

Mediation aligned analysis with a survival outcome and missing data using med4way

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Health and Care Research

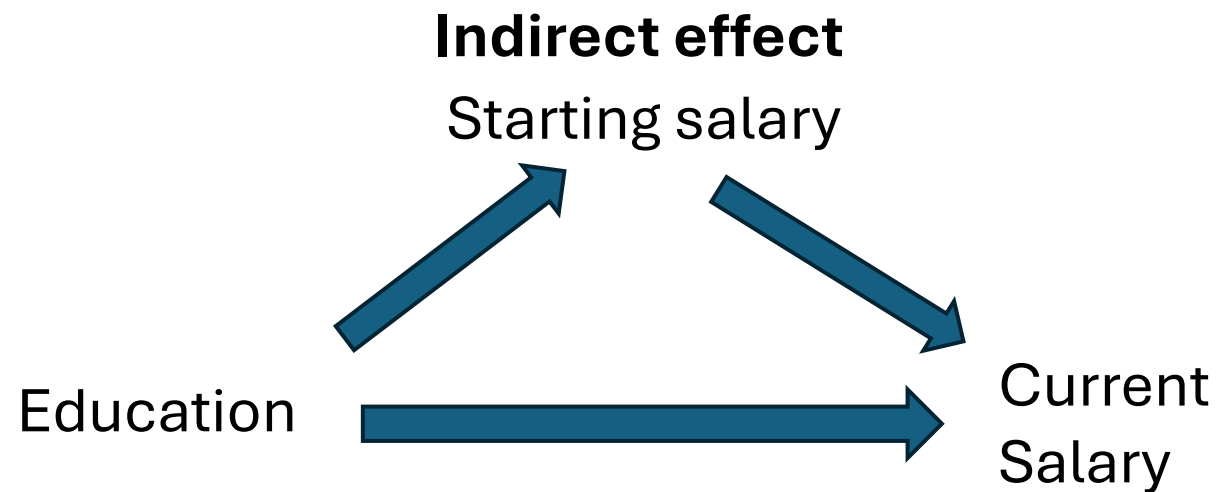
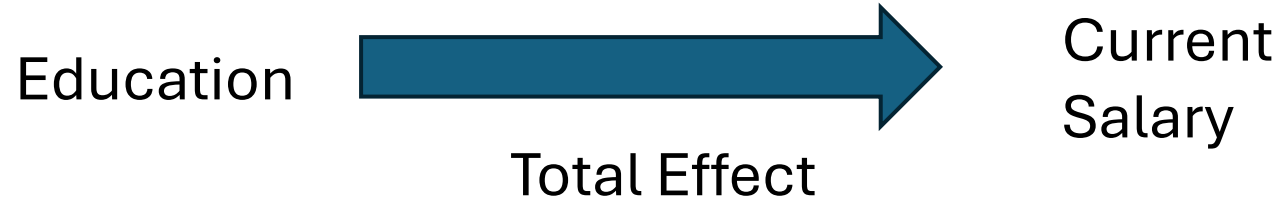
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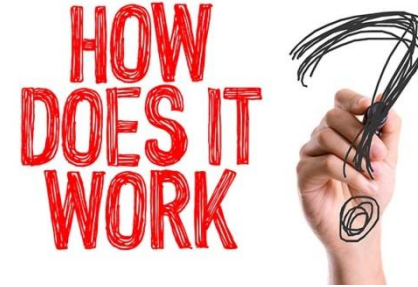


Mediation – what is it?

A mediator is part of the causal pathway, explaining how an effect takes place.



Treatment mechanisms of change (mediators): Why are we interested?



- Further develop or confirm postulated theoretical treatment models
- Can highlight ways in which treatment can be developed, tailored or refined
 - Treatment failed to change hypothesized *mediator*? Change treatment.
 - *Mediator* failed to influence *outcome*? Change mediator/target.

So we can...

