A review of mediation analysis in Stata: principles, methods and applications

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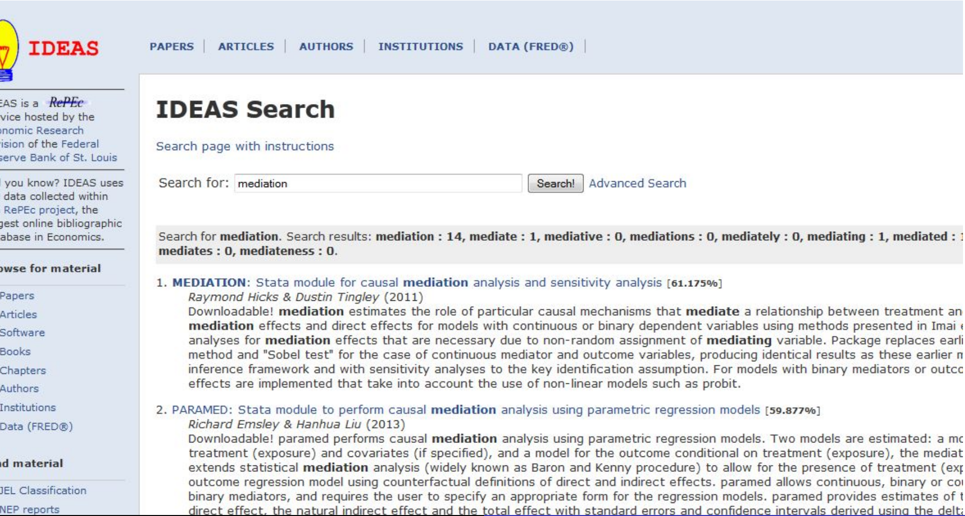
Mediation analysis



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mediates : 0, mediateness : 0.

1. **MEDIATION**: Stata module for causal **mediation** analysis and sensitivity analysis [**61.175%**]
Raymond Hicks & Dustin Tingley (2011)
Downloadable! **mediation** estimates the role of particular causal mechanisms that **mediate** a relationship between treatment an
mediation effects and direct effects for models with continuous or binary dependent variables using methods presented in Imai e
analyses for **mediation** effects that are necessary due to non-random assignment of **mediating** variable. Package replaces earli
method and "Sobel test" for the case of continuous mediator and outcome variables, producing identical results as these earlier m
inference framework and with sensitivity analyses to the key identification assumption. For models with binary mediators or outco
effects are implemented that take into account the use of non-linear models such as probit.

2. PARAMED: Stata module to perform causal **mediation** analysis using parametric regression models [**59.877%**]
Richard Emsley & Hanhua Liu (2013)
Downloadable! paramed performs causal **mediation** analysis using parametric regression models. Two models are estimated: a mo
treatment (exposure) and covariates (if specified), and a model for the outcome conditional on treatment (exposure), the mediat
extends statistical **mediation** analysis (widely known as Baron and Kenny procedure) to allow for the presence of treatment (exp
outcome regression model using counterfactual definitions of direct and indirect effects. paramed allows continuous, binary or co
binary mediators, and requires the user to specify an appropriate form for the regression models. paramed provides estimates of t
direct effect, the natural indirect effect and the total effect with standard errors and confidence intervals derived using the delta

Mediation analysis

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Search for **mediation**. Search results: **mediation : 14, mediate : 1, mediative : 0, mediations : 0, mediately : 0, mediating : 1, mediated : 1, mediates : 0, mediateness : 0**. Results **1-4** of **4**. Search took **0.959** seconds

