the mediator is the indirect effect:

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

- The direct effect of the treatment is:

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

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

$$\tau = \delta(t) + \zeta(t)$$

Two treatment effect decompositions

- If we include a treatment-mediator interaction, the total treatment effect can be decomposed in two different ways.
- We can decompose the total effect using components
  $\delta(0) \equiv E[Y_i(0, M_i(1))] - E[Y_i(0, M_i(0))]$ and
  $\zeta(0) \equiv E[Y_i(1, M_i(0))] - E[Y_i(0, M_i(0))]$
- ... as well as
  $\delta(1) \equiv E[Y_i(1, M_i(1))] - E[Y_i(1, M_i(0))]$ and
  $\zeta(1) \equiv E[Y_i(1, M_i(1))] - E[Y_i(0, M_i(1))]$
- If we do not include a treatment-mediator interaction, i.e., we impose the assumption that the effect of the mediator on the outcome does not vary across treatment groups, we have that $\delta(0) = \delta(1)$ and $\zeta(0) = \zeta(1)$.

Estimands

- Denoting $E[Y_i(t, M_i(t'))]$ 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**)	$Y_{1M_1} - Y_{0M_0}$

How to identify potential outcome means?

- 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:

$$f[Y_i(t, M_i(t'))|\boldsymbol{X_i} = \boldsymbol{x}] = \int f[Y_i|M_i = m, T_i = t, \boldsymbol{X_i} = \boldsymbol{x}]\, dF[m|T_i = t', \boldsymbol{X_i} = \boldsymbol{x}]$$

- This is sometimes referred to as the "mediation formula".
- It expresses the potential outcomes as a function of the conditional distribution of M_i given T_i and $\boldsymbol{X}_i$, and that of Y_i given M_i, T_i, and $\boldsymbol{X}_i$.
- Notice that this is a nonparametric identification result.

Illustrative example using a linear model (1)

- Suppose we have the following model with two equations:

$$Y_i = \beta_0 + \beta_1 M_i + \beta_2 T_i + \epsilon_i$$
$$M_i = \alpha_0 + \alpha_1 T_i + \nu_i$$

- To calculate the natural indirect effect (NIE), we need estimates for potential-outcome means $E[Y_i(1, M_i(1))]$ and $E[Y_i(1, M_i(0))]$.
- With the linear model, we can write the model in reduced form and yield the conditional expectation of outcome Y:

$$\begin{aligned} E[Y_i|M_i, T_i] &= \beta_0 + \beta_1(\alpha_0 + \alpha_1 T_i) + \beta_2 T_i \\ &= \beta_0 + \beta_1\alpha_0 + \beta_1\alpha_1 T_i + \beta_2 T_i \end{aligned}$$

- To obtain the potential-outcome means, we can modify the reduced-form model by replacing M_i with the expectation of M_i that we would observe if T_i had taken on the value t' for every unit in the population:

$$E[Y_i(t, M_i(t'))] = \beta_0 + \beta_1 E[M_i(t')] + \beta_2 t, \quad t \in \{0, 1\}$$

Illustrative example using a linear model (2)

- Now, to compute the potential-outcome mean $E[Y_i(1, M_i(1))]$, we must set the treatment T_i to 1 in both the outcome and the mediator equations. In other words, we fix both t and t' at 1:

$$\begin{aligned} E[Y_i(1, M_i(1))] &= \beta_0 + \beta_1 E[M_i(t')] + \beta_2 t, \quad t = t' = 1 \\ &= \beta_0 + \beta_1\alpha_0 + \beta_1\alpha_1 \times 1 + \beta_2 \times 1 \\ &= \beta_0 + \beta_1\alpha_0 + \beta_1\alpha_1 + \beta_2 \end{aligned}$$

- To compute $E[Y_i(1, M_i(0))]$, we need to set treatment T_i to 1 in the outcome equation but set it to 0 in the mediator equation. Specifically, we fix $t' = 0$ and $t = 1$:

$$\begin{aligned} E[Y_i(1, M_i(0))] &= \beta_0 + \beta_1 E[M_i(t')] + \beta_2 t, \quad t = 1;\ t' = 0 \\ &= \beta_0 + \beta_1\alpha_0 + \beta_1\alpha_1 \times 0 + \beta_2 \times 1 \\ &= \beta_0 + \beta_1\alpha_0 + \beta_2 \end{aligned}$$

Illustrative example using a linear model (3)

- Calculating the difference yields the indirect treatment effect

$$\begin{aligned}\delta(1) &= (\beta_0 + \beta_1\alpha_0 + \beta_1\alpha_1 + \beta_2) - (\beta_0 + \beta_1\alpha_0 + \beta_2) \\ &= \beta_0 + \beta_1\alpha_0 + \beta_1\alpha_1 + \beta_2 - \beta_0 - \beta_1\alpha_0 - \beta_2 \\ &= \beta_1\alpha_1\end{aligned}$$

- We are left with the product of the treatment coefficient from the mediator equation and the mediator coefficient from the outcome equation.
- This is congruent with the classical product-of-coefficients method.
- Had we included a treatment-mediator interaction, the result would be $\delta(1) = (\beta_1 + \beta_3)\alpha_1$.
- Not as simple for models other than the linear model.

Assumptions for identifying estimands of interest

- SUTVA, overlap, **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.

Stata's `mediate` command

- New in Stata 18: `mediate` (single mediator)
- `mediate` performs causal mediation analysis for linear and generalized linear models.
- It uses analytical expressions to compute potential outcome means based on parametric models.
- Outcome and mediator variables may be continuous, binary, or count.
- Treatment may be binary, multivalued, or continuous.
- Linear, logit, probit, Poisson, and exponential-mean models for outcome and mediator.
- Special-purpose postestimation commands.

Outcome and mediator model combinations

	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 supported model combination

Postestimation commands

- Special-purpose postestimation commands include
  - `estat proportion` proportion mediated
  - `estat cde` controlled direct effects
  - `estat rr` treatment effects as risk ratios
  - `estat or` treatment effects as odds ratios
  - `estat irr` treatment effects as incidence-rate ratios
  - `estat effectsplot` plot treatment effects

Treatment effects on different scales (1)

- If the outcome is binary, and if the outcome model is either `logit` or `probit`, we can express the treatment effects as risk ratios or odds ratios.
- If the outcome model is Poisson/exponential mean, treatment effects can be expressed as incidence-rate ratios.
- The treatment effects on risk-ratio and incidence-rate-ratio scales are ratios of potential-outcome means:

$$
\begin{aligned}
\text{NIE}^{\text{RR}} &\equiv Y_{1M_1} / Y_{1M_0} \\
\text{NDE}^{\text{RR}} &\equiv Y_{1M_0} / Y_{0M_0} \\
\text{PNIE}^{\text{RR}} &\equiv Y_{0M_1} / Y_{0M_0} \\
\text{TNDE}^{\text{RR}} &\equiv Y_{1M_1} / Y_{0M_1} \\
\text{TE}^{\text{RR}} &\equiv Y_{1M_1} / Y_{0M_0}
\end{aligned}
$$

Treatment effects on different scales (2)

- For logit and probit outcome models, $Y_{tM_{t'}}$ are probabilities, and so the treatment effects on odds-ratio scale are

$$
\begin{aligned}
\text{NIE}^{\text{OR}} &\equiv Y_{1M_1}/(1-Y_{1M_1})/\{Y_{1M_0}/(1-Y_{1M_0})\} \\
\text{NDE}^{\text{OR}} &\equiv Y_{1M_0}/(1-Y_{1M_0})/\{Y_{0M_0}/(1-Y_{0M_0})\} \\
\text{PNIE}^{\text{OR}} &\equiv Y_{0M_1}/(1-Y_{0M_1})/\{Y_{0M_0}/(1-Y_{0M_0})\} \\
\text{TNDE}^{\text{OR}} &\equiv Y_{1M_1}/(1-Y_{1M_1})/\{Y_{0M_1}/(1-Y_{0M_1})\} \\
\text{TE}^{\text{OR}} &\equiv Y_{1M_1}/(1-Y_{1M_1})/\{Y_{0M_0}/(1-Y_{0M_0})\}
\end{aligned}
$$

- Notice that for all of these scales, the decomposition becomes multiplicative; that is, the total effect becomes the product of direct and indirect effects.