- Ask not just whether a treatment works....
- But also how it works....
- And if it didn't work, why this might have happened
- Giving us more information about treatments from trials, which are expensive and time-consuming

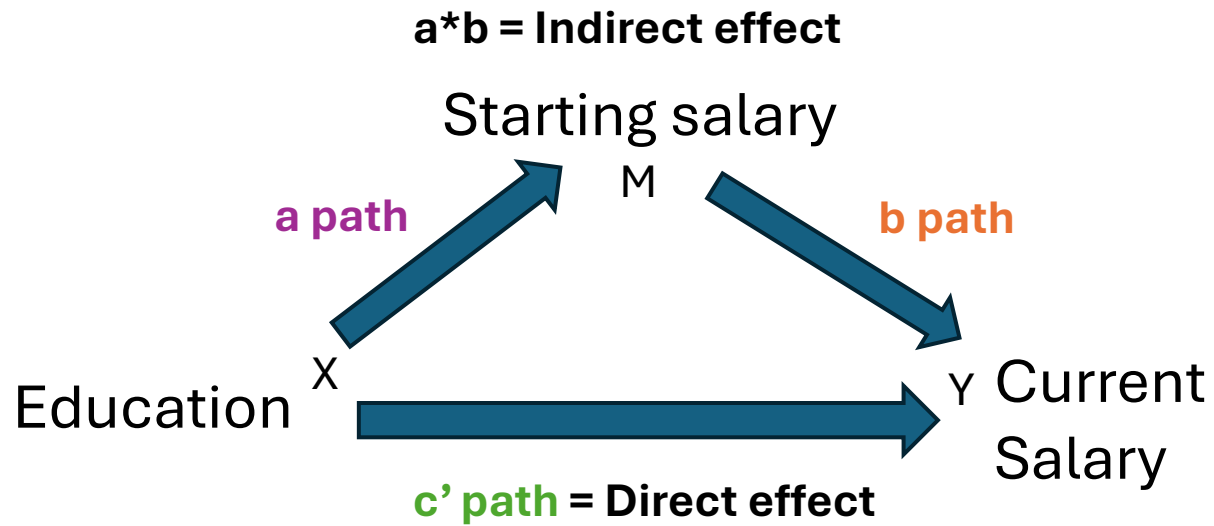


Mediation – calculation?

A mediator is part of the causal pathway, explaining how an effect takes place.

$$M = \alpha_1 + aX + \varepsilon_1$$

$$Y = \alpha_2 + c'X + bM + \varepsilon_2$$



The PRAISe trial - Opioid Use Disorder

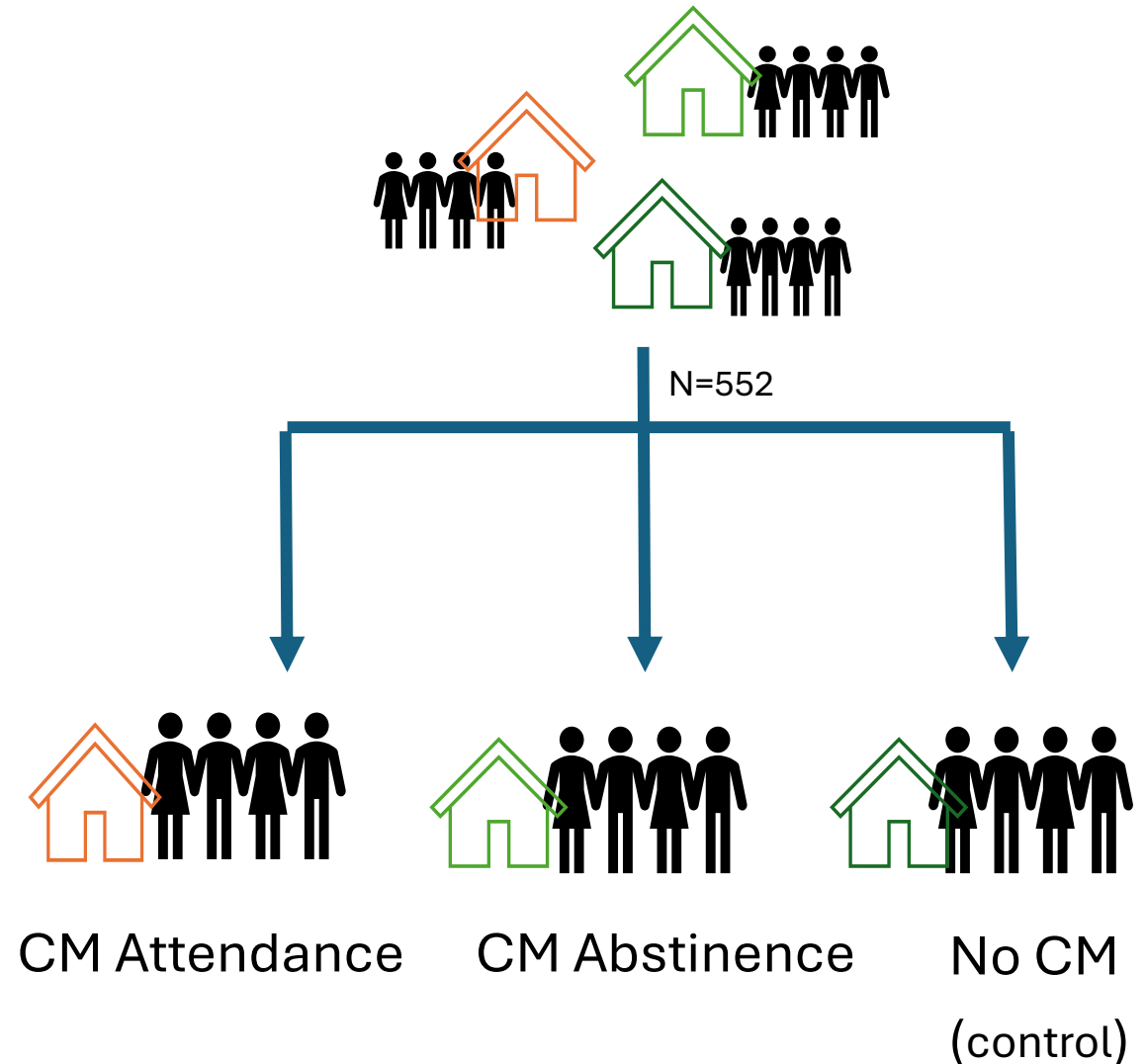
Opioid Use Disorder (OUD):