1. **MEDIATION**: Stata module for causal **mediation** analysis and sensitivity analysis [**61.175%**]
   Raymond Hicks & Dustin Tingley (2011)
   Downloadable! **mediation** estimates the role of particular causal mechanisms that **mediate** a relationship between treatment and outcome variables. Calculates causal **mediation** effects and direct effects for models with continuous or binary dependent variables using methods presented in Imai et al 2010. Also calculates sensitivity analyses for **mediation** effects that are necessary due to non-random assignment of **mediating** variable. Package replaces earlier approaches like the "Baron-Kenny" method and "Sobel test" for the case of continuous mediator and outcome variables, producing identical results as these earlier methods but not put in a causal inference framework and with sensitivity analyses to the key identification assumption. For models with binary mediators or outcomes, correct calculation of **mediation** effects are implemented that take into account the use of non-linear models such as probit.
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   Downloadable! paramed performs causal **mediation** analysis using parametric regression models. Two models are estimated: a model for the mediator conditional on treatment (exposure) and covariates (if specified), and a model for the outcome conditional on treatment (exposure), the mediator and covariates (if specified). It extends statistical **mediation** analysis (widely known as Baron and Kenny procedure) to allow for the presence of treatment (exposure)-mediator interactions in the outcome regression model using counterfactual definitions of direct and indirect effects. paramed allows continuous, binary or count outcomes, and continuous or binary mediators, and requires the user to specify an appropriate form for the regression models. paramed provides estimates of the controlled direct effect, the natural direct effect, the natural indirect effect and the total effect with standard errors and confidence intervals derived using the delta method by default, with a bootstrap option also available.
3. GFORMULA: Stata module to implement the g-computation formula for estimating causal effects in the presence of time-varying conf [**47.580%**]
   Rhian Daniel (2010)
   Downloadable! gformula is an implementation of the g-computation procedure, used to estimate the causal effect of time-varying exposure(s) (A) on an outcome (Y) in the presence of time-varying confounders (L) that are themselves also affected by the exposure(s). The procedure can also be used to address the related problem of estimating controlled direct effects and natural direct/indirect effects when the causal effect of the exposure(s) on an outcome is **mediated** by intermediate variables, and in particular when confounders of the mediator-outcome relationships are themselves affected by the exposure(s).
4. LDECOMP: Stata module decomposing the total effects in a logistic regression into direct and indirect effects [**33.812%**]
   Maarten L. Buis (2008)
   Downloadable! ldecomp decomposes the total effects of a categorical variable in logistic regresion into direct and indirect effects using a method method by Erikson et al. (2005) and a generalization of this method by Buis (2008). Consider an example where social class has an indirect effect on attending college through academic performance in high school. The indirect effect is obtained by comparing the proportion of lower class students that attend college with the counterfactual proportion of lower class students if they had the distribution of performance of the higher class students. This captures the association between class and attending college due to differences in performance. The direct effect of class is obtained by comparing the proportion of higher class students with the counterfactual proportion of lower

Summary

1. Motivating example

Summary

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2. Causal mediation analysis

Summary

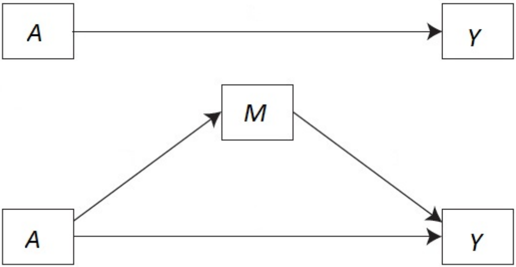
Summary

Summary

Summary

Why mediation analysis?

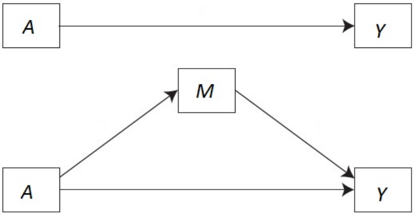
The aim is to understand *if* and *to which extent* the effect of a *treatment* variable A on an *outcome* variable Y is mediated through a variable M



Mediation analysis - example

We could be interested in ...

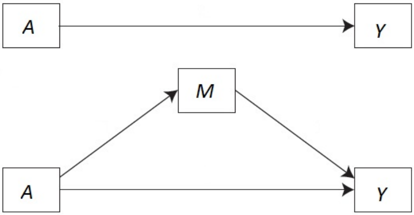
1. studying the relation between physical activity (A) and myocardial infarction (Y)
2. evaluating the role of BMI (M) as potential mediator



Mediation analysis - example

We could be interested in ...