Controlled direct effects

- A controlled direct effect (CDE) is the effect of a treatment on an outcome when the mediator is fixed at a particular value.
- To estimate controlled direct effects, we use only the results of the outcome equation.
- Rather than having potential outcomes of the form $Y_i(t, M_i(t'))$, here we have potential outcomes $Y_i(t|M_i = m)$.
- That is, we have potential outcomes for each treatment level t that are evaluated at value m of the mediator.
- CDE(m) is then the average of the differences between potential outcomes.
- For binary treatment, CDE(m) is defined as $Y_i(1|M_i = m) - Y_i(0|M_i = m)$.
- Letting Y_{tm} be a shorthand for $Y_i(t|M_i = m)$, we have that

$$
\begin{aligned}
\text{CDE(m)} &\equiv Y_{1m} - Y_{0m} \\
\text{CDE(m)}^{\text{RR}} &\equiv Y_{1m}/Y_{0m} \\
\text{CDE(m)}^{\text{IRR}} &\equiv Y_{1m}/Y_{0m} \\
\text{CDE(m)}^{\text{OR}} &\equiv Y_{1m}/(1 - Y_{1m})/\{Y_{0m}/(1 - Y_{0m})\}
\end{aligned}
$$

`mediate` syntax, single mediator

Syntax

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

ovar is a continuous, binary, or count outcome of interest.

omvarlist specifies the covariates in the outcome model.

mvar is the mediator variable and may be continuous, binary, or count.

mmvarlist specifies the covariates in the mediator model.

tvar is the treatment variable and may be binary, multivalued, or continuous.

Example data (1)

```
. webuse wellbeing
(Fictional well-being data)

. list wellbeing bonotonin exercise age gender in 1/5, abbreviate(12) clean

     wellbeing   bonotonin   exercise   age   gender
  1.   71.73816    196.5467    Control    58     Male
  2.   68.66573    195.8572   Exercise    38   Female
  3.   71.05155    228.6035   Exercise    53   Female
  4.   69.44469    206.6651   Exercise    44   Female
  5.   75.62035    261.6855   Exercise    28   Female
```

Linear models with no treatment-mediator interaction

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

Iteration 0:  EE criterion =  6.800e-28
Iteration 1:  EE criterion =  1.777e-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)	9.694617	.377312	25.69	0.000	8.955099	10.43413
NDE						
exercise (Exercise vs Control)	2.996658	.2109357	14.21	0.000	2.583231	3.410084
TE						
exercise (Exercise vs Control)	12.69127	.4005769	31.68	0.000	11.90616	13.47639

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

Proportion mediated

```
. estat proportion
```

Proportion mediated — Number of obs = 2,000

wellbeing	Proportion	Robust std. err.	z	P>|z|	[95% conf.	interval]
exercise (Exercise vs Control)	.7638805	.0154928	49.31	0.000	.7335151	.7942459

Linear models with treatment-mediator interaction

```
. mediate (wellbeing basewell age gender hstatus)          ///
>         (bonotonin basebono age gender hstatus)          ///
>         (exercise)

Iteration 0:  EE criterion =  2.004e-27
Iteration 1:  EE criterion =  2.804e-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)	10.02204	.2256812	44.41	0.000	9.579717	10.46437
NDE						
exercise (Exercise vs Control)	3.085412	.168631	18.30	0.000	2.754901	3.415922
TE						
exercise (Exercise vs Control)	13.10746	.2304752	56.87	0.000	12.65573	13.55918

```
Note: Outcome equation includes treatment-mediator interaction.
```

Estimating potential outcome means

```
. mediate (wellbeing basewell age gender hstatus)          ///
>         (bonotonin basebono age gender hstatus)          ///
>         (exercise), pom

Iteration 0:  EE criterion =  2.050e-27
Iteration 1:  EE criterion =  2.775e-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	56.89975	.228515	249.00	0.000	56.45187	57.34763
Y1M0	59.98516	.2555341	234.74	0.000	59.48432	60.486
Y0M1	66.83246	.2644294	252.74	0.000	66.31419	67.35073
Y1M1	70.0072	.2314185	302.51	0.000	69.55363	70.46077

```
Note: Outcome equation includes treatment-mediator interaction.
```

Estimating all effects and potential outcome means

```
. mediate (wellbeing basewell age gender hstatus)          ///
>         (bonotonin basebono age gender hstatus)          ///
>         (exercise), all

Iteration 0:  EE criterion =  2.132e-27
Iteration 1:  EE criterion =  3.527e-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	56.89975	.228515	249.00	0.000	56.45187	57.34763
Y1M0	59.98516	.2555341	234.74	0.000	59.48432	60.486
Y0M1	66.83246	.2644294	252.74	0.000	66.31419	67.35073
Y1M1	70.0072	.2314185	302.51	0.000	69.55363	70.46077
NIE						
exercise (Exercise vs Control)	10.02204	.2256812	44.41	0.000	9.579717	10.46437
NDE						
exercise (Exercise vs Control)	3.085412	.168631	18.30	0.000	2.754901	3.415922
PNIE						
exercise (Exercise vs Control)	9.932713	.2290178	43.37	0.000	9.483846	10.38158
TNDE						
exercise (Exercise vs Control)	3.174743	.1808011	17.56	0.000	2.820379	3.529107
TE						
exercise (Exercise vs Control)	13.10746	.2304752	56.87	0.000	12.65573	13.55918

Note: Outcome equation includes treatment-mediator interaction.

Auxiliary parameters

```
. mediate, aequations
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	56.89975	.228515	249.00	0.000	56.45187	57.34763
Y1M0	59.98516	.2555341	234.74	0.000	59.48432	60.486
Y0M1	66.83246	.2644294	252.74	0.000	66.31419	67.35073
Y1M1	70.0072	.2314185	302.51	0.000	69.55363	70.46077
NIE						
exercise (Exercise vs Control)	10.02204	.2256812	44.41	0.000	9.579717	10.46437
NDE						
exercise (Exercise vs Control)	3.085412	.168631	18.30	0.000	2.754901	3.415922
PNIE						
exercise (Exercise vs Control)	9.932713	.2290178	43.37	0.000	9.483846	10.38158
TNDE						
exercise (Exercise vs Control)	3.174743	.1808011	17.56	0.000	2.820379	3.529107
TE						
exercise (Exercise vs Control)	13.10746	.2304752	56.87	0.000	12.65573	13.55918
wellbeing						
exercise						
Exercise	2.777685	.6449446	4.31	0.000	1.513616	4.041753
bonotonin	.2141319	.0026418	81.05	0.000	.208954	.2193099
exercise# c.bonotonin						
Exercise	.0019258	.0034941	0.55	0.582	-.0049224	.0087741
basewell	.1685634	.0038294	44.02	0.000	.1610579	.1760689
age	.0266714	.0072856	3.66	0.000	.012392	.0409509
gender	-.1031899	.1282411	-0.80	0.421	-.3545379	.1481581
hstatus	.9787586	.0773014	12.66	0.000	.8272506	1.130267
_cons	9.508461	.5918832	16.06	0.000	8.348391	10.66853
bonotonin						
exercise						
Exercise	46.38595	.8963335	51.75	0.000	44.62916	48.14273
basebono	1.019825	.0154741	65.91	0.000	.9894966	1.050154
age	.368765	.049656	7.43	0.000	.271441	.466089
gender	5.648102	.8946093	6.31	0.000	3.8947	7.401504
hstatus	3.662454	.5353618	6.84	0.000	2.613164	4.711743
_cons	-40.92391	3.646124	-11.22	0.000	-48.07018	-33.77764

Note: Outcome equation includes treatment-mediator interaction.

