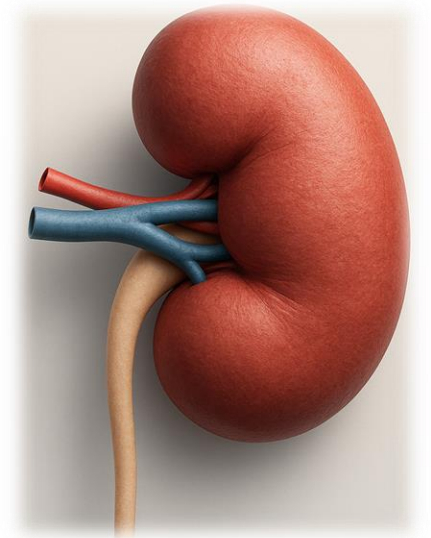


Comparing the efficacy of self-management interventions for chronic kidney disease

A systematic review and component network meta-analysis

Journal Club

16th January, 2026



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Research question



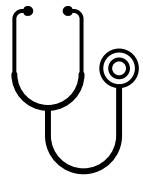
Population

Patients with CKD not receiving renal replacement therapies.



Intervention

Self-management interventions (SMIs).



Comparators

Usual care or other SMIs.



Study design

Systematic review and component network meta-analysis.

Outcomes



❖ Renal function

- eGFR

❖ Modifiable risk factors

- Systolic blood pressure (SBP)
- Diastolic blood pressure (DBP)
- Body mass index (BMI)

❖ Patient-reported outcomes

- Quality of life
- Self-management score
- Self-efficacy score

❖ Long-term clinical outcomes

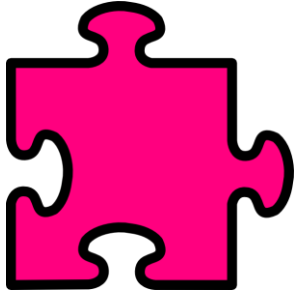
- Risk of death
- Risk of developing ESKD
- Risk of hospitalization
- Risk of initiating renal replacement therapies

Definition of components

SMI components	Definition*
Edu	<u>Education</u> : Providing information and/or skills related to the nature of the disease, CKD self-management behaviors (specifically action plan), and the positive and negative of not adopting health recommendation
Diet	<u>Dietary</u> : Apply the concept of cognitive-behavioral psychology to help patients build the skills necessary to adhere to the treatment and use techniques such as reminders, memory aids, synchronizing therapeutic activities with routine life events, goal-setting, self-monitoring, contracting, skill-building, and rewards to change their dietary behaviors.
PA	<u>Physical activity</u> : Apply the concept of cognitive-behavioral psychology to help patients build the skills necessary to adhere to the treatment and use techniques such as reminders, memory aids, synchronizing therapeutic activities with routine life events, goal-setting, self-monitoring, contracting, skill-building, and rewards to improve the level of physical activity.
Psycho	<u>Psychosocial</u> : Providing support to promote positive beliefs and attitudes toward the treatment such as rapport building through frequent telephone contact, home visits, family-based approaches, and intervention to enhance self-efficacy.

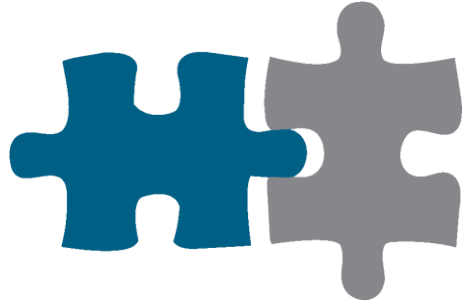
* The definition of SMI components was adapted from Dhippayom et al (2022) (10.1016/j.jaip.2021.09.049). A network meta-analysis of self-management interventions for asthma patients.