1. studying the relation between physical activity (A) and myocardial infarction (Y) (total effect)
2. evaluating the role of BMI (M) as potential mediator (direct/indirect effects)



Mediation analysis - other examples (I)

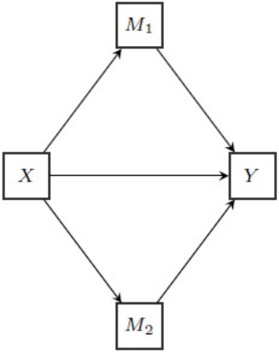


Figure 1 : Rosseel, 2013

Mediation analysis - other examples (II)

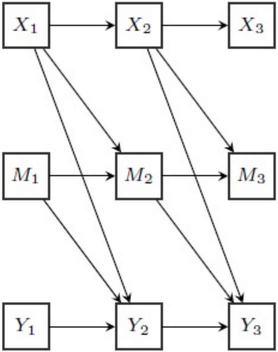


Figure 2 : Rosseel, 2013

Summary

Standard approach - Baron and Kenny, 1986

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- Model for the outcome (with mediator)

$$E[Y \mid a, m] = \alpha_1 + \beta_1 a + \theta m$$

- Model for the mediator

$$E[M \mid a] = \alpha_2 + \gamma a$$

Standard approach - Baron and Kenny, 1986

- Model for the outcome (with mediator)

$$E[Y \mid a, m] = \alpha_1 + \beta_1 a + \theta m$$

- Model for the mediator

$$E[M \mid a] = \alpha_2 + \gamma a$$

- Direct effect: β_1
- Indirect effect (product method): $\theta\gamma$

Standard approach - Baron and Kenny, 1986

- linear models
- no exposure-mediator interaction
- causal interpretation?

Modern approach to mediation analysis

- Robins and Greenland (1992), Pearl (2001)
- based on conterfactuals
- more general settings
- assumptions and sensitivity analyses

Causal inference framework

Causal inference framework

- Let A be a treatment, M be a mediator, Y be an outcome,

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- Let $Y(a)$ be the potential outcome Y when intervening to set A to a

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Causal inference framework

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- Let $Y(a)$ be the potential outcome Y when intervening to set A to a
- Let $M(a)$ be the potential outcome M when intervening to set A to a
- Let $Y(a, m)$ be the potential outcome Y when intervening to set A to a and M to m

Controlled direct effects

- Controlled direct effect, that compares outcomes under treatment level $A = 1$ vs. $A = 0$, fixing $M = m$:

$$CDE(m) = E(Y(1, m)) - E(Y(0, m))$$

- CDE(m) depends on M level m.
- no analougous definition of controlled indirect effect

Natural direct and indirect effects (I)

- Natural direct effect, that compares outcomes under treatment level $A = 1$ vs. $A = 0$, fixing $M = M(0)$:

$$NDE_0 = E(Y(1, M(0)) - E(Y(0, M(0))$$

- Natural indirect effect, that compares outcomes under $M = M(1)$ vs. $M = M(0)$, fixing $A = 1$:

$$NIE_1 = E(Y(1, M(1)) - E(Y(1, M(0))$$

- Total causal effect can be decomposed as:

$$TCE = E(Y(1)) - E(Y(0)) = NDE + NIE$$

Natural direct and indirect effects (II)

- Natural direct effect, that compares outcomes under treatment level $A = 1$ vs. $A = 0$, fixing $M = M(1)$:

$$NDE_1 = E(Y(1, M(1)) - E(Y(0, M(1))$$

- Natural indirect effect, that compares outcomes under $M = M(1)$ vs. $M = M(0)$, fixing $A = 0$:

$$NIE_0 = E(Y(0, M(1)) - E(Y(0, M(0))$$

- Total causal effect can be decomposed as:

$$TCE = E(Y(1)) - E(Y(0)) = NDE + NIE$$

Natural direct and indirect effects (II)