Binary outcome and mediator

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

Iteration 0:  EE criterion =  1.413e-18
Iteration 1:  EE criterion =  1.371e-32

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)	.1053001	.0142631	7.38	0.000	.0773449	.1332553
NDE						
exercise (Exercise vs Control)	.1528838	.0189013	8.09	0.000	.115838	.1899296
TE						
exercise (Exercise vs Control)	.2581839	.014312	18.04	0.000	.2301328	.286235

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

Treatment effects as 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)	1.22985	.0383193	6.64	0.000	1.156993	1.307295
NDE						
exercise (Exercise vs Control)	1.500861	.0714322	8.53	0.000	1.367188	1.647603
TE						
exercise (Exercise vs Control)	1.845833	.0706637	16.01	0.000	1.712403	1.98966

Treatment effects as 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)	1.526485	.087768	7.36	0.000	1.363802	1.708575
NDE						
exercise (Exercise vs Control)	1.924312	.1529157	8.24	0.000	1.646777	2.248621
TE						
exercise (Exercise vs Control)	2.937434	.1841548	17.19	0.000	2.597791	3.321482

Example data (2)

```
. webuse birthweight
(Fictional birthweight data)

. list bweight ncigs college ses sespar age in 1/5, clean

     bweight   ncigs   college        ses     sespar   age
  1.    3621       1        No     5.3581   3.308523    29
  2.    3278       0       Yes   9.556957   4.376035    38
  3.    3073       1        No   3.980829   6.580275    39
  4.    3306       0       Yes   11.17643   12.12075    30
  5.    4517       0       Yes   9.026146   4.738766    28
```

Exponential mean and Poisson models

```
. mediate (bweight sespar c.age##c.age, expmean) ///
>         (ncigs sespar c.age##c.age, poisson) ///
>         (college), nointeract

Iteration 0:  EE criterion =  3.250e-13
Iteration 1:  EE criterion =  9.147e-18

Causal mediation analysis                              Number of obs = 2,000

Outcome model:     Exponential mean
Mediator model:    Poisson
Mediator variable: ncigs
Treatment type:    Binary
```

bweight	Coefficient	Robust std. err.	z	P>|z|	[95% conf.	interval]
NIE						
college (Yes vs No)	198.978	23.53279	8.46	0.000	152.8546	245.1014
NDE						
college (Yes vs No)	320.3318	34.47792	9.29	0.000	252.7563	387.9072
TE						
college (Yes vs No)	519.3098	28.70435	18.09	0.000	463.0503	575.5693

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

Estimating incidence-rate ratios

```
. estat irr
estat irr requires potential-outcome means; refitting model ...
```

Transformed treatment effects — Number of obs = 2,000

bweight	IRR	Robust std. err.	z	P>|z|	[95% conf.	interval]
NIE						
college (Yes vs No)	1.057819	.0072037	8.25	0.000	1.043794	1.072033
NDE						
college (Yes vs No)	1.102636	.0113921	9.46	0.000	1.080533	1.125192
TE						
college (Yes vs No)	1.16639	.009948	18.05	0.000	1.147055	1.186052

Estimating controlled direct effects

```
. estat cde, mvalue(0 1)

Controlled direct effect                          Number of obs = 2,000

Mediator variable: ncigs
Mediator values:
  1._at: ncigs = 0
  2._at: ncigs = 1
```

	Delta-method					
	CDE	std. err.	z	P>|z|	[95% conf.	interval]
college@_at						
(Yes vs No)						
1	341.955	35.26807	9.70	0.000	272.8308	411.0791
(Yes vs No)						
2	332.6419	34.94916	9.52	0.000	264.1428	401.141

Estimating differences between controlled direct effects

```
. estat cde, mvalue(0 1) contrast

Controlled direct effect                          Number of obs = 2,000

Mediator variable: ncigs
Mediator values:
  1._at: ncigs = 0
  2._at: ncigs = 1
```

	Delta-method					
	CDE	std. err.	z	P>|z|	[95% conf.	interval]
_at#college (2 vs 1) (Yes vs No)	-9.313066	.9748033	-9.55	0.000	-11.22365	-7.402487

More treatment interactions

```
. mediate (bweight sespar c.age##c.age                                  ///
>                 i.college#(c.sespar c.age##c.age), expmean)    ///
>         (ncigs c.sespar c.age##c.age                                  ///
>                 i.college#(c.sespar c.age##c.age), poisson)    ///
>         (college)

Iteration 0:  EE criterion =  1.691e-12
Iteration 1:  EE criterion =  1.122e-14

Causal mediation analysis                          Number of obs = 2,000

Outcome model:     Exponential mean
Mediator model:    Poisson
Mediator variable: ncigs
Treatment type:    Binary
```

bweight	Coefficient	Robust std. err.	z	P>|z|	[95% conf.	interval]
NIE						
college (Yes vs No)	111.6007	67.53715	1.65	0.098	-20.76971	243.971
NDE						
college (Yes vs No)	407.5962	72.49614	5.62	0.000	265.5063	549.686
TE						
college (Yes vs No)	519.1968	28.71853	18.08	0.000	462.9095	575.4841

Note: Outcome equation includes treatment-mediator interaction.

Mediator interactions

```
. mediate (bweight sespar c.age##c.age                              ///
>                 c.ncigs#(c.sespar c.age##c.age), expmean)         ///
>         (ncigs c.sespar c.age##c.age, poisson)                    ///
>         (college)

Iteration 0:  EE criterion =  6.460e-11
Iteration 1:  EE criterion =  5.837e-15

Causal mediation analysis                          Number of obs = 2,000

Outcome model:     Exponential mean
Mediator model:    Poisson
Mediator variable: ncigs
Treatment type:    Binary
```

bweight	Coefficient	Robust std. err.	z	P>|z|	[95% conf.	interval]
NIE						
college (Yes vs No)	86.26849	68.96645	1.25	0.211	-48.90328	221.4403
NDE						
college (Yes vs No)	431.5822	73.70305	5.86	0.000	287.1269	576.0375
TE						
college (Yes vs No)	517.8507	28.64809	18.08	0.000	461.7015	573.9999

Note: Outcome equation includes treatment-mediator interaction.

Multivalued treatment

```
. mediate (wellbeing age gender i.hstatus basewell)       ///
>         (bonotonin basebono)                            ///
>         (mexercise)

Iteration 0:  EE criterion =  1.778e-27
Iteration 1:  EE criterion =  1.198e-27

Causal mediation analysis                                 Number of obs = 2,000

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

wellbeing	Coefficient	Robust std. err.	z	P>|z|	[95% conf.	interval]
NIE						
mexercise (45 minutes vs Control)	5.128899	.3505171	14.63	0.000	4.441898	5.815899
mexercise (90 minutes vs Control)	9.780537	.2880877	33.95	0.000	9.215895	10.34518
NDE						
mexercise (45 minutes vs Control)	1.197498	.1750038	6.84	0.000	.8544965	1.540499
mexercise (90 minutes vs Control)	3.051084	.2071236	14.73	0.000	2.645129	3.457039
TE						
mexercise (45 minutes vs Control)	6.326396	.3894269	16.25	0.000	5.563134	7.089659
mexercise (90 minutes vs Control)	12.83162	.2967962	43.23	0.000	12.24991	13.41333

```
Note: Outcome equation includes treatment-mediator interaction.
```

Continuous treatment

```
. webuse birthweight
(Fictional birthweight data)

. qui sum ses

. generate std_ses = (ses-r(mean))/r(sd)

. mediate (bweight sespar c.age##c.age, expmean)  ///
>         (ncigs sespar c.age##c.age, poisson)    ///
>         (std_ses, continuous(0 2)), nointeract

Iteration 0:  EE criterion =  1.470e-12
Iteration 1:  EE criterion =  1.816e-17

Causal mediation analysis                          Number of obs = 2,000

Outcome model:     Exponential mean
Mediator model:    Poisson
Mediator variable: ncigs
Treatment type:    Continuous

Continuous treatment levels:
  0: std_ses = 0 (control)
  1: std_ses = 2
```

bweight	Coefficient	Robust std. err.	z	P>|z|	[95% conf.	interval]
NIE						
std_ses (1 vs 0)	110.1346	8.724232	12.62	0.000	93.03538	127.2337
NDE						
std_ses (1 vs 0)	180.0172	34.77372	5.18	0.000	111.8619	248.1724
TE						
std_ses (1 vs 0)	290.1517	33.85571	8.57	0.000	223.7958	356.5077

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

Continuous treatment with multiple evaluation points

