`compmed`: A new command for estimating causal mediation effects with non-adherence to treatment allocation

Anca Chis Ster, Sabine Landau, Richard Emsley
Department of Biostatistics and Health Informatics, King's College London, United Kingdom

Thursday 12rd September 2024
2024 UK Stata Conference

NIHR | National Institute for Health and Care Research

KING'S College LONDON

STATA

NIHR | Maudsley Biomedical Research Centre

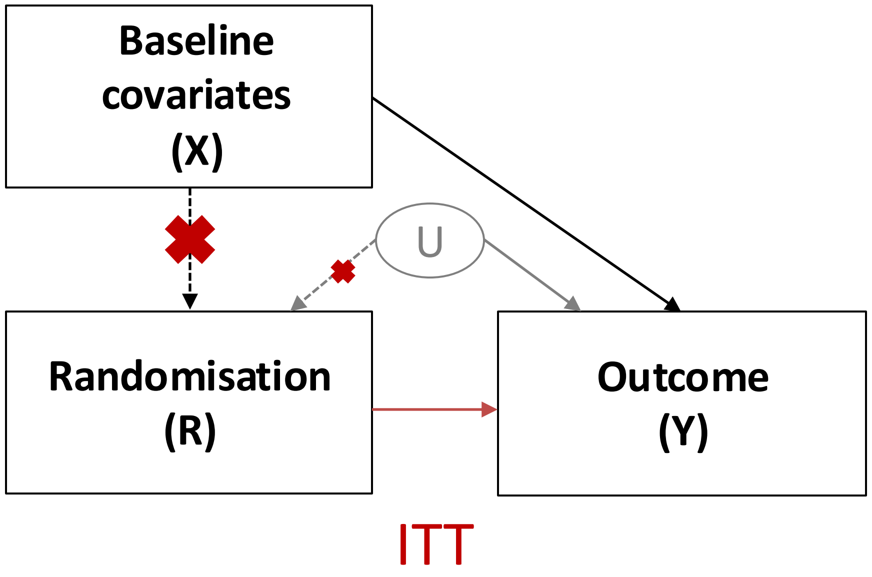
KING'S HEALTH PARTNERS

Motivation for handling nonadherence in mediation

- Trials in mental health often evaluate **complex** interventions, such as therapy or psychotherapy
- One guideline for evaluating complex interventions is to understand the treatment **mechanism**, i.e., understand how the treatment works in practice
- Trials in mental health are faced with the challenge of **nonadherence** to treatment allocation
- It's currently unclear how to account for nonadherence in a mechanism evaluation, or how to practically implement this within a statistical package, e.g., STATA

Anca Chis Ster
King's College London
anca.m.chis_ster@kcl.ac.uk

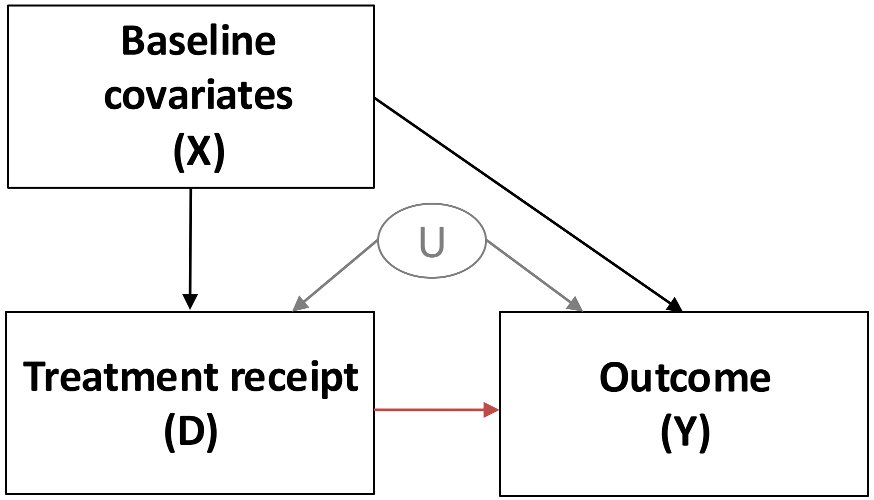
Background: The challenge of non-adherence in trials



X, U = measured or unmeasured variables
ITT = Intention-to-treat
CACE = Complier Average Causal Effect
NDE = Natural Direct Effect
NIE = Natural Indirect Effect