- Natural direct effect, that compares outcomes under treatment level $A = 1$ vs. $A = 0$, fixing $M = M(1)$:

$$NDE_1 = E(Y(1, M(1)) - E(Y(0, M(1))$$

- Natural indirect effect, that compares outcomes under $M = M(1)$ vs. $M = M(0)$, fixing $A = 0$:

$$NIE_0 = E(Y(0, M(1)) - E(Y(0, M(0))$$

- Proportion of mediation can be computed as:

$$PM = \frac{NIE}{NIE + NDE} = \frac{NIE}{TCE}$$

Decomposition for dichotomous outcomes

- Natural direct effect

$$OR_0^{NDE} = \frac{P(Y_{1M_0} = 1)/P(Y_{1M_0} = 0)}{P(Y_{0M_0} = 1)/P(Y_{0M_0} = 0)}$$

- Natural indirect effect

$$OR_1^{NIE} = \frac{P(Y_{1M_1} = 1)/P(Y_{1M_1} = 0)}{P(Y_{1M_0} = 1)/P(Y_{1M_0} = 0)}$$

- Total causal effect

$$OR^{TE} = OR^{NIE} \times OR^{NDE}$$

Assumptions (I)

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- no unmeasured exposure-outcome confounding

Assumptions (I)

- no unmeasured exposure-outcome confounding

- no unmeasured exposure-mediator confounding
- no unmeasured mediator-outcome confounding

Assumptions (I)

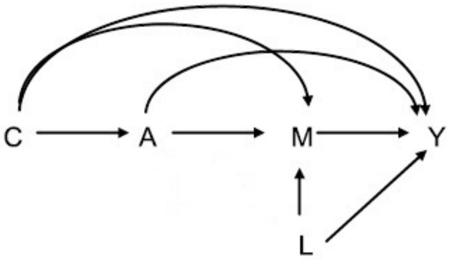

Figure 3 : VanderWeele, 2009

Assumptions (cont'd)

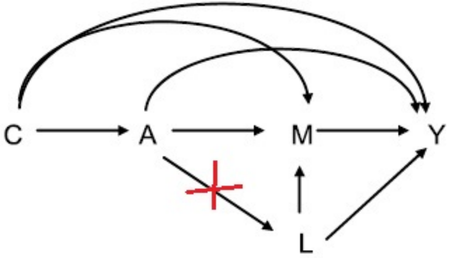

Figure 4 : VanderWeele, 2009

Summary

Data

The Swedish National March Cohort - 1997

- 43,863 subjects, men and women

Data

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- 43,863 subjects, men and women

Exposure, mediator and outcome

- past physical activity: PA, binary (87% physical active)
- body mass index in 1997: BMI, continuous (mean 24.7; std.dev. 3.5)
- myocardial infarction in 1997-2007: MI, binary (1,200 events)

Mediation analysis in Stata

- paramed (Emsley et al., 2012)
- ldecomp (Buis, 2010)
- medeff (Hicks and Tingley, 2011)
- gformula (Daniel, De Stavola and Cousens, 2012)

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- gformula (Daniel, De Stavola and Cousens, 2012)

paramed

- Valeri, L. and VanderWeele, T.J. (2013). *Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros*
- macro is available also in SAS and SPSS
- parametric approach

paramed - models

- Outcome model

$$logit\{P(Y = 1 \mid a, m, c)\} = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta_4' c$$

- Mediator model

$$E(M = 1 \mid a, c) = \beta_0 + \beta_1 a + \beta_2' c$$

where **c** is the set of **known confounders** of the relationships:

- exposure-outcome
- exposure-mediator
- mediator-outcome

paramed - estimation

If the outcome Y is rare, then:

$$log(OR^{NDE} \mid c) \approx \left\{\theta_1 + \theta_3(\beta_0 + \beta_1 a^* + \beta_2^{'} c + \theta_2 \sigma^2)\right\}(a - a^*) + 0.5\theta_3^2 \sigma^2 (a^2 - a^{*2})$$

$$log(OR^{NIE} \mid c) \approx (\theta_2 \beta_1 + \theta_3 \beta_1 a)(a - a^*)$$

where a, a^* are the treatment levels and σ^2 is the variance of the gaussian error term in the mediator model