```
. mediate (bweight sespar c.age##c.age, expmean)  ///
>         (ncigs sespar c.age##c.age, poisson)    ///
>         (std_ses, continuous(0 -2 -1 1 2)), nointeract

Iteration 0:  EE criterion =  1.470e-12
Iteration 1:  EE criterion =  2.374e-17

Causal mediation analysis                              Number of obs = 2,000

Outcome model:     Exponential mean
Mediator model:    Poisson
Mediator variable: ncigs
Treatment type:    Continuous

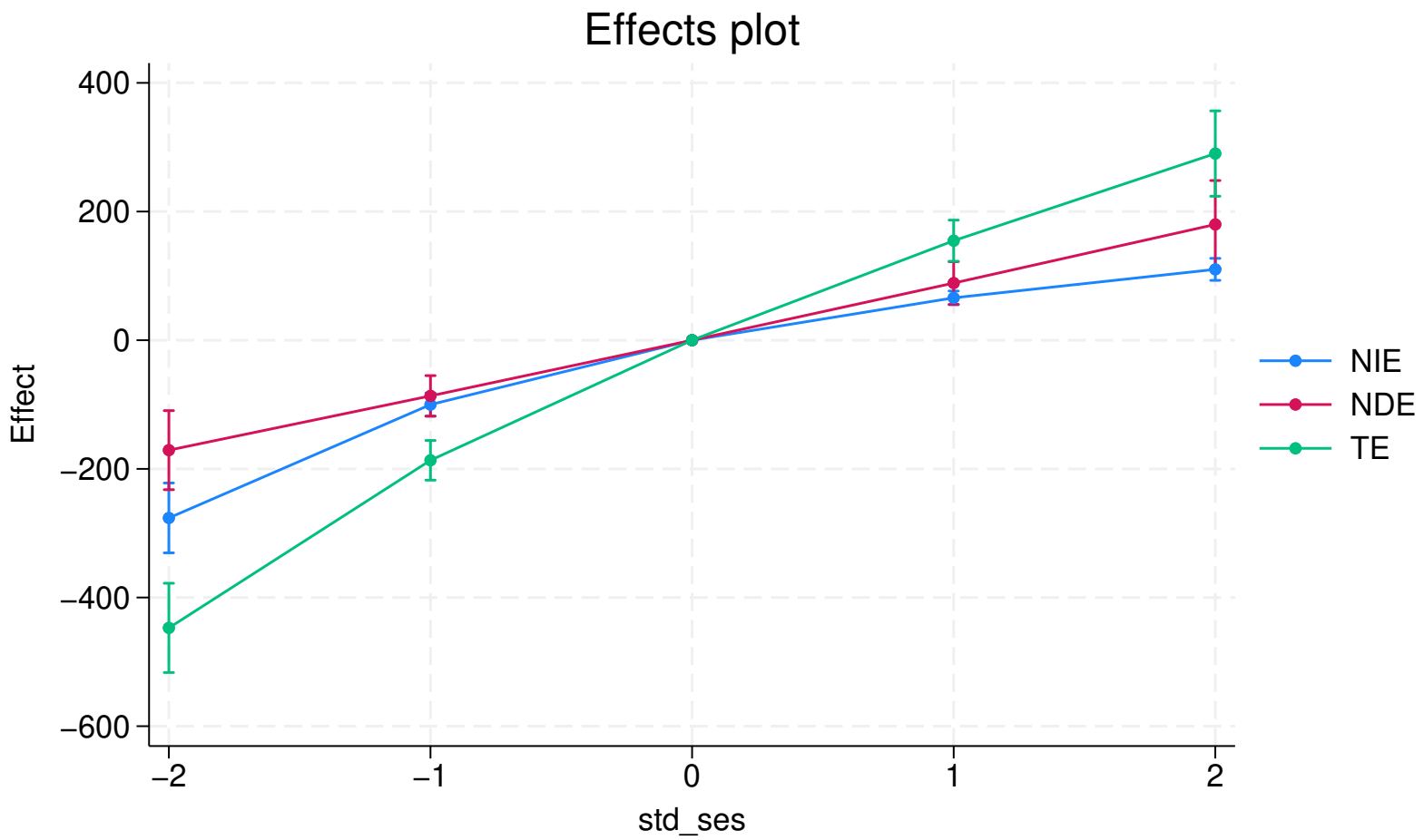
Continuous treatment levels:
  0: std_ses =  0 (control)
  1: std_ses = -2
  2: std_ses = -1
  3: std_ses =  1
  4: std_ses =  2
```

bweight	Coefficient	Robust std. err.	z	P>|z|	[95% conf.	interval]
NIE						
std_ses						
(1 vs 0)	-276.2757	27.69004	-9.98	0.000	-330.5471	-222.0042
(2 vs 0)	-100.1155	9.170566	-10.92	0.000	-118.0894	-82.14148
(3 vs 0)	65.84585	5.423096	12.14	0.000	55.21678	76.47493
(4 vs 0)	110.1346	8.724232	12.62	0.000	93.03538	127.2337
NDE						
std_ses						
(1 vs 0)	-170.9012	31.33649	-5.45	0.000	-232.3196	-109.4828
(2 vs 0)	-86.56069	16.08129	-5.38	0.000	-118.0794	-55.04193
(3 vs 0)	88.83929	16.94031	5.24	0.000	55.6369	122.0417
(4 vs 0)	180.0172	34.77372	5.18	0.000	111.8619	248.1724
TE						
std_ses						
(1 vs 0)	-447.1769	35.41401	-12.63	0.000	-516.5871	-377.7667
(2 vs 0)	-186.6761	15.73291	-11.87	0.000	-217.5121	-155.8402
(3 vs 0)	154.6851	16.31969	9.48	0.000	122.6991	186.6712
(4 vs 0)	290.1517	33.85571	8.57	0.000	223.7958	356.5077

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

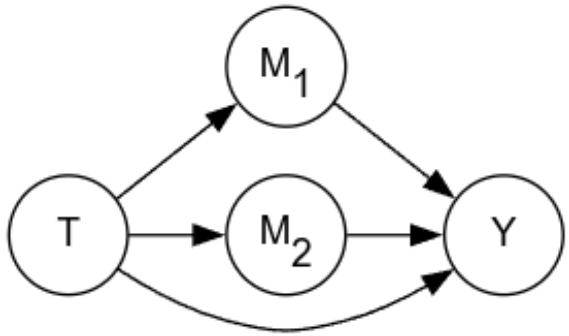
. estat effectplot
```

Plotting treatment effects

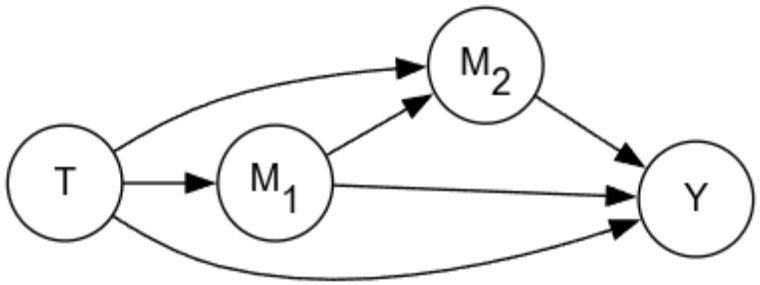


DAG illustration with two mediators

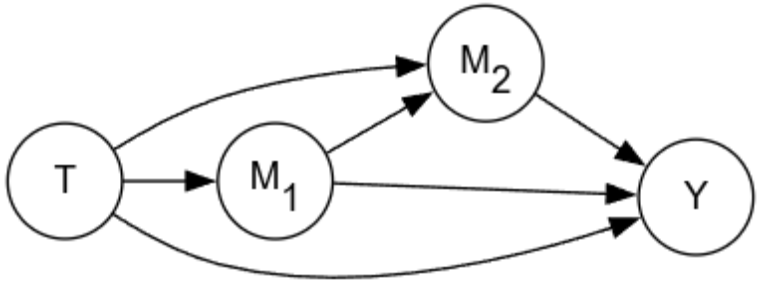
- Parallel mediation: mediators that are not causally ordered