Anca Chis Ster
King's College London
anca.m.chis_ster@kcl.ac.uk

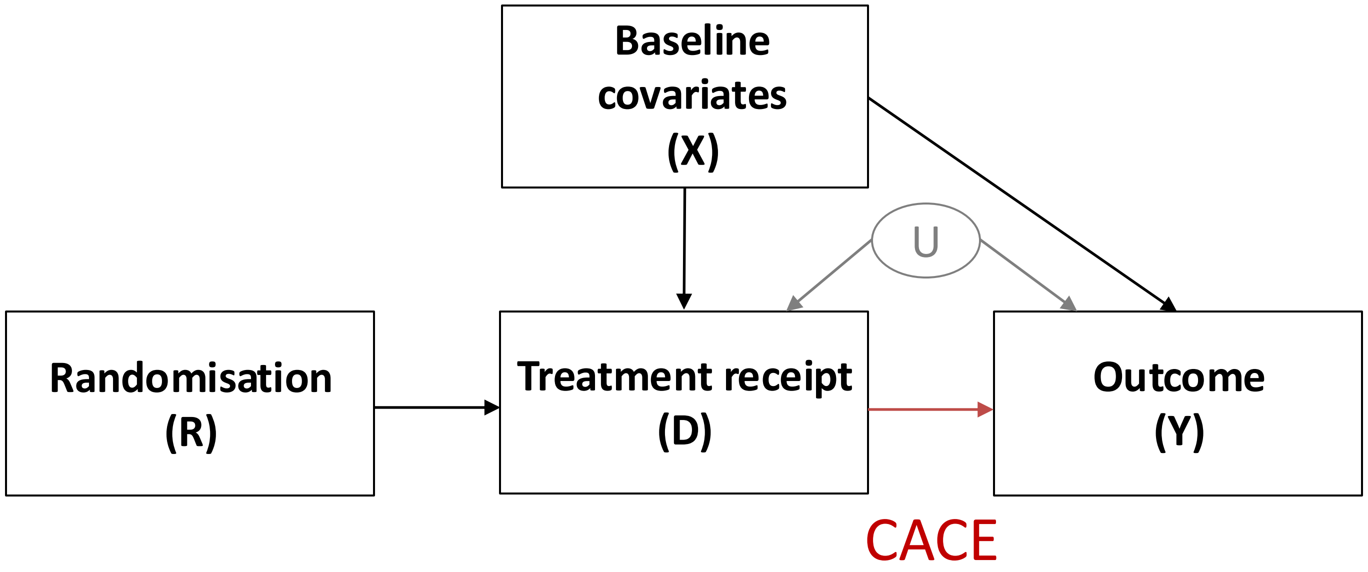
Background: The challenge of non-adherence in trials



X, U = measured or unmeasured variables
ITT = Intention-to-treat
CACE = Complier Average Causal Effect
NDE = Natural Direct Effect
NIE = Natural Indirect Effect

Anca Chis Ster
King’s College London
anca.m.chis_ster@kcl.ac.uk

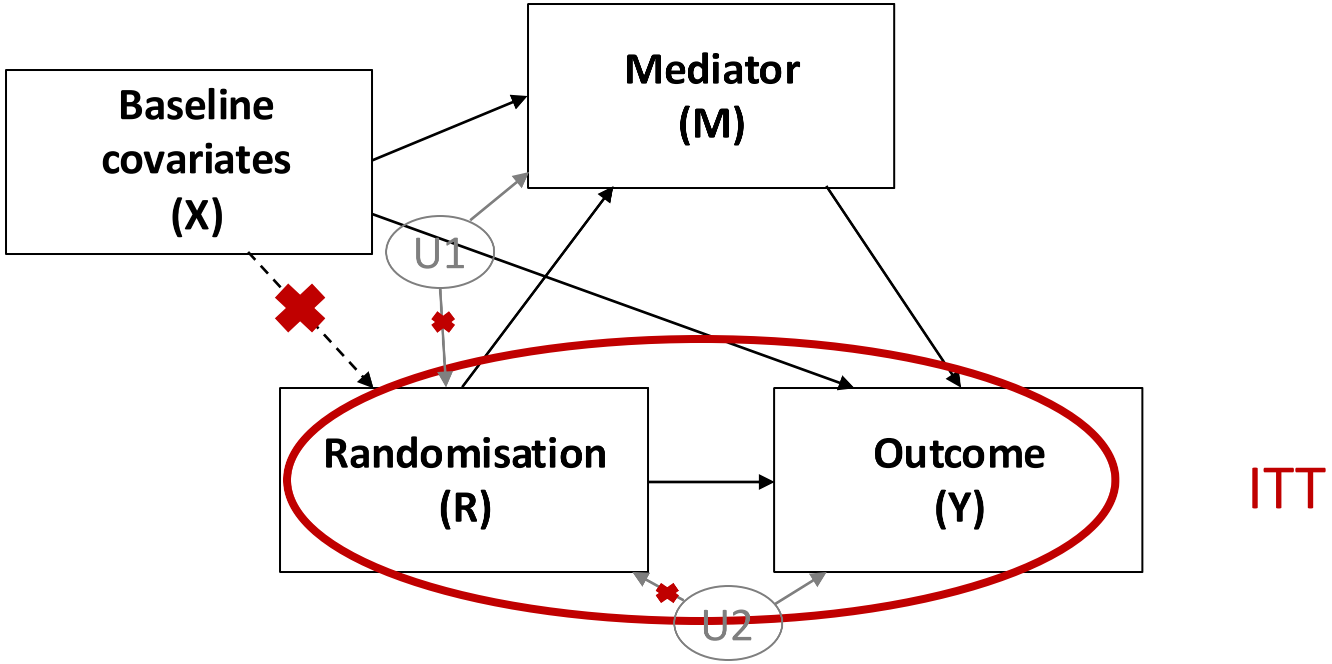
Background: The challenge of non-adherence in trials



X, U = measured or unmeasured variables
ITT = Intention-to-treat
CACE = Complier Average Causal Effect
NDE = Natural Direct Effect
NIE = Natural Indirect Effect