Possible SMIs



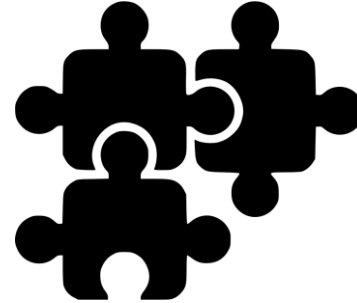
Mono-component SMIs

- Education (Edu)
- Dietary (Diet)
- Physical activity (PA)
- Psychosocial (Psycho)



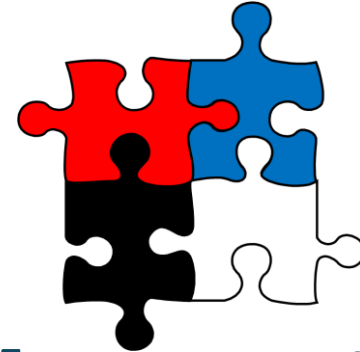
Two-component SMIs

- Edu + Diet
- Edu + PA
- Edu + Psycho
- Diet + PA
- Diet + Psycho
- PA + Psycho



Three-component SMIs

- Edu + Diet + PA
- Edu + Diet + Psycho
- Edu + PA + Psycho
- Diet + PA + Psycho



Four-component SMIs

- Edu + Diet + PA + Psycho

15 self-management interventions

Why CNMA rather than SNMA?

Why CNMA rather than SNMA?

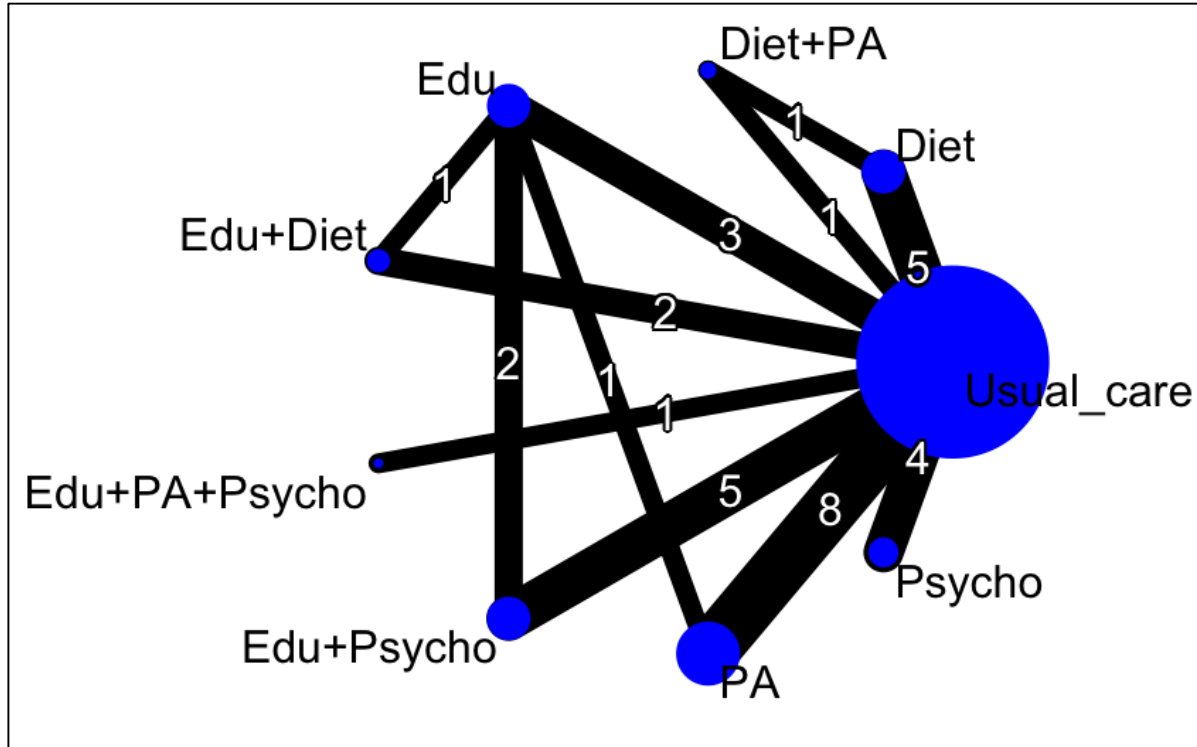


Figure: Network map for eGFR outcome

This network map:

- Sparse network.
- **8 interventions** + usual care.
- 12 direct comparisons.
- PA vs Usual care was the most common.

(Standard) network meta-analysis (SNMA)

Which type of intervention has the greatest probability of being most effective?

Why CNMA rather than SNMA?