- 260,000 UK long term users
- Treatment?

Contingency management (CM)?

"Behavioural intervention based on rewarding patients with positive incentives contingent on achieving a target behaviour"

- Strong evidence base from US
- Can be delivered alongside treatment
- Effective at promoting abstinence and/or attendance

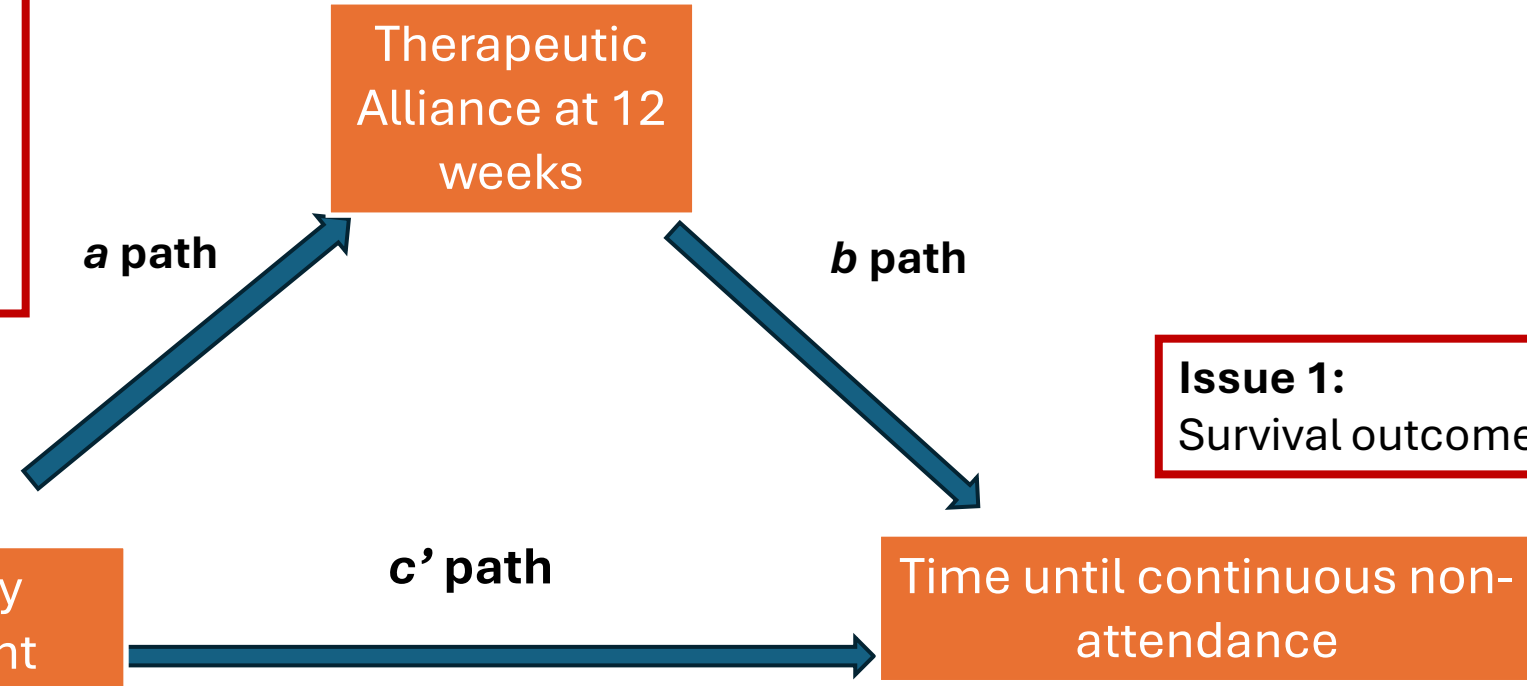


My 'mediation' model:

Issue 3:

Approximately 40% of my mediator data is missing

And need bootstrapping to construct indirect effect CI



Issue 1:

Survival outcome

Issue 2:

3 arm trial

med4way

Using causal inference methods:

Syntax:

```
med4way [yvar] avar mvar [cvars] [if] [in], a0(##)
a1(##) m(##) yreg(string) mreg(string)
[ options ]
```

For survival outcome, use stset first

* Run med4way

```
capture med4way trialarm_med armmeanscore12 stratifier, ///
yreg(aft, we) mreg(linear) ///
a0(0) a1(1) m(6.04) ///
fulloutput
```

ISSUE 1: yvar - Outcome can be **survival**,
AFT Weibull distribution used

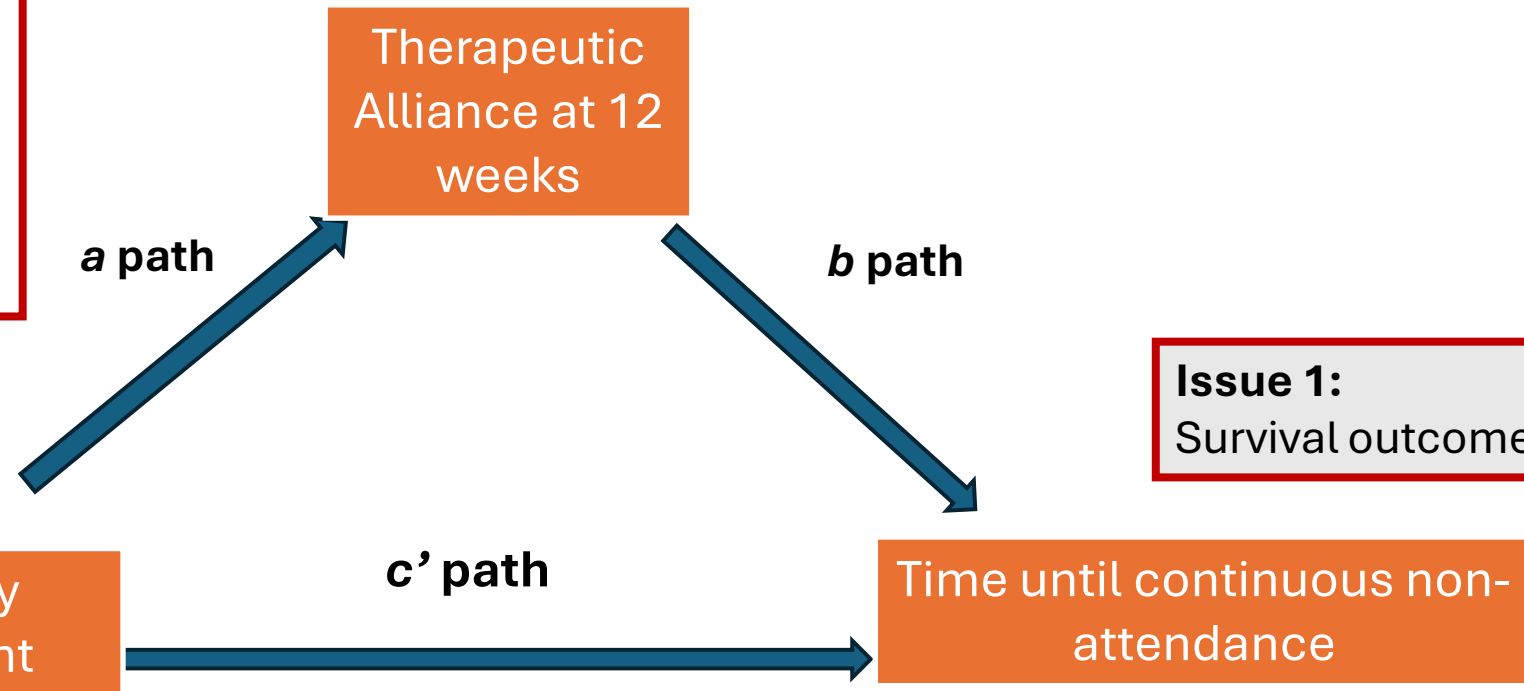
ISSUE 2/NOT SOLVED: A0/a1 - Treatment
could only be binary and not 3-level, but
instead we separated data into
datasets: Treatment A vs no CM and
Treatment B vs no CM