Anca Chis Ster
King's College London
anca.m.chis_ster@kcl.ac.uk

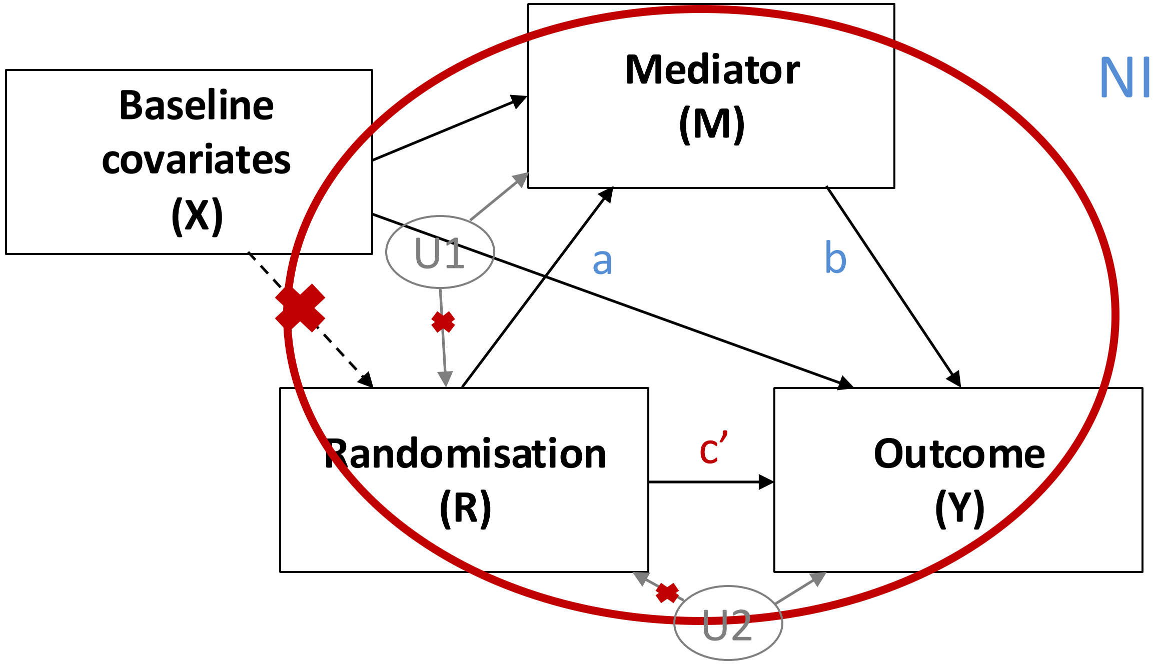
Background: Mechanism evaluation



X, U = measured or unmeasured variables
ITT = Intention-to-treat
CACE = Complier Average Causal Effect
NDE = Natural Direct Effect
NIE = Natural Indirect Effect

Anca Chis Ster
King's College London
anca.m.chis_ster@kcl.ac.uk

Background: Mechanism evaluation



NIE = a*b

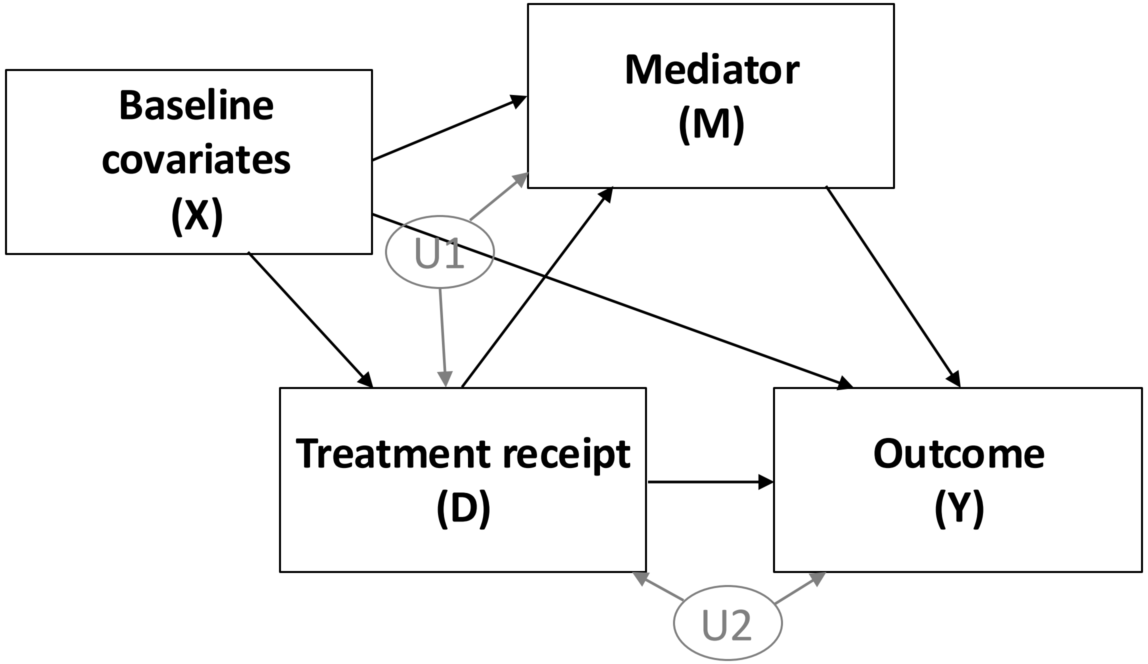
ITT = NDE + NIE

NDE = c'

X, U = measured or unmeasured variables
ITT = Intention-to-treat
CACE = Complier Average Causal Effect
NDE = Natural Direct Effect
NIE = Natural Indirect Effect