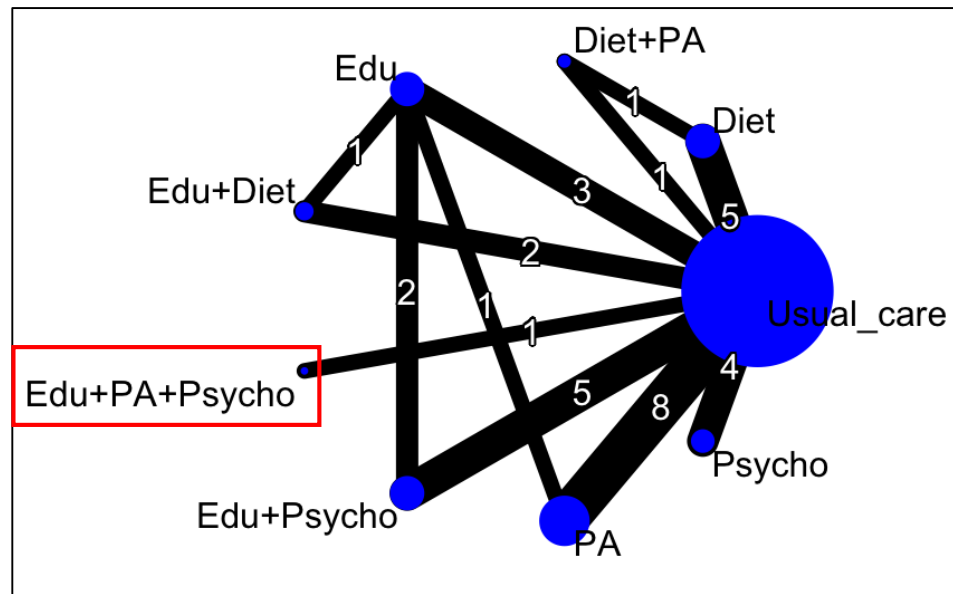


Figure: Network map for eGFR outcome

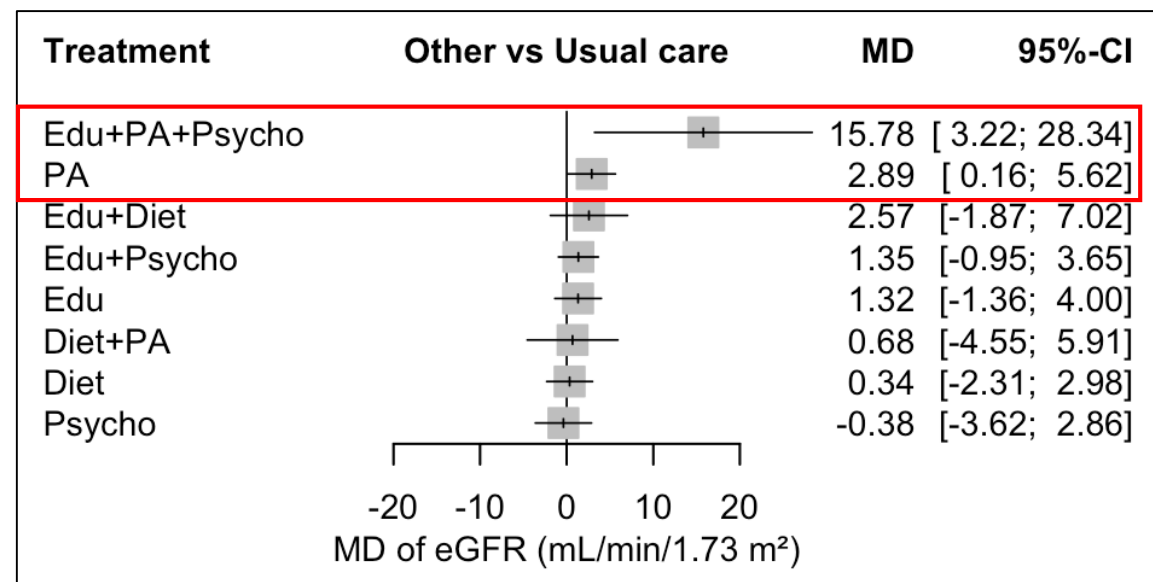


Figure: Forest plot for eGFR outcome (SNMA)

The results of SNMA showed:

- Only **Edu+PA+Psycho** and **PA** significantly improved eGFR compared to **Usual care**.
- Other interventions had no effect on eGFR.
- However, the treatment effect (TE) of **Edu+PA+Psycho** was based on only **one trial** with a very **high TE and wide CI**.