paramed

- advantages: continuous, binary or count Y, and continuous or binary M; A-M interaction; bootstrap; case-control
- limitations: no sensitivity analyses routines

paramed - syntax

```
paramed mi,

avar(pa) mvar(bmi)

a0(0) a1(1) m(0)

yreg(logistic) mreg(linear)

nointer cvars(age)
```

paramed - output

```
             |   Estimate      Std Err    P>|z|    [95% Conf    Interval]
-------------+-----------------------------------------------------------
             |
  nde = cde  |  .76972671    .0867014    0.003    .64943371    .91230128
        nie  |  .94409039   .00944413    0.000    .92677556    .96172871
             |
         te  |  .72669159   .08615045    0.000    .61378659    .86036528
```

paramed - output

```
             |   Estimate     Std Err    P>|z|    [95% Conf    Interval]
-------------+-------------------------------------------------------
             |
   nde = cde |  .76972671    .0867014    0.003    .64943371    .91230128
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             |
          te |  .72669159   .08615045    0.000    .61378659    .86036528
```

Total effect $= 0.73$

- odds for MI if everyone had been active vs. odds for MI if everyone had been inactive

paramed - output

	Estimate	Std Err	P>|z|	[95% Conf	Interval]
nde = cde	.76972671	.0867014	0.003	.64943371	.91230128
nie	.94409039	.00944413	0.000	.92677556	.96172871
te	.72669159	.08615045	0.000	.61378659	.86036528

Natural direct effect $= 0.77$

- we fix BMI to the value that it would have taken without physical activity
- we compare odds for MI if everyone had been active vs. odds for MI if everyone had been inactive

paramed - output

```
             |   Estimate      Std Err    P>|z|    [95% Conf    Interval]
-------------+-------------------------------------------------------------
             |
   nde = cde |  .76972671     .0867014    0.003    .64943371    .91230128
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             |
          te |  .72669159    .08615045    0.000    .61378659    .86036528
```

Natural indirect effect $= 0.94$

- we assume that everyone is physically active
- we compare the odds for MI, when BMI changes from the value with physical activity to the one without physical activity

Mediation analysis in Stata

- paramed (Emsley et al., 2012)
- ldecomp (Buis, 2010)
- medeff (Hicks and Tingley, 2011)
- gformula (Daniel, De Stavola and Cousens, 2012)

ldecomp

- Buis, M.L. (2011). *Direct and indirect effects in a logit model*
- advantages: multiple mediators; mediators can follow any distribution; A-M interaction
- limitations: binary Y; no sensitivity analyses routines

ldecomp - syntax

```
ldecomp mi age,

direct(pa) indirect(bmi)

or rindirect

reps(1000)
```

ldecomp - output

	Observed Odds Ratio	Bootstrap Std. Err.	z	P>|z|	Normal-based [95% Conf.	Interval]
1/0						
total	.7227368	.0640098	-3.67	0.000	.6075651	.8597408
indirect1	.9387875	.0103436	-5.73	0.000	.9187319	.959281
direct1	.7698619	.0680928	-2.96	0.003	.64733	.9155877
indirect2	.9386944	.0103766	-5.72	0.000	.9185754	.959254
direct2	.7699383	.0680732	-2.96	0.003	.6474377	.9156171

ldecomp - output

```
--------------------------
             |   Observed
             | Odds Ratio
-------------+------------
1/0r         |
             |
     method1 |   .1945307
     method2 |   .1948362
             |
     average |   .1946834
--------------------------
```

On average ...

- the indirect effect represents the 19% of the total effect

Mediation analysis in Stata

- paramed (Emsley et al., 2012)
- ldecomp (Buis, 2010)
- medeff (Hicks and Tingley, 2011)
- gformula (Daniel, De Stavola and Cousens, 2012)

medeff

- Imai, K., Keele, L. and Tingley, D. (2010). *A general approach to causal mediation analysis*
- parametric approach
- non-parametric extension in R
- quasi-Bayesian Monte Carlo algorithm (King et al., 2000)

medeff

- advantages: continuous and binary Y and M; A-M interaction; sensitivity analyses (medsens)
- limitations: no decomposition in terms of OR; computationally intensive