Anca Chis Ster
King's College London
anca.m.chis_ster@kcl.ac.uk

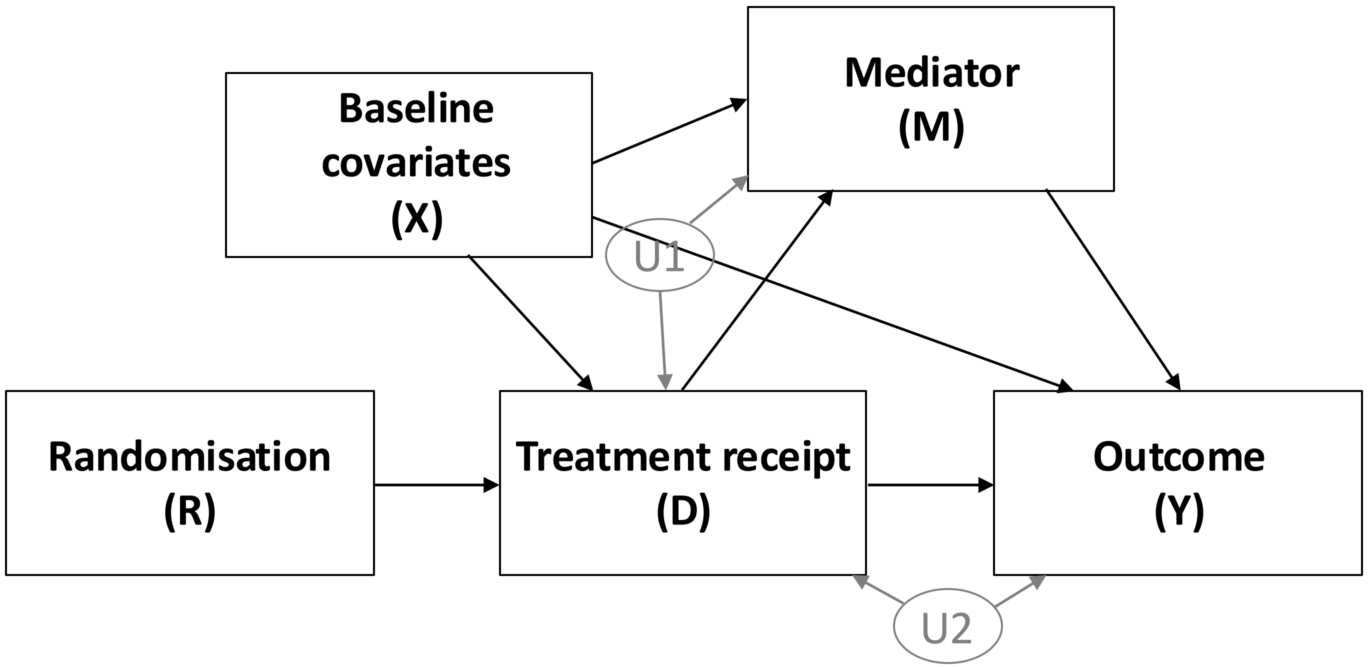
Background: Mechanism evaluation



X, U = measured or unmeasured variables
ITT = Intention-to-treat
CACE = Complier Average Causal Effect
NDE = Natural Direct Effect
NIE = Natural Indirect Effect