Difficult to interpret and explain the results (even after 2 – 3 team meetings)

Why CNMA rather than SNMA?

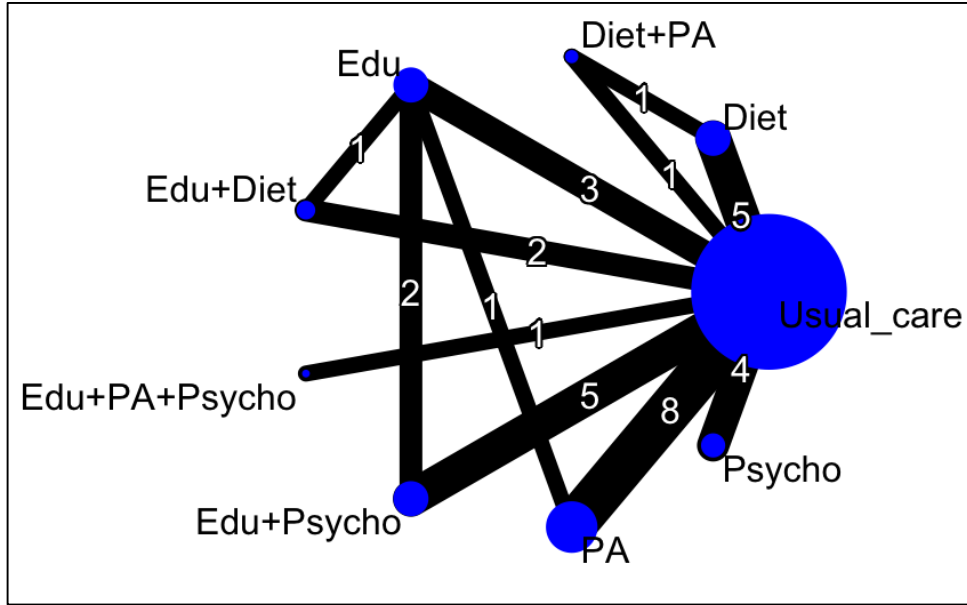


Figure: Network map for eGFR outcome

Component network meta-analysis

1. Which components work?
2. Does adding more components increase the treatment effect?

In addition, this network map also has:

- **8 interventions** + usual care.

- 4 single interventions:

- Education (**Edu**)
- Dietary (**Diet**)
- Physical activity (**PA**)
- Psychosocial (**Psycho**)

- 4 combination interventions:

- Edu+Diet
- Diet+PA
- Edu+Psycho
- Edu+PA+Psycho

**Complex,
multicomponent
interventions**

They shared the common components.

Why CNMA rather than SNMA?

Issues	SNMA	CNMA
Sparse network	<ul style="list-style-type: none">- Each node is considered a unique intervention.- Results may reflect those of single studies in which the intervention's effect is very strong.	<ul style="list-style-type: none">- Unit of analysis: component.- Provides more precise estimates of intervention effects by using evidence from all studies that share the same components.
Unobserved combinations	<ul style="list-style-type: none">- Cannot estimate the TE of unobserved combinations.	<ul style="list-style-type: none">- Can estimate the TE of unobserved combinations.
➔ CNMA is a suitable analytical approach for complex interventions such as SMIs.		

How was the data analysis done in R?
(eGFR outcome)

Model and assumption

- **Model used:** Additive model
- **Assumption:** $d_{\text{SMI (combination)}} = d_{\text{component 1}} + d_{\text{component 2}} (+ \dots + d_{\text{component 4}})$

Components	Treatment effect
Edu	d_{Edu}
Diet	d_{Diet}
PA	d_{PA}
Psycho	d_{Psycho}