- Sequential mediation: causally ordered mediators



Sequential mediation



- Four path-specific effects of interest:
  - direct effect from T to Y (effect of T on Y not mediated by either M_1 or M_2)
  - one effect through M_1 alone
  - one effect through M_2 alone
  - one effect through both M_1 and M_2
- Goal is to decompose the total causal effect into these four components

Potential outcomes (sequential mediation)

- In the single-mediator case, we had $Y_i\{t, M_i(t')\}$
- Multiple mediators increase the complexity and number of potential outcomes
- With two causally ordered mediators, we have nested potential outcomes $Y_i[t, M_{1i}(t'), M_{2i}\{t'', M_{1i}(t''')\}]$
- t can now be counterfactually set in four places:
  - with respect to the outcome
  - with respect to the first mediator
  - with respect to the second mediator
  - with respect to the first mediator as component of the potential outcomes of the second mediator
- direct and indirect effects are derived as expected differences in these potential outcomes
- eight variations of each path-specific effect rather than the two variations (pure and total) in the single-mediator case

Number of effects and distinct decompositions

- With 4 path-specific effects of interest and 8 variations of each one, we can estimate a maximum of 32 effects (plus the total effect) for 2 causally ordered mediators
- with a single mediator, we had two possible decompositions of the total effect into direct and indirect effects
- with multiple mediators, there are many ways that total effect can be decomposed into sums of its path-specific components
- with k mediators, there are $2^k!$ decompositions
- 24 distinct decompositions of the total causal effect with two causally ordered mediators
- with only 3 mediators, the number of distinct decompositions is 40,320
- with 4 mediators, this number would grow to over 20 trillion

Effect estimands and potential outcome mean contrasts

Path	Effect	Definition
Direct (through neither M_1 nor M_2)	NDE-000	$E(Y[1, M_1(0), M_2\{0, M_1(0)\}] - Y[0, M_1(0), M_2\{0, M_1(0)\}])$
	NDE-100	$E(Y[1, M_1(1), M_2\{0, M_1(0)\}] - Y[0, M_1(1), M_2\{0, M_1(0)\}])$
	NDE-010	$E(Y[1, M_1(0), M_2\{1, M_1(0)\}] - Y[0, M_1(0), M_2\{1, M_1(0)\}])$
	NDE-001	$E(Y[1, M_1(0), M_2\{0, M_1(1)\}] - Y[0, M_1(0), M_2\{0, M_1(1)\}])$
	NDE-110	$E(Y[1, M_1(1), M_2\{1, M_1(0)\}] - Y[0, M_1(1), M_2\{1, M_1(0)\}])$
	NDE-101	$E(Y[1, M_1(1), M_2\{0, M_1(1)\}] - Y[0, M_1(1), M_2\{0, M_1(1)\}])$
	NDE-011	$E(Y[1, M_1(0), M_2\{1, M_1(1)\}] - Y[0, M_1(0), M_2\{1, M_1(1)\}])$
	NDE-111	$E(Y[1, M_1(1), M_2\{1, M_1(1)\}] - Y[0, M_1(1), M_2\{1, M_1(1)\}])$
Indirect through M_1 only	NIE_1-000	$E(Y[0, M_1(1), M_2\{0, M_1(0)\}] - Y[0, M_1(0), M_2\{0, M_1(0)\}])$
	NIE_1-100	$E(Y[1, M_1(1), M_2\{0, M_1(0)\}] - Y[1, M_1(0), M_2\{0, M_1(0)\}])$
	NIE_1-010	$E(Y[0, M_1(1), M_2\{1, M_1(0)\}] - Y[0, M_1(0), M_2\{1, M_1(0)\}])$
	NIE_1-001	$E(Y[0, M_1(1), M_2\{0, M_1(1)\}] - Y[0, M_1(0), M_2\{0, M_1(1)\}])$
	NIE_1-110	$E(Y[1, M_1(1), M_2\{1, M_1(0)\}] - Y[1, M_1(0), M_2\{1, M_1(0)\}])$
	NIE_1-101	$E(Y[1, M_1(1), M_2\{0, M_1(1)\}] - Y[1, M_1(0), M_2\{0, M_1(1)\}])$
	NIE_1-011	$E(Y[0, M_1(1), M_2\{1, M_1(1)\}] - Y[0, M_1(0), M_2\{1, M_1(1)\}])$
	NIE_1-111	$E(Y[1, M_1(1), M_2\{1, M_1(1)\}] - Y[1, M_1(0), M_2\{1, M_1(1)\}])$

. . .

Distinct decompositions

Decomposition	Total effect
1	NDE-000 + NIE_1-100 + NIE_2-110 + NIE_{12}-111
2	NDE-000 + NIE_1-100 + NIE_2-111 + NIE_{12}-110
3	NDE-000 + NIE_1-110 + NIE_2-100 + NIE_{12}-111
4	NDE-000 + NIE_1-101 + NIE_2-111 + NIE_{12}-100
5	NDE-000 + NIE_1-111 + NIE_2-100 + NIE_{12}-101
6	NDE-000 + NIE_1-111 + NIE_2-101 + NIE_{12}-100
7	NDE-100 + NIE_1-000 + NIE_2-110 + NIE_{12}-111
8	NDE-100 + NIE_1-000 + NIE_2-111 + NIE_{12}-110
9	NDE-010 + NIE_1-110 + NIE_2-000 + NIE_{12}-111
10	NDE-010 + NIE_1-111 + NIE_2-000 + NIE_{12}-101
11	NDE-001 + NIE_1-101 + NIE_2-111 + NIE_{12}-000
12	NDE-001 + NIE_1-111 + NIE_2-101 + NIE_{12}-000
13	NDE-110 + NIE_1-000 + NIE_2-010 + NIE_{12}-111
14	NDE-110 + NIE_1-010 + NIE_2-000 + NIE_{12}-111
15	NDE-101 + NIE_1-000 + NIE_2-111 + NIE_{12}-010
16	NDE-101 + NIE_1-001 + NIE_2-111 + NIE_{12}-000
17	NDE-011 + NIE_1-111 + NIE_2-000 + NIE_{12}-001
18	NDE-011 + NIE_1-111 + NIE_2-001 + NIE_{12}-000
19	NDE-111 + NIE_1-000 + NIE_2-010 + NIE_{12}-011
20	NDE-111 + NIE_1-000 + NIE_2-011 + NIE_{12}-010
21	NDE-111 + NIE_1-010 + NIE_2-000 + NIE_{12}-011
22	NDE-111 + NIE_1-001 + NIE_2-011 + NIE_{12}-000
23	NDE-111 + NIE_1-011 + NIE_2-000 + NIE_{12}-001
24	NDE-111 + NIE_1-011 + NIE_2-001 + NIE_{12}-000

Source: Decompositions from Daniel et al. (2015).