Anca Chis Ster
King's College London
anca.m.chis_ster@kcl.ac.uk

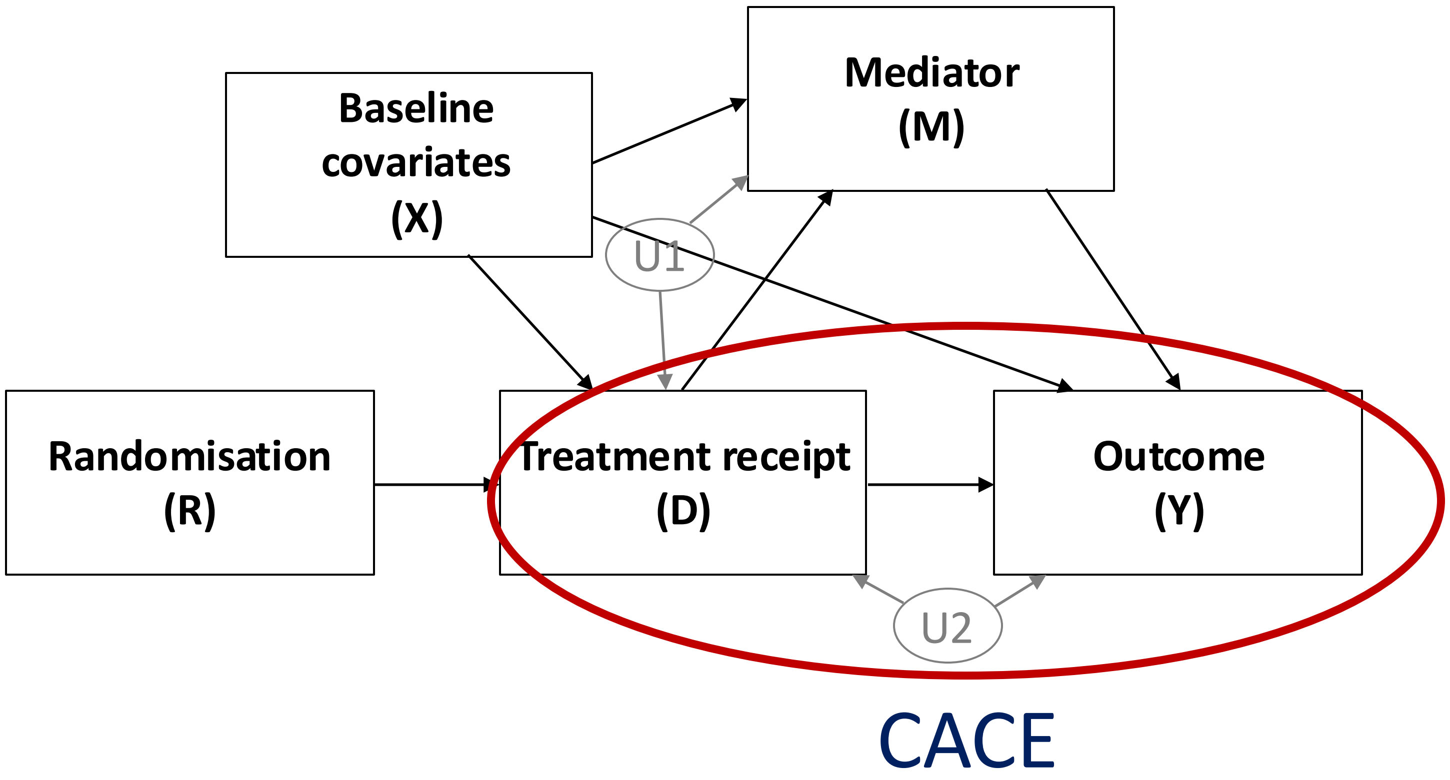
Background: Mechanism evaluation



X, U = measured or unmeasured variables
ITT = Intention-to-treat
CACE = Complier Average Causal Effect
NDE = Natural Direct Effect
NIE = Natural Indirect Effect

Anca Chis Ster
King's College London
anca.m.chis_ster@kcl.ac.uk

Combining mediation and non-adherence: Identification



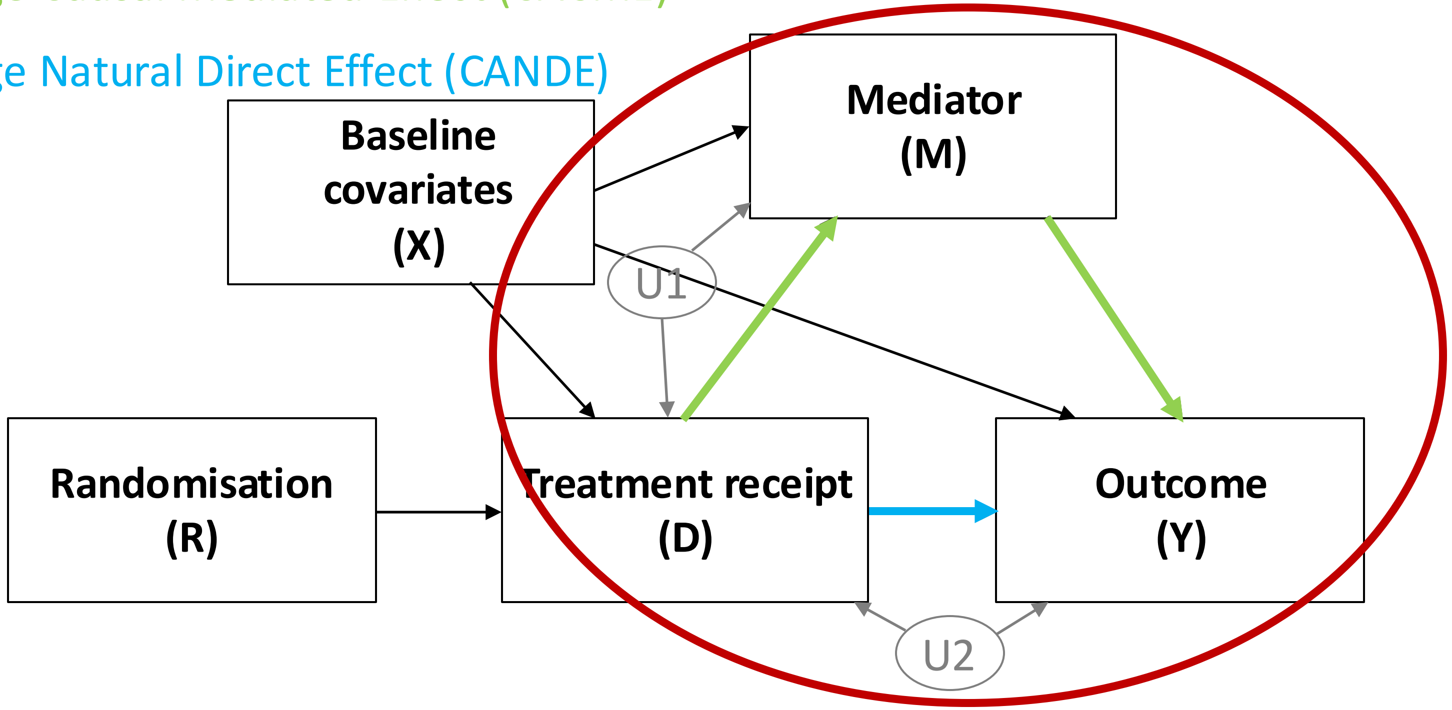
X, U = measured or unmeasured variables
ITT = Intention-to-treat
CACE = Complier Average Causal Effect
NDE = Natural Direct Effect
NIE = Natural Indirect Effect

Anca Chis Ster
King's College London
anca.m.chis_ster@kcl.ac.uk

Combining mediation and non-adherence: Identification

The CACE can be partitioned into a:

- Complier-Average Causal Mediated Effect (CACME)
- Complier-Average Natural Direct Effect (CANDE)



CACE = CACME + CANDE

X, U = measured or unmeasured variables
ITT = Intention-to-treat
CACE = Complier Average Causal Effect
NDE = Natural Direct Effect
NIE = Natural Indirect Effect

Anca Chis Ster
King's College London
anca.m.chis_ster@kcl.ac.uk

Combining mediation and non-adherence: Assumptions

The CACME and CANDE can be identified under:

(1) Conditionally ignorable treatment assignment

- No variables that influence the randomisation variable

(2) Monotonicity

- No individuals who would receive the opposite intervention to the one offered

(3) Exclusion restriction for non-compliers

- Randomisation cannot directly influence the mediator or outcome variables

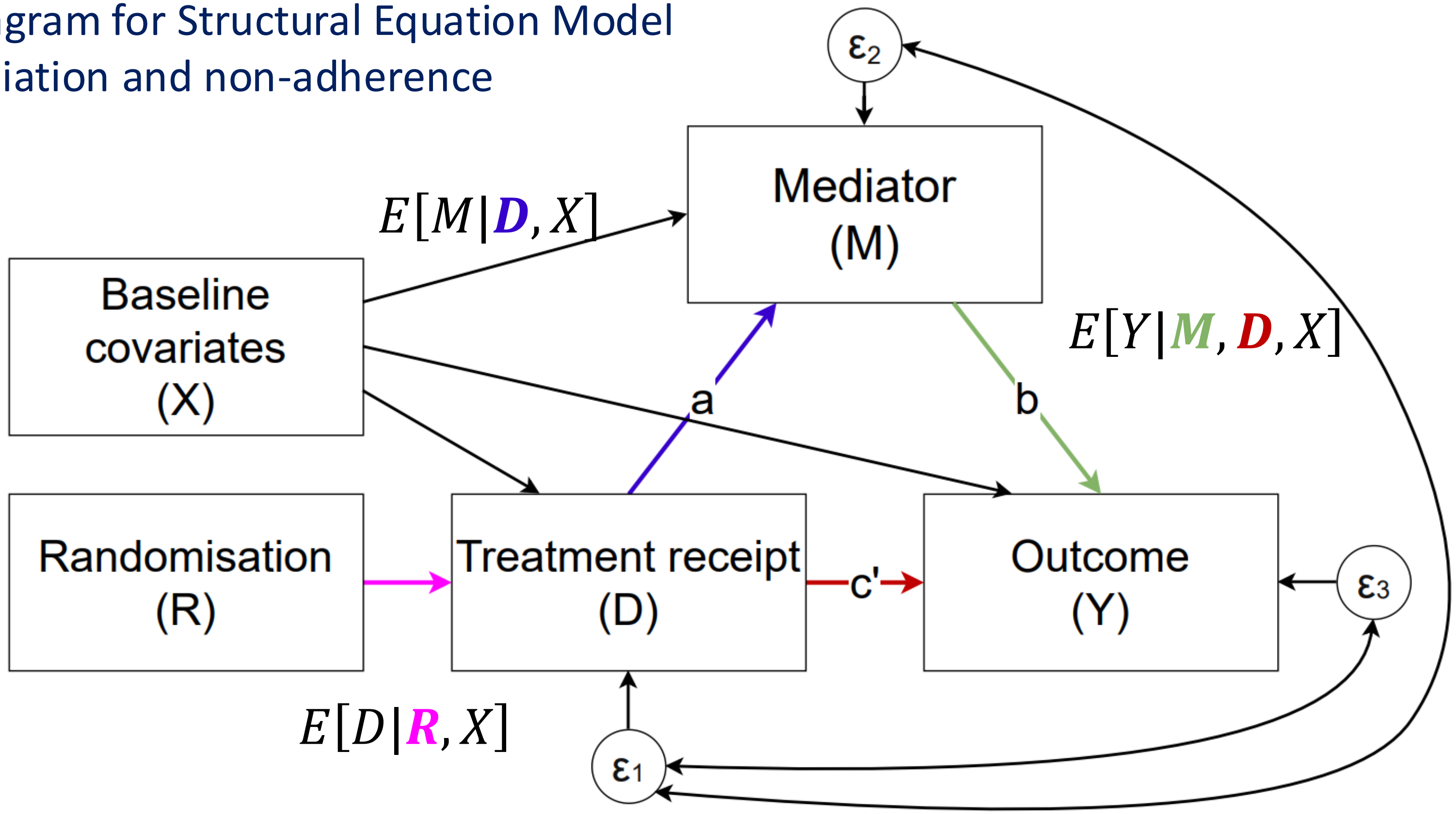
(4) Conditionally ignorable observed mediator among compliers

- No unmeasured confounding between the mediator and outcome

CACE = Complier Average Causal Effect
CANDE = Complier Average Natural Direct Effect
CACME = Complier Average Causal Mediated Effect

Combining mediation and non-adherence: Estimation

Figure: Path diagram for Structural Equation Model combining mediation and non-adherence



CACME = a * b

CANDE = c’

Anca Chis Ster
King’s College London
anca.m.chis_ster@kcl.ac.uk

CACE = Complier Average Causal Effect
CANDE = Complier Average Natural Direct Effect
CACME = Complier Average Causal Mediated Effect

Illustrating example: The AVATAR study

- 150 participants randomised 1:1 to receive **AVATAR therapy** or supportive counselling for psychosis related symptoms
- The primary outcome was the total score on the **Psychotic Symptom Rating Scales** at 12 weeks and was analysed with the **ITT principle**
- 84% compliance (attended ≥3 of 6 sessions)
- Mediator of interest is the participants **acceptance-based attitudes** in relation to their auditory hallucinations

Craig, T. K. J., Rus-Calafell, M., Ward, T., Leff, J. P., Huckvale, M., Howarth, E., . . . Garety, P. A. (2018). AVATAR therapy for auditory verbal hallucinations in people with psychosis: a single-blind, randomised controlled trial. *The Lancet Psychiatry, 5*(1), 31-40. doi:10.1016/S2215-0366(17)30427-3