Combinations	Treatment effect
Edu+Diet	$= d_{\text{Edu}} + d_{\text{Diet}}$
Edu+PA	$= d_{\text{Edu}} + d_{\text{PA}}$
Edu+Psycho	$= d_{\text{Edu}} + d_{\text{Psycho}}$
Diet+PA	$= d_{\text{Diet}} + d_{\text{PA}}$
Diet+Psycho	$= d_{\text{Diet}} + d_{\text{Psycho}}$
PA+Psycho	$= d_{\text{PA}} + d_{\text{Psycho}}$
Edu+Diet+PA	$= d_{\text{Edu}} + d_{\text{Diet}} + d_{\text{PA}}$
Edu+Diet+Psycho	$= d_{\text{Edu}} + d_{\text{Diet}} + d_{\text{Psycho}}$
Diet+PA+Psycho	$= d_{\text{Diet}} + d_{\text{PA}} + d_{\text{Psycho}}$
Edu+PA+Psycho	$= d_{\text{Edu}} + d_{\text{PA}} + d_{\text{Psycho}}$
Edu+Diet+PA+Psycho	$= d_{\text{Edu}} + d_{\text{Diet}} + d_{\text{PA}} + d_{\text{Psycho}}$

d: Treatment effect

Prepare data

- Data can be prepared in long or wide format:
 - **Long format:** One row = one intervention (one study \geq two rows).
 - Wide format: One row = one study.

study_id	author	year	intervention	n	end_mean	end_sd	mean change	sd change
SMI_039	Hotu	2010	Edu+Psycho	30	33	17	-3	11.47
SMI_039	Hotu	2010	Edu	32	41	18	2	11.92
SMI_018	Chen	2011	Edu+Diet	27	29.11	20.61	1.98	13.65
SMI_018	Chen	2011	Usual_care	27	15.7	10.67	-7.93	8.68
SMI_085	Zuilen	2011	Psycho	395	36.2	16.4	-2.2	11.23
SMI_085	Zuilen	2011	Usual_care	393	35	16.2	-2.7	10.87
SMI_066	Paes-Barreto	2013	Edu+Diet	56	33.7	15.6	1.7	10.43
SMI_066	Paes-Barreto	2013	Usual_care	56	34.1	13.5	0	9.07
SMI_075	Haan	2013	Psycho	99	48.6	8.7	-0.5	5.92
SMI_075	Haan	2013	Usual_care	76	49.4	8	-0.6	5.34
SMI_008	Baria	2014	PA	19	30.16	10.44	2.65	7.25
SMI_008	Baria	2014	Usual_care	10	25.9	14.4	-1.8	10.41
SMI_005	Aoike_2	2015	PA	14	31.9	13.7	3.5	9.16
SMI_005	Aoike_2	2015	Usual_care	14	23.9	12.2	-1.4	9.12
SMI_084	Van Craenenbroeck	2015	PA	25	38.6	14.2	0.74	5.11
SMI_084	Van Craenenbroeck	2015	Usual_care	23	39.2	15.2	-0.33	4.16
SMI_053	Leehey	2016	Diet+PA	18	39.6	19.9	-1.9	13.72
SMI_053	Leehey	2016	Diet	18	35.8	20.2	-3.1	14.32

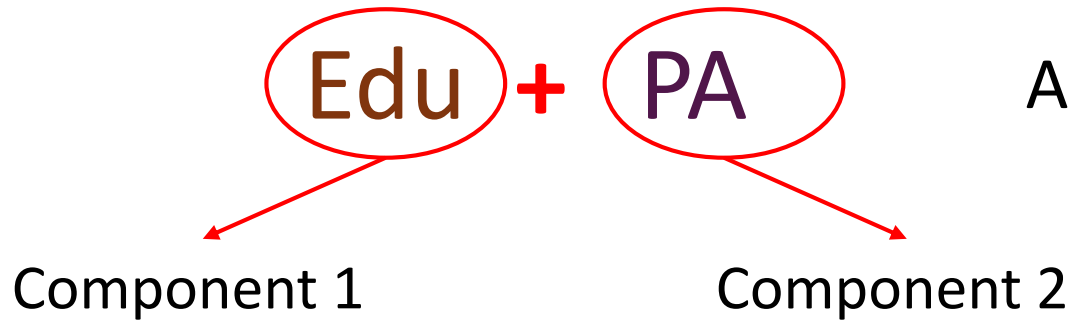
Require information:

- Study ID/author, year
- Intervention/treatment name
- n
- Mean
- SD

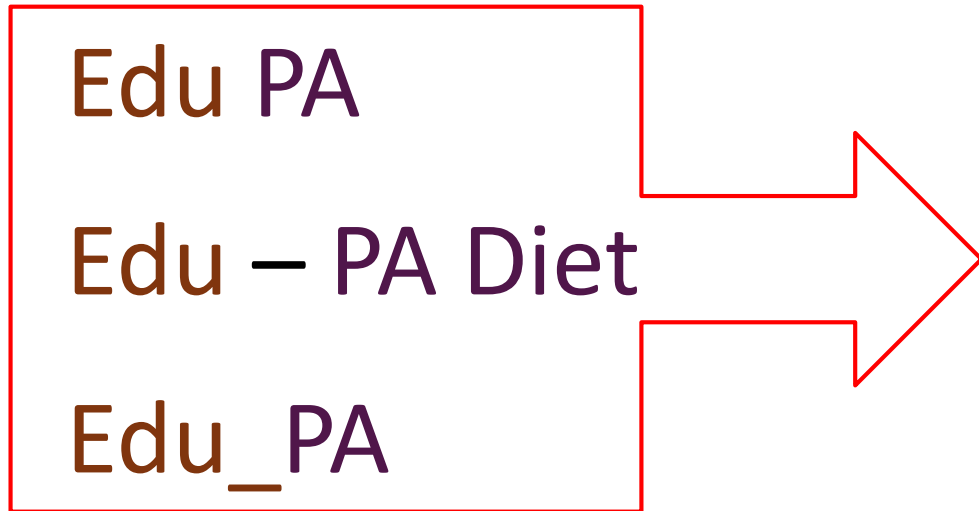
Data can be imported into RStudio from various formats, including Excel, Stata, SAS, SPSS, and text.

Prepare data

Make sure that the components within an intervention are connected by “+”!



A combination of two components



Single intervention (one component)

Packages required

- For the **import dataset**:
 - haven (for Stata, SPSS, SAS files)
 - readxl (for Excel files)
- For **data analysis**:
 - meta (draw forest plots from NMA)
 - netmeta (for CNMA)
- For **data visualization**:
 - ggplot2
 - grid
- **Others**: dplyr (data manipulation), stringr.

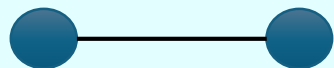
Steps of analysis



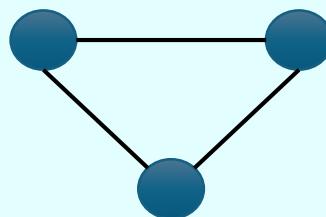
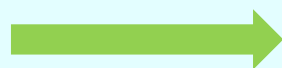
Studio®

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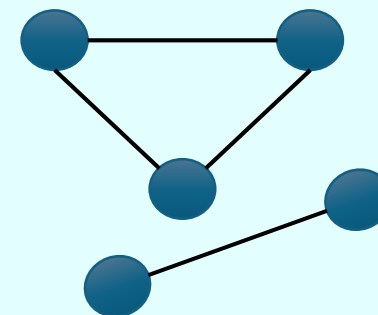
netmeta



**Pair-wise
meta-analysis**



**Standard network meta-
analysis**



**Component network meta-
analysis**

Steps of analysis

1. Pair-wise meta-analysis

```
pw_eGFR <- pairwise(studlab = study_id, treat = intervention, n =  
n, mean = end_mean, sd = end_sd, data = SMIs_for_CKD_eGFR_End, sm =  
"MD", common = FALSE)
```

=> Prepare data for SNMA.

2. Standard network meta-analysis

```
netSMI_eGFR <- netmeta(pw_eGFR, ref = "Usual_care", common = FALSE)
```

Steps of analysis

2. Standard network meta-analysis

Treatment estimate (sm = 'MD', comparison: other treatments vs 'Usual_care'):

	MD	95%-CI	z	p-value
Diet	0.3376	[-2.3056; 2.9808]	0.25	0.8023
Diet+PA	0.6766	[-4.5522; 5.9054]	0.25	0.7998
Edu	1.3164	[-1.3632; 3.9960]	0.96	0.3356
Edu+Diet	2.5730	[-1.8709; 7.0168]	1.13	0.2565
Edu+PA+