medeff - syntax

```
medeff

(regress bmi pa age)

(logit mi pa bmi age),

mediate(bmi) treat(pa)

sims(1000)
```

medeff - output

Effect	Mean	[95% Conf.	Interval]
ACME1	-.0015834	-.0022292	-.0010069
ACME0	-.002114	-.0030084	-.0013764
Direct Effect 1	-.0114884	-.0183685	-.0051785
Direct Effect 0	-.012019	-.0192047	-.0054538
Total Effect	-.0136024	-.0208373	-.0071637

medeff - output

```
--------------------------------------------------------------------------------
      Effect                  |  Mean           [95% Conf. Interval]
------------------------------+-------------------------------------------------
                              |
      ACME1                   | -.0015834     -.0022292     -.0010069
      ACME0                   |  -.002114     -.0030084     -.0013764
                              |
      Direct Effect 1         | -.0114884     -.0183685     -.0051785
      Direct Effect 0         |  -.012019     -.0192047     -.0054538
                              |
      Total Effect            | -.0136024     -.0208373     -.0071637
--------------------------------------------------------------------------------
```

Note that ...

- A.C.M.E. is the Average Causal Mediated Effect
- effects are marginal

medeff - output

Effect	Mean	[95% Conf.	Interval]
Average Mediation	-.0018487	-.0026075	-.0012015
Average Direct Effect	-.0117537	-.018795	-.0053152
% of Tot Eff mediated	.1367193	.0887204	.2580612

On average ...

- the indirect effect represents the 14% of the total effect

medsens

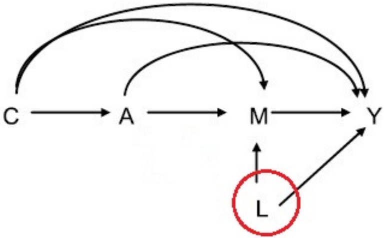


Figure 5 : VanderWeele, 2009

- sensitivity analyses are based on the correlation between the error terms of the mediator and of the outcome

Mediation analysis in Stata

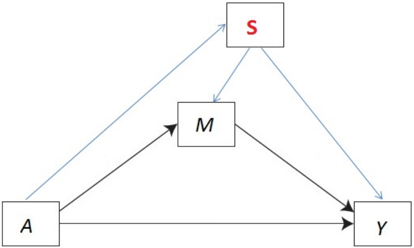
- paramed (Emsley et al., 2012)
- ldecomp (Buis, 2010)
- medeff (Hicks and Tingley, 2011)
- gformula (Daniel, De Stavola and Cousens, 2012)

gformula

- Daniel, R.M., De Stavola, B.L., and Cousens S.N. (2011). *gformula: Estimating causal effects in the presence of time-varying confounding or mediation using the g-computation formula*
- SAS macro
- implements gformula computation developed by Robin (1986)

gformula

mediator-outcome confounder: smoking status



Daniel et al. showed that this setting is methodologically related to the setting in which time-varying confounding occurs

gformula

- advantages: continuous and binary Y and M; A-M interaction; developed for settings in which there are post treatment M-Y confounders; missing values imputation option
- limitations: not suitable for settings in which there is no post-treatment confounding

gformula - syntax

```
gformula mi bmi pa age smoke,

mediation

out(mi) mediator(bmi) ex(pa) baseline(0)

base_confs(age) post_confs(smoke)

com(mi: logit, bmi: regress, smoke: logit)

eq(mi: bmi pa age smoke, bmi: pa age smoke, smoke: pa age)
```

gformula - output

	G-computation estimate	Bootstrap Std. Err.	z	P>|z|	Normal-based [95% Conf.	Interval]
TCE	-.008248	.0031653	-2.61	0.009	-.0144519	-.0020441
NDE	-.0058544	.0031253	-1.87	0.061	-.0119799	.0002712
NIE	-.0023937	.0012857	-1.86	0.063	-.0049135	.0001262

Note that ...

- effects are marginal

Summary

Further remarks

- other tools?
- causal effect measure choice
- sensitivity analyses

Summary

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Thank you!