Estimation via –`sem`–

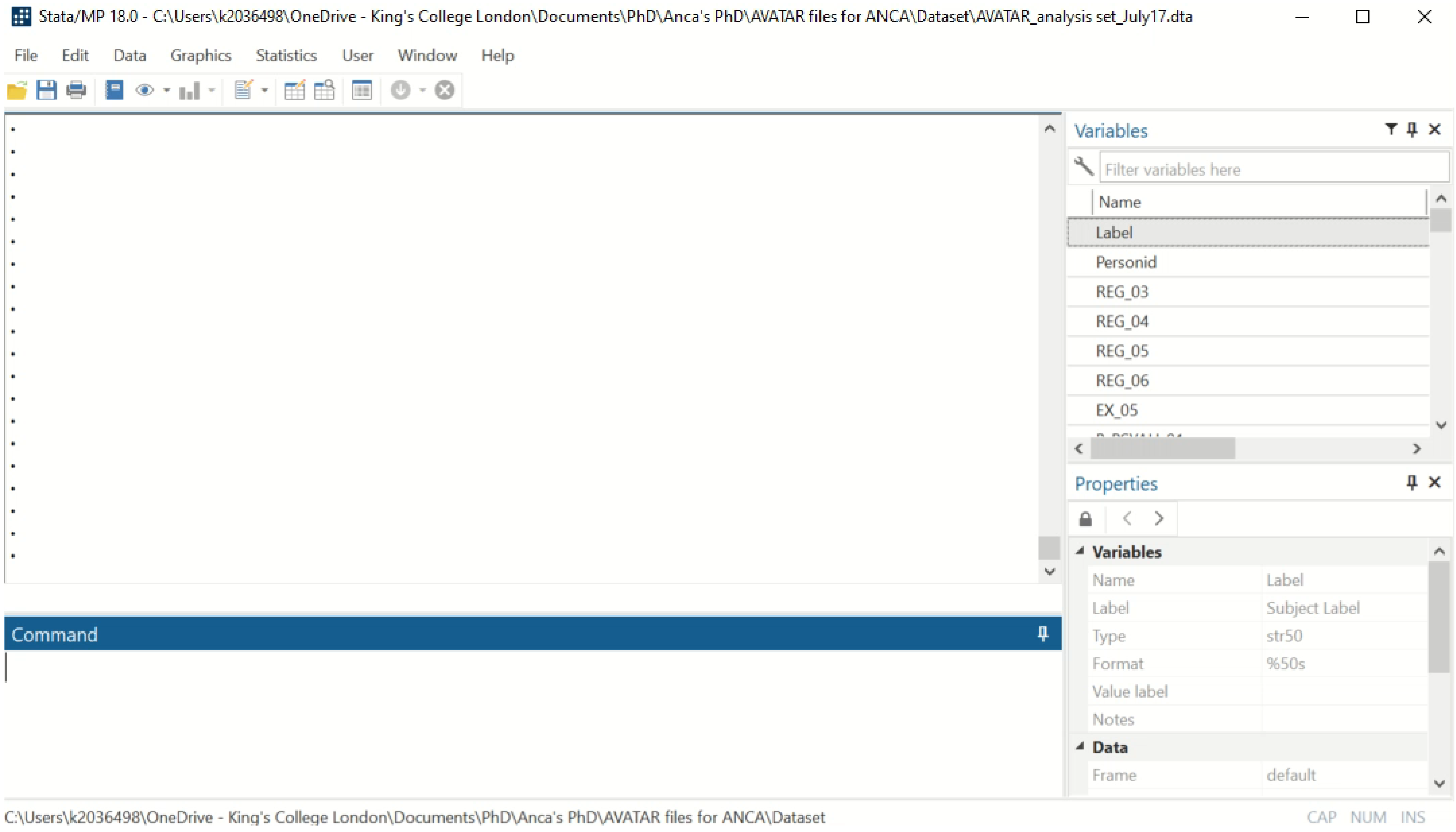
```
sem (R -> D) (D -> M) (D M -> Y),
cov(e.D*e.M) cov(e.D*e.Y)
```

- The path `(R -> D)` implements IV theory and accounts for the endogeneity in D
- The covariances `cov(e.D*e.M)` and `cov(e.D*e.Y)` are essential as they allow for unmeasured confounding between D-M and D-Y

```
estat teffects
```

- Produces many results and paths – many are not relevant
- Can be difficult to identify which paths correspond to the CACME and CANDE

Estimation via the –`sem`– command



The –`compmed`– command: Motivation

- Estimating the CACME and CANDE requires
  (1) Knowledge of SEMs and the SEM Stata package
  (2) Fitting the correct Structural Equation Model
  (3) Identifying the correct pathways that correspond to the CACME and CANDE
- `compmed` offers a standardised approach for estimating the CACME and CANDE in Stata using a single, more intuitive, and user-friendly programme.