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Issue 1:

Survival outcome

Issue 2:

3 arm trial

Mi impute

Syntax:

Mi set

Mi register

mi impute pmm ivar [indepvars] [if]
[weight] , knn(#) [impute_options
options]

```
*Start imputation
mi set wide

* Register variables: imputed and passive/regular
mi register imputed armmeanscore12
mi register regular trialarm stratifier att_time2 failure_indicator
subscale2 time_trt rand_age gender homelessness site OI_07d OI_09d
audittotal

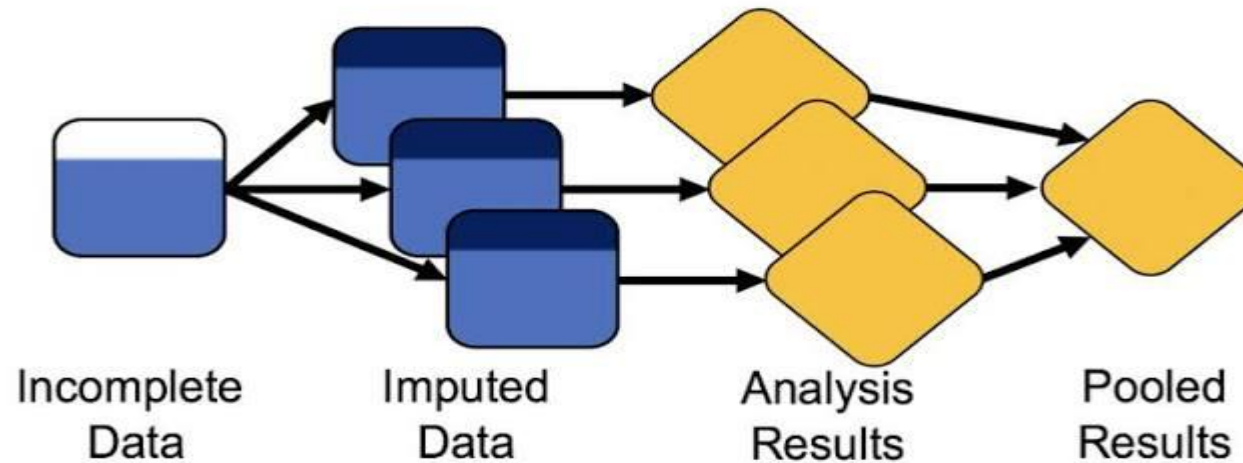
*Impute m=30
mi impute pmm armmeanscore12 trialarm stratifier att_time2 failure_indicator
subscale2 time_trt rand_age gender homelessness site OI_07d OI_09d
audittotal, add(30) rseed(1234) knn(5) force

save "mi_med_data.dta", replace
```

ISSUE 3:

- med4way is not supported by mi estimate, a stata command which combines estimates from imputed mi data, adjusting coefficients and standard errors between imputations, based on Rubins rules (builds normal-based CI)
- > Individually run med4way on each imputed sample, and combine

How to combine Multiple imputation estimates?



ISSUE 1.2:

- Rubin's rules rely on normality of the sampling distribution for the construction of the CI
- For the four-way decomposition (Direct and indirect effects) – which are compound functions of Weibull distribution, these are unlikely to be normally distributed.