Modeling and estimation (1)

- So far we have looked at the nonparametric part of treatment effects identification
- Given the causal mediation model with two causally ordered mediators, and ignoring covariates, we can specify the following system of three equations:

$$
\begin{aligned}
Y &= \beta_0 + \beta_1 T + \beta_2 M_1 + \beta_3 M_2 + \beta_4 TM_1 + \beta_5 TM_2 + \beta_6 M_1 M_2 + \beta_7 TM_1 M_2 + \epsilon_Y \\
M_2 &= \gamma_0 + \gamma_1 T + \gamma_2 M_1 + \gamma_3 TM_1 + \epsilon_{M_2} \\
M_1 &= \alpha_0 + \alpha_1 T + \epsilon_{M_1}
\end{aligned}
$$

- Y is the outcome variable, M_1 and M_2 are our first and second mediators, respectively, and T is our treatment variable.
- Error terms ϵ_{M_1}, ϵ_{M_2}, and ϵ_Y are assumed to have zero mean and be independent
- Parameters $\boldsymbol{\beta} \equiv (\beta_0, \ldots, \beta_7)$, $\boldsymbol{\gamma} \equiv (\gamma_0, \ldots, \gamma_3)$, and $\boldsymbol{\alpha} \equiv (\alpha_0, \alpha_1)$ are to be estimated

Modeling and estimation (2)

- Fit each equation separately and estimate coefficients by OLS
- Plugging equations for M_1 and M_2 into the outcome equation yields:

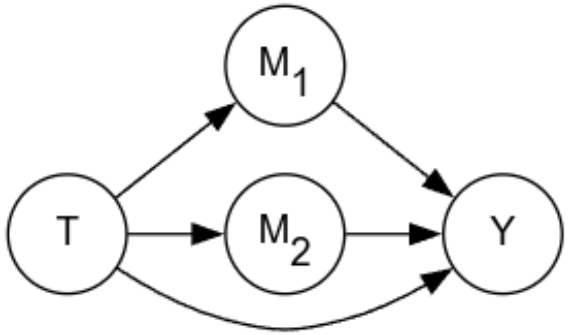
$$
\begin{aligned}
Y[t, M_1(t'), M_2\{t'', M_1(t''')\}] =& \beta_0 + \beta_1 t + (\beta_2 + \beta_4 t)(\alpha_0 + \alpha_1 t' + \epsilon_{M_1}) + \\
& (\beta_3 + \beta_5 t)(\gamma_0 + \gamma_1 t'' + (\gamma_2 + \gamma_3 t'')(\alpha_0 + \alpha_1 t''' + \epsilon_{M_1}) + \epsilon_{M_2}) + \\
& (\beta_6 + \beta_7 t)\Big\{(\alpha_0 + \alpha_1 t' + \epsilon_{M_1})(\gamma_0 + \gamma_1 t'' + (\gamma_2 + \gamma_3 t'') \\
& (\alpha_0 + \alpha_1 t''' + \epsilon_{M_1}) + \epsilon_{M_2})\Big\} + \epsilon_Y
\end{aligned}
$$

Modeling and estimation (3)

- Replacing error terms with their expectations yields:

$$
\begin{aligned}
E(Y[t, M_1(t'), M_2\{t'', M_1(t''')\}]) =& \beta_0 + \beta_1 t + (\beta_2 + \beta_4 t)(\alpha_0 + \alpha_1 t') + \\
& (\beta_3 + \beta_5 t)(\gamma_0 + \gamma_1 t'' + (\gamma_2 + \gamma_3 t'')(\alpha_0 + \alpha_1 t''')) + \\
& (\beta_6 + \beta_7 t)\Big\{(\alpha_0 + \alpha_1 t')(\gamma_0 + \gamma_1 t'' + \\
& (\gamma_2 + \gamma_3 t'')(\alpha_0 + \alpha_1 t'''))\Big\} + \\
& (\beta_6 + \beta_7 t)(\gamma_2 + \gamma_3 t'')E[\epsilon_{M_1}\epsilon_{M_1}] \\
=& \beta_0 + \beta_1 t + (\beta_2 + \beta_4 t)(\alpha_0 + \alpha_1 t') + \\
& (\beta_3 + \beta_5 t)(\gamma_0 + \gamma_1 t'' + (\gamma_2 + \gamma_3 t'')(\alpha_0 + \alpha_1 t''')) + \\
& (\beta_6 + \beta_7 t)\Big\{(\alpha_0 + \alpha_1 t')(\gamma_0 + \gamma_1 t'' + \\
& (\gamma_2 + \gamma_3 t'')(\alpha_0 + \alpha_1 t'''))\Big\} + \\
& (\beta_6 + \beta_7 t)(\gamma_2 + \gamma_3 t'')\sigma^2_{M_1}
\end{aligned}
$$

Parallel mediation



- Three path-specific effects of interest:
  - effect through neither M_1 nor M_2 (natural direct effect)
  - effect through M_1 only
  - effect through M_2 only
- With mediators that are not causally ordered, estimand complexity is reduced because potential outcomes are no longer nested
- Instead of potential outcomes of the form $Y_i[t, M_{1i}(t'), M_{2i}\{t'', M_{1i}(t''')\}]$, we simply have $Y_i[t, M_{1i}(t'), M_{2i}(t')]$
- This yields at most 4 estimands over 3 effects for a total of 12 estimands

Parallel mediation estimation

- Again using linear models with interactions (and ignoring covariates), we have the system of equations:

$$
\begin{aligned}
Y &= \beta_0 + \beta_1 T + \beta_2 M_1 + \beta_3 M_2 + \beta_4 TM_1 + \beta_5 TM_2 + \beta_6 M_1 M_2 + \beta_7 TM_1 M_2 + \epsilon_Y \\
M_2 &= \gamma_0 + \gamma_1 T + \epsilon_{M_2} \\
M_1 &= \alpha_0 + \alpha_1 T + \epsilon_{M_1}
\end{aligned}
$$

- Plugging the equations for M_1 and M_2 into the outcome equation and replacing error terms with their expectations yields:

$$
\begin{aligned}
E[Y\{t, M_1(t'), M_2(t'')\}] =& \beta_0 + \beta_1 t + (\beta_2 + \beta_4 t)(\alpha_0 + \alpha_1 t') + (\beta_3 + \beta_5 t)(\gamma_0 + \gamma_1 t'') + \\
& (\beta_6 + \beta_7 t)(\alpha_0 + \alpha_1 t')(\gamma_0 + \gamma_1 t'')
\end{aligned}
$$

Effect estimands and potential outcome mean contrasts

Path	Effect	Definition
Direct (through neither M_1 nor M_2)	NDE-00	$E[Y\{1, M_1(0), M_2(0)\} - Y\{0, M_1(0), M_2(0)\}]$
	NDE-10	$E[Y\{1, M_1(1), M_2(0)\} - Y\{0, M_1(1), M_2(0)\}]$
	NDE-01	$E[Y\{1, M_1(0), M_2(1)\} - Y\{0, M_1(0), M_2(1)\}]$
	NDE-11	$E[Y\{1, M_1(1), M_2(1)\} - Y\{0, M_1(1), M_2(1)\}]$
Indirect through M_1	NIE_1-00	$E[Y\{0, M_1(1), M_2(0)\} - Y\{0, M_1(0), M_2(0)\}]$
	NIE_1-10	$E[Y\{1, M_1(1), M_2(0)\} - Y\{1, M_1(0), M_2(0)\}]$
	NIE_1-01	$E[Y\{0, M_1(1), M_2(1)\} - Y\{0, M_1(0), M_2(1)\}]$
	NIE_1-11	$E[Y\{1, M_1(1), M_2(1)\} - Y\{1, M_1(0), M_2(1)\}]$
Indirect through M_2	NIE_2-00	$E[Y\{0, M_1(0), M_2(1)\} - Y\{0, M_1(0), M_2(0)\}]$
	NIE_2-10	$E[Y\{1, M_1(0), M_2(1)\} - Y\{1, M_1(0), M_2(0)\}]$
	NIE_2-01	$E[Y\{0, M_1(1), M_2(1)\} - Y\{0, M_1(1), M_2(0)\}]$
	NIE_2-11	$E[Y\{1, M_1(1), M_2(1)\} - Y\{1, M_1(1), M_2(0)\}]$

Source: Definitions from Daniel et al. (2015).

Distinct decompositions

Decomposition	Total effect
1	NDE-00 + NIE_1-10 + NIE_2-11
2	NDE-00 + NIE_1-11 + NIE_2-10
3	NDE-10 + NIE_1-00 + NIE_2-11
4	NDE-01 + NIE_1-11 + NIE_2-00
5	NDE-11 + NIE_1-00 + NIE_2-01
6	NDE-11 + NIE_1-01 + NIE_2-00

Source: Decompositions from Daniel et al. (2015).

Stata's `mediate` command for two mediators

- New in Stata 19: `mediate` (two mediators)
- It uses analytical expressions to compute potential outcome means based on parametric models
- Full path-specific decomposition and mediator-specific natural effects
- Treatment may be binary or continuous
- Special-purpose postestimation commands:
  - `estat cde` controlled direct effects
  - `estat smsensitivity` sensitivity analysis

`mediate` syntax, two mediators

Syntax

```
mediate (ovar [omvarlist, noconstant])
    (mvar2 [mmvarlist2, noconstant])
    (mvar1 [mmvarlist1, noconstant])
    (tvar [, continuous(numlist)]) [if] [in] [weight] [, stat options]
```

ovar is a continuous outcome of interest.

omvarlist specifies the covariates in the outcome model.