Anca Chis Ster
King's College London
anca.m.chis_ster@kcl.ac.uk

The –`compmed`– command: Syntax

```
compmed Y, mvar(M) dvar(D) rvar(R) cvars(varlist)
[, vce(vcetype) FULLoutput]
```

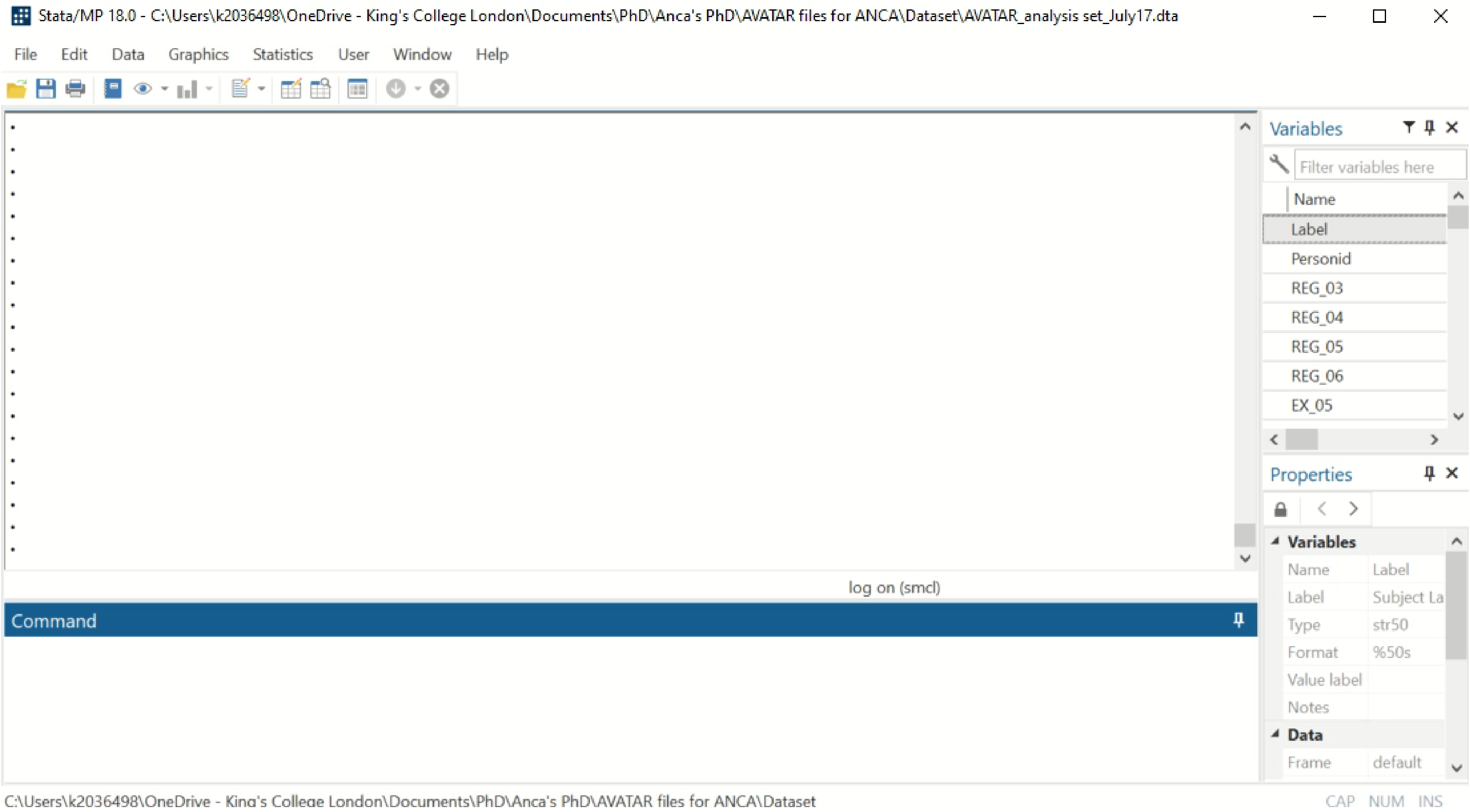
`cvars(varlist)` determines the list of covariates that are included in the outcome and mediator models.

`vce(vcetype)` calculates the standard error of the estimator. vcetype can be `oim` (observed information matrix), `robust` (Huber/White/sandwich estimator), `bootstrap`, or `cluster` (generalized Huber/White/sandwich estimator). If the option is not specified, the default is `oim`.

`FULLoutput` reports the full decomposition of effects into total, direct, and indirect effects, along with standard errors obtained by the delta method (Sobel, 1987). This option is equivalent to the ‘`estat teffects`’ command that is for use after running an the `sem` command in Stata.

Anca Chis Ster
King’s College London
anca.m.chis_ster@kcl.ac.uk

The –compmed– command: Demonstration



Anca Chis Ster
King’s College London
anca.m.chis_ster@kcl.ac.uk

Missing data consideration

- Both `-sem-` and `-compmed-` undertake a **complete-case analysis**, i.e., observations with missing values are dropped from the analysis
- The analysis is therefore valid provided the missing data are **MCAR**, or **MAR** (provided all variables that drive missingness are in the analysis model)
  - ✓ Information on non-adherence, a common predictor of missingness, is already included in the analysis model
- A Monte Carlo simulation study demonstrates that unbiased estimates of CACME, CANDE, and CACE can be obtained under the MCAR and MAR scenarios explored (full results and details not described here)

Final remarks

- The CACE can be partitioned into a CACME and CANDE under a given set of assumptions and can be estimated with linear SEMs
- A new Stata program, `compmed`, provides a practical tool for undertaking causal mediation analysis with non-adherence
  1. Fits the correct SEM model
  2. Automatically identifies the paths that correspond to the CACME and CANDE
  3. Outputs a nice and simple table with these estimates

Anca Chis Ster
King’s College London
anca.m.chis_ster@kcl.ac.uk

Questions

anca.m.chis_ster@kcl.ac.uk
@anca_chisster