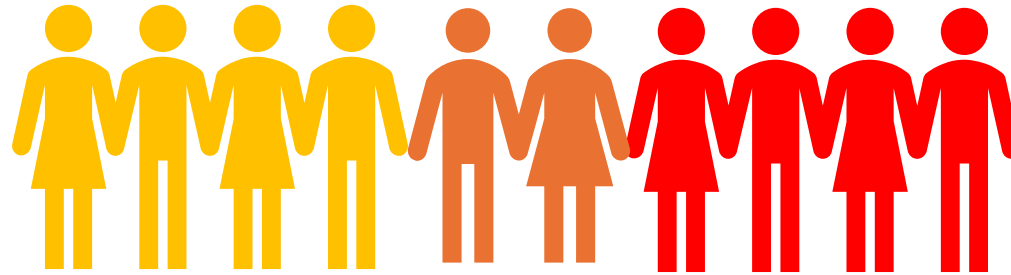


BOOTSTRAPPING?

Schomaker M, Heumann C. Bootstrap inference when using multiple imputation. *Stat Med*. 2018;37(14):2252-2266. doi:10.1002/sim.7654

What is bootstrapping?

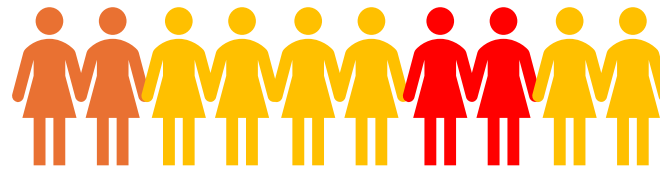
Original Sample – N=10



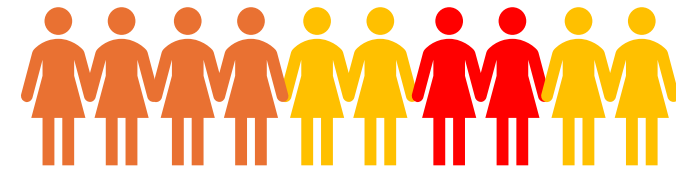
Sampling with replacement



Bootstrap sample 1

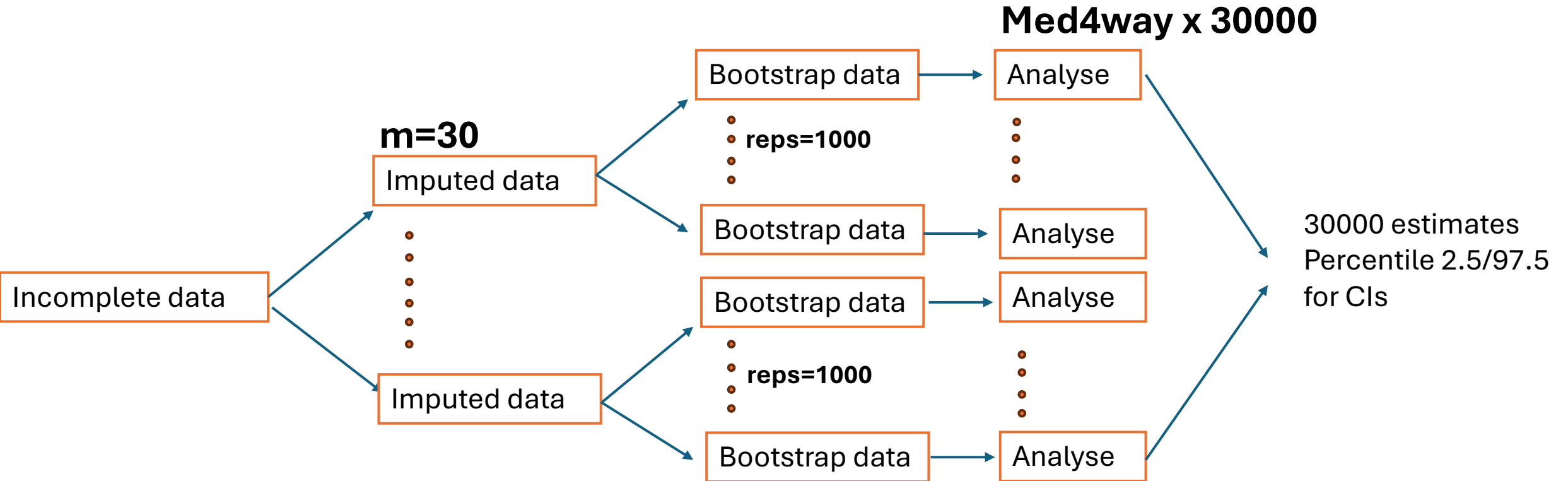


Bootstrap sample 2



Bootstrap sample 3

Option 1: MI BOOT (Pooled Sample)