$mvar_2$ is a continuous mediator variable (the second mediator for sequential mediators).

$mmvarlist_2$ specifies the covariates in the $mvar_2$ model.

$mvar_1$ is a continuous mediator variable (the first mediator for sequential mediators).

$mmvarlist_1$ specifies the covariates in the $mvar_1$ model.

tvar is the treatment variable and may be binary or continuous.

Example data

```
. webuse qoflife
(Artificial quality-of-life data)

. list hrqol depress physact arthritis male age in 1/5, ab(12) clean

        hrqol    depress   physact   arthritis   male    age
  1.   33.58646   6.161322         4          No    Yes     34
  2.   33.09237   6.321835         4         Yes    Yes     35
  3.   40.68521   5.355282         9          No    Yes     30
  4.   34.04324   6.025885         3          No     No     38
  5.   28.16133   6.586061         0          No    Yes     48
```

Simple parallel mediation (without interactions)

```
. mediate (hrqol) (depress) (physact) (arthritis)

Iteration 0:  EE criterion = 1.537e-27
Iteration 1:  EE criterion = 8.303e-30

Causal mediation analysis                                  Number of obs = 2,000

Mediation type: Parallel
Mediator 1:     physact
Mediator 2:     depress
Treatment type: Binary
```

hrqol	Coefficient	Robust std. err.	z	P>|z|	[95% conf.	interval]
NDE						
arthritis (Yes vs No)	-1.71165	.1496673	-11.44	0.000	-2.004993	-1.418308
NIE1						
arthritis (Yes vs No)	-1.814969	.1817366	-9.99	0.000	-2.171166	-1.458772
NIE2						
arthritis (Yes vs No)	-1.252368	.2507925	-4.99	0.000	-1.743912	-.7608239
TE						
arthritis (Yes vs No)	-4.778988	.2912224	-16.41	0.000	-5.349773	-4.208202

Parallel mediation with treatment-mediator interactions

```
. mediate (hrqol) (depress) (physact) (arthritis), tinteraction

Iteration 0:  EE criterion = 1.158e-25
Iteration 1:  EE criterion = 3.275e-28

Causal mediation analysis                                  Number of obs = 2,000

Mediation type: Parallel
Mediator 1:     physact
Mediator 2:     depress
Treatment type: Binary
```

hrqol	Coefficient	Robust std. err.	z	P>|z|	[95% conf.	interval]
NDE						
00	-1.863452	.1961826	-9.50	0.000	-2.247963	-1.478941
10	-2.7116	.3099477	-8.75	0.000	-3.319086	-2.104114
01	-.7317365	.3513065	-2.08	0.037	-1.420285	-.0431885
11	-1.579885	.1577089	-10.02	0.000	-1.888988	-1.270781
NIE1						
00	-1.582646	.1686346	-9.39	0.000	-1.913164	-1.252129
11	-2.430795	.3236353	-7.51	0.000	-3.065108	-1.796481
NIE2						
00	-1.616457	.2614895	-6.18	0.000	-2.128967	-1.103947
11	-.4847413	.2181954	-2.22	0.026	-.9123964	-.0570863
TE						
arthritis (Yes vs No)	-4.778988	.2912224	-16.41	0.000	-5.349773	-4.208202

Note: Outcome equation includes treatment-mediator interactions.

Adding mediator-mediator interaction

```
. mediate (hrqol) (depress) (physact) (arthritis), tinteraction minteraction

Iteration 0:  EE criterion = 2.526e-26
Iteration 1:  EE criterion = 1.137e-28

Causal mediation analysis                                  Number of obs = 2,000

Mediation type: Parallel
Mediator 1:     physact
Mediator 2:     depress
Treatment type: Binary
```

		Robust				
	hrqol	Coefficient	std. err.	z	P>|z|	[95% conf.	interval]
NDE						
	00	-1.745654	.1767601	-9.88	0.000	-2.092097	-1.39921
	10	-1.449735	.2693148	-5.38	0.000	-1.977582	-.9218876
	01	-1.804018	.2952766	-6.11	0.000	-2.38275	-1.225287
	11	-1.638622	.139265	-11.77	0.000	-1.911576	-1.365667
NIE1						
	00	-3.277243	.3619214	-9.06	0.000	-3.986596	-2.56789
	10	-2.981325	.3508021	-8.50	0.000	-3.668884	-2.293765
	01	-3.389729	.3789566	-8.94	0.000	-4.132471	-2.646988
	11	-3.224333	.4005567	-8.05	0.000	-4.00941	-2.439256
NIE2						
	00	-.174545	.1703176	-1.02	0.305	-.5083614	.1592713
	10	-.2329098	.2139202	-1.09	0.276	-.6521856	.186366
	01	-.2870311	.1642122	-1.75	0.080	-.6088811	.0348188
	11	-.4759182	.2112993	-2.25	0.024	-.8900573	-.0617791
TE						
	arthritis					
	(Yes vs No)	-5.202896	.3531395	-14.73	0.000	-5.895037	-4.510756

```
Note: Outcome equation includes treatment-mediator interactions and
      mediator-mediator interaction.
```

Additional interactions

```
. mediate (hrqol age c.depress#c.age c.physact#c.age)
>         (depress i.male)
>         (physact i.male)
>         (arthritis), tinteraction minteraction

Iteration 0:  EE criterion = 1.762e-25
Iteration 1:  EE criterion = 8.149e-30

Causal mediation analysis                               Number of obs = 2,000

Mediation type: Parallel
Mediator 1:     physact
Mediator 2:     depress
Treatment type: Binary
```

hrqol	Coefficient	Robust std. err.	z	P>|z|	[95% conf.	interval]
NDE						
00	-2.93327	.0986156	-29.74	0.000	-3.126553	-2.739987
10	-2.2664	.1321111	-17.16	0.000	-2.525333	-2.007467
01	-3.13574	.1548724	-20.25	0.000	-3.439284	-2.832196
11	-2.441183	.0633247	-38.55	0.000	-2.565297	-2.317068
NIE1						
00	-2.559244	.2330217	-10.98	0.000	-3.015958	-2.102529
10	-1.892373	.1842448	-10.27	0.000	-2.253486	-1.53126
01	-2.596165	.2396821	-10.83	0.000	-3.065933	-2.126396
11	-1.901607	.1889659	-10.06	0.000	-2.271974	-1.531241
NIE2						
00	-.4994956	.0965284	-5.17	0.000	-.6886879	-.3103033
10	-.7019653	.1137533	-6.17	0.000	-.9249177	-.4790128
01	-.5364167	.0960709	-5.58	0.000	-.7247123	-.3481211
11	-.7111994	.1138654	-6.25	0.000	-.9343716	-.4880273
TE						
arthritis (Yes vs No)	-5.536843	.2526692	-21.91	0.000	-6.032065	-5.04162

```
Note: Outcome equation includes treatment-mediator interactions and
      mediator-mediator interaction
```

Sequential mediation

```
. mediate (hrqol) (depress) (physact) (arthritis), sequential

Iteration 0:  EE criterion = 1.539e-27
Iteration 1:  EE criterion = 5.798e-29

Causal mediation analysis                              Number of obs = 2,000

Mediation type: Sequential
Mediator 1:     physact
Mediator 2:     depress
Treatment type: Binary
```

hrqol	Coefficient	Robust std. err.	z	P>|z|	[95% conf.	interval]
NDE						
arthritis (Yes vs No)	-1.71165	.1496673	-11.44	0.000	-2.004993	-1.418308
NIE1						
arthritis (Yes vs No)	-1.814969	.1817366	-9.99	0.000	-2.171166	-1.458772
NIE2						
arthritis (Yes vs No)	-.5203296	.1197562	-4.34	0.000	-.7550474	-.2856118
NIE12						
arthritis (Yes vs No)	-.7320385	.1400059	-5.23	0.000	-1.006445	-.457632
TE						
arthritis (Yes vs No)	-4.778988	.2912224	-16.41	0.000	-5.349773	-4.208202

Sequential model with treatment-mediator interactions

```
. mediate (hrqol) (depress) (physact) (arthritis), sequential
> tinteraction

Iteration 0:  EE criterion = 1.158e-25
Iteration 1:  EE criterion = 5.666e-28

Causal mediation analysis                          Number of obs = 2,000

Mediation type: Sequential
Mediator 1:     physact
Mediator 2:     depress
Treatment type: Binary
```

		Robust				
	hrqol	Coefficient	std. err.	z	P>|z|	[95% conf.	interval]
NDE						
	000	-1.863452	.1961826	-9.50	0.000	-2.247963	-1.478941
	100	-2.7116	.3099477	-8.75	0.000	-3.319086	-2.104114
	010	-1.393251	.2242743	-6.21	0.000	-1.83282	-.9536811
	001	-1.201938	.2449106	-4.91	0.000	-1.681954	-.7219218
	110	-2.241399	.203996	-10.99	0.000	-2.641224	-1.841574
	101	-2.050086	.1664379	-12.32	0.000	-2.376298	-1.723873
	011	-.7317365	.3513065	-2.08	0.037	-1.420285	-.0431885
	111	-1.579885	.1577089	-10.02	0.000	-1.888988	-1.270781
NIE1						
	000	-1.582646	.1686346	-9.39	0.000	-1.913164	-1.252129
	111	-2.430795	.3236353	-7.51	0.000	-3.065108	-1.796481
NIE2						
	000	-.6715998	.129398	-5.19	0.000	-.9252152	-.4179843
	111	-.2013986	.0907096	-2.22	0.026	-.3791862	-.0236111
NIE12						
	000	-.9448568	.1463968	-6.45	0.000	-1.231789	-.6579242
	111	-.2833427	.1292444	-2.19	0.028	-.536657	-.0300283
TE						
arthritis (Yes vs No)		-4.778988	.2912224	-16.41	0.000	-5.349773	-4.208202

Complete set of interactions

```
. mediate (hrqol) (depress) (physact) (arthritis), sequential
> tinteraction minteraction meqtinteraction

Iteration 0:  EE criterion = 6.373e-21
Iteration 1:  EE criterion = 5.935e-28

Causal mediation analysis                          Number of obs = 2,000

Mediation type: Sequential
Mediator 1:     physact
Mediator 2:     depress
Treatment type: Binary
```

		Robust				
	hrqol	Coefficient	std. err.	z	P>|z|	[95% conf.	interval]
NDE						
	000	-2.137034	.1755708	-12.17	0.000	-2.481146	-1.792921
	100	-1.841115	.2914441	-6.32	0.000	-2.412335	-1.269895
	010	-2.175025	.1867005	-11.65	0.000	-2.540951	-1.809098
	001	-2.170996	.1970605	-11.02	0.000	-2.557228	-1.784765
	110	-1.93079	.2240868	-8.62	0.000	-2.369992	-1.491587
	101	-1.951029	.1944125	-10.04	0.000	-2.33207	-1.569987
	011	-2.210278	.284549	-7.77	0.000	-2.767984	-1.652573
	111	-2.044882	.1971614	-10.37	0.000	-2.431311	-1.658453
NIE1						
	000	-3.277243	.3619214	-9.06	0.000	-3.986596	-2.56789
	100	-2.981325	.3508021	-8.50	0.000	-3.668884	-2.293765
	010	-3.321785	.3659441	-9.08	0.000	-4.039022	-2.604548
	001	-3.342699	.3726794	-8.97	0.000	-4.073137	-2.612261
	110	-3.07755	.3644594	-8.44	0.000	-3.791877	-2.363223
	101	-3.122732	.3817002	-8.18	0.000	-3.87085	-2.374613
	011	-3.389729	.3789566	-8.94	0.000	-4.132471	-2.646988
	111	-3.224333	.4005567	-8.05	0.000	-4.00941	-2.439256
NIE2						
	000	-.0819393	.0646655	-1.27	0.205	-.2086815	.0448028
	100	-.1199303	.0962299	-1.25	0.213	-.3085375	.0686768
	010	-.126481	.0623618	-2.03	0.043	-.2487078	-.0042542
	001	-.0858009	.068813	-1.25	0.212	-.2206718	.04907
	110	-.2161557	.0956439	-2.26	0.024	-.4036142	-.0286971

Adding interactions of covariates with mediators and treatment

```
. mediate (hrqol age i.male i.male#c.(depress physact) i.male#i.arthritis)
>         (depress i.male i.male#(c.physact i.arthritis))
>         (physact i.male i.male#i.arthritis)
>         (arthritis), sequential tinteraction minteraction meqtinteraction

Iteration 0:  EE criterion = 7.489e-21
Iteration 1:  EE criterion = 1.034e-28

Causal mediation analysis                              Number of obs = 2,000

Mediation type: Sequential
Mediator 1:     physact
Mediator 2:     depress
Treatment type: Binary
```

hrqol	Coefficient	Robust std. err.	z	P>|z|	[95% conf.	interval]
NDE						
000	-2.861964	.0939964	-30.45	0.000	-3.046194	-2.677735
100	-2.217973	.1583486	-14.01	0.000	-2.52833	-1.907615
010	-2.949311	.0976019	-30.22	0.000	-3.140608	-2.758015
001	-2.972083	.1109218	-26.79	0.000	-3.189485	-2.75468
110	-2.297695	.0963058	-23.86	0.000	-2.486451	-2.108939
101	-2.317705	.0815672	-28.41	0.000	-2.477574	-2.157837
011	-3.047135	.1569048	-19.42	0.000	-3.354663	-2.739607
111	-2.386283	.0686456	-34.76	0.000	-2.520826	-2.25174
NIE1						
000	-2.465474	.2288064	-10.78	0.000	-2.913926	-2.017022
100	-1.821483	.1850826	-9.84	0.000	-2.184238	-1.458728
010	-2.484133	.2312894	-10.74	0.000	-2.937452	-2.030815
001	-2.490889	.233858	-10.65	0.000	-2.949243	-2.032536
110	-1.832517	.1875503	-9.77	0.000	-2.200109	-1.464925
101	-1.836512	.1893983	-9.70	0.000	-2.207726	-1.465298
011	-2.506735	.2357752	-10.63	0.000	-2.968846	-2.044624
111	-1.845883	.191579	-9.64	0.000	-2.22137	-1.470395
NIE2						

Sensitivity analysis

```
. estat smsensitivity
Sequential mediation sensitivity analysis
Number of obs = 2,000

Correlation assumed in fitted model: rho = 1

Evaluating effects at rho = 0.0  ...
                      rho = 0.5  ...
```

	rho=0.00	rho=0.50	rho=1.00
NDE			
000	-2.900	-2.881	-2.862
	(0.108)	(0.100)	(0.094)
100	-2.256	-2.237	-2.218
	(0.156)	(0.156)	(0.158)
010	-2.983	-2.966	-2.949
	(0.113)	(0.104)	(0.098)
001	-3.010	-2.991	-2.972
	(0.126)	(0.118)	(0.111)
110	-2.331	-2.315	-2.298
	(0.094)	(0.094)	(0.096)
101	-2.356	-2.337	-2.318
	(0.078)	(0.078)	(0.082)
011	-3.081	-3.064	-3.047
	(0.169)	(0.162)	(0.157)
111	-2.420	-2.403	-2.386
	(0.066)	(0.066)	(0.069)
NIE1			
000	-2.465	-2.465	-2.465
	(0.229)	(0.229)	(0.229)
<output omitted>			
TE			
Arthritis			
(Yes vs No)	-5.477	-5.455	-5.433
	(0.254)	(0.251)	(0.249)

Learn more

- Causal mediation intro:
  https://www.stata.com/manuals/causalmediateintro.pdf
- Single mediator:
  https://www.stata.com/manuals/causalmediate.pdf
- Two mediators:
  https://www.stata.com/manuals/causalmediatemultiple.pdf

Thank you!