Code for MI BOOT (Pooled Sample)

```
* Initialise storage matrices - rows = m*reps = 30000, 5 cols
matrix BOOT_ALL = J(`m' * `reps', 5, .)
forvalues i = 1/`m' {

    use "mi_med_data.dta", clear
    *drop trial arm not using
    keep if trialarm_2 == 1 | trialarm_2 == 2

    *extract imputed data x
    mi extract `i', clear
    * Save this imputed dataset temporarily
    save "temp_imputed.dta", replace

    forvalues r = 1/`reps' {
        local row = (`i' - 1) * `reps' + `r'

        * Draw bootstrap sample with replacement
        use "temp_imputed.dta", clear
        bsample

        * Run med4way WITHOUT bootstrap option
        capture quietly med4way trialarm_med armmeanscore12 stratifier, ///
            yreg(aft, we) mreg(linear) ///
            a0(0) a1(1) m(6.2) ///
            fulloutput
    }
}
```

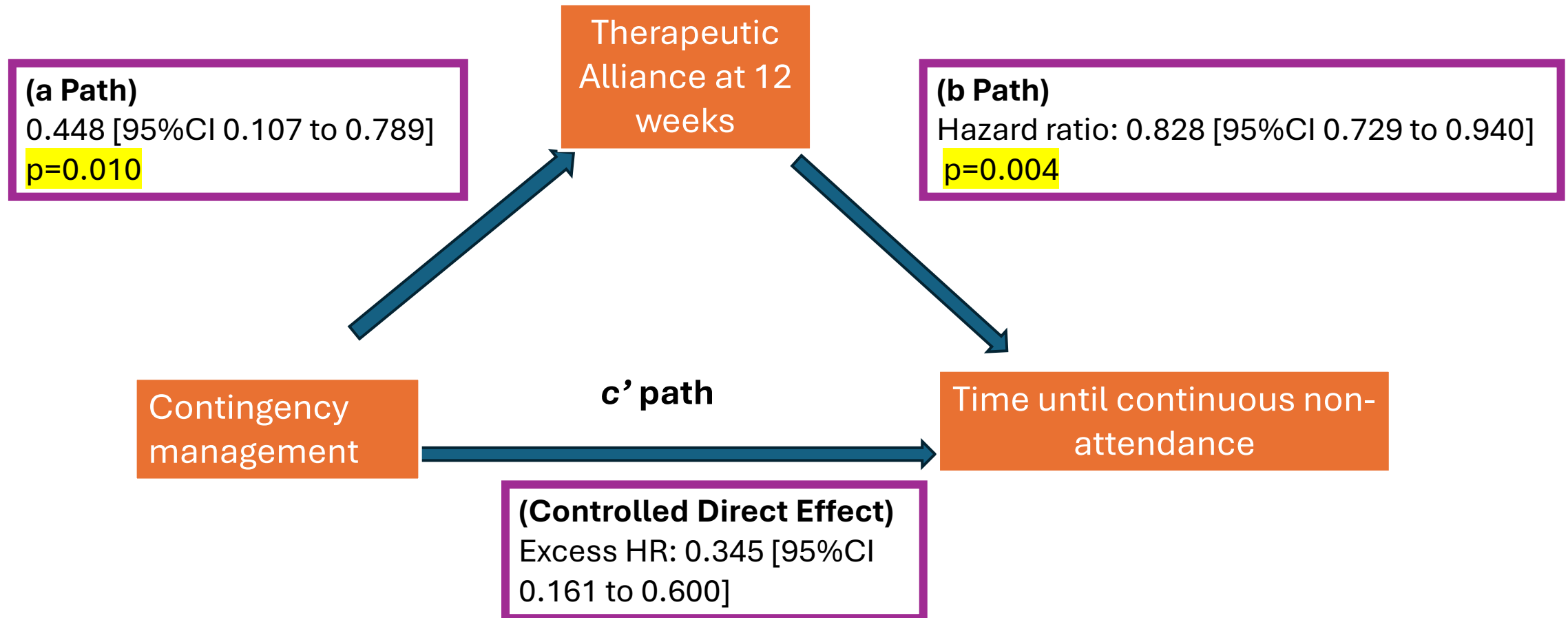
Results

(Total Effect)

Excess HR: 0.396 [95%CI 0.198 to 0.684]

(Pure Indirect Effect)

Excess HR - 0.020 [95%CI -0.018 to 0.086]





Thank you and thank you to all the participants of the PRAISE trial

Contact details/for more information:

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mediate

Syntax:

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

I first worked with mediate:

- ovar - Outcome can be **count** (poisson model)
- tvar - Treatment could be **multivalued**

Uses the **potential outcomes framework** – gives **two-way composition**

- Calculates Natural Indirect effect (NIE)
- Natural direct effect (NDE)
- Pure natural Indirect effect (PNIE)
- Pure natural direct effect (PDE)

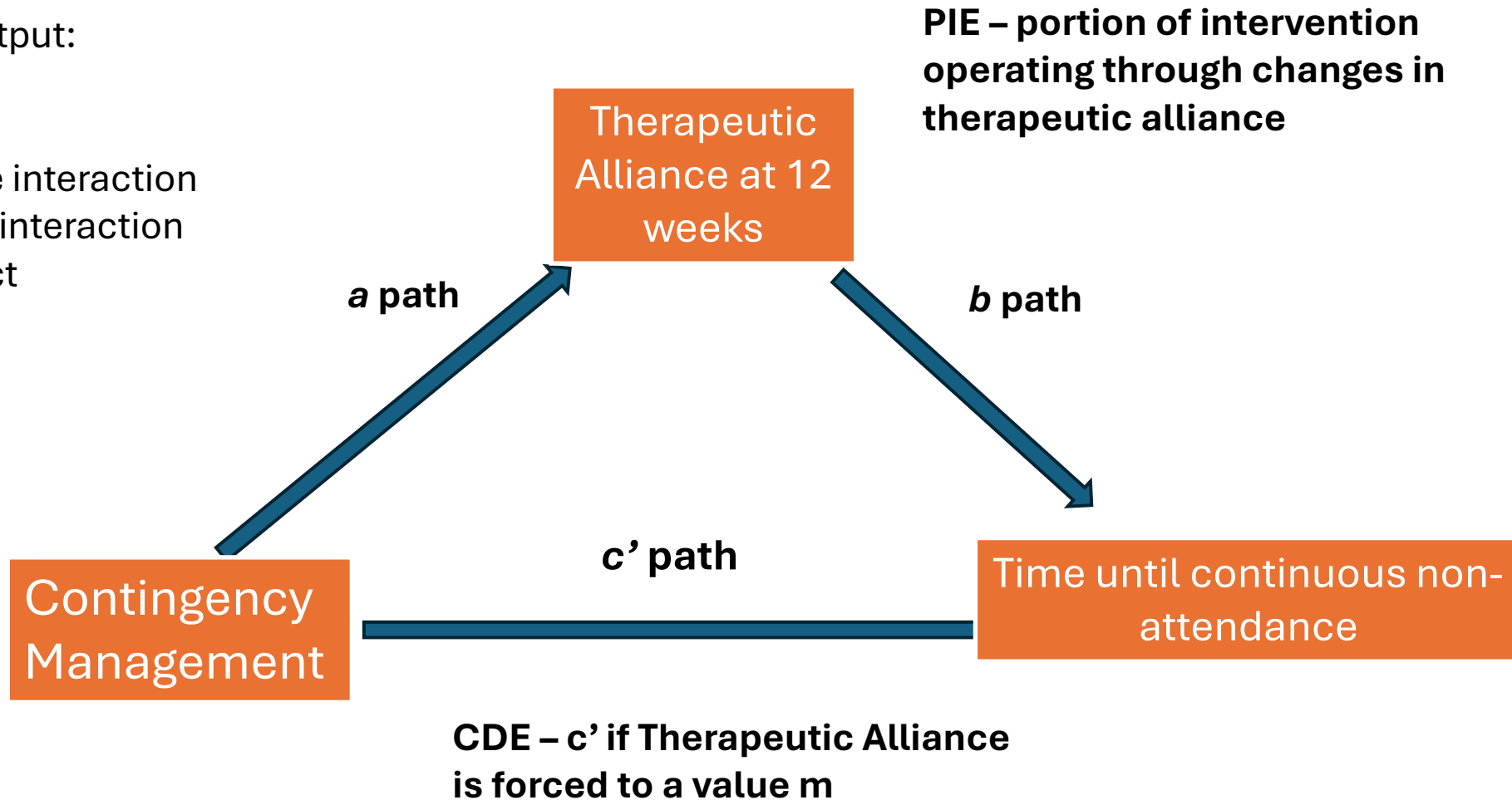
- Can also give Controlled Direct effect (CDE)

My mediation model:

Using causal inference methods:

Med4way output:

- PIE
- CDE
- Reference interaction
- Mediated interaction
- Total effect



Option 1: BOOT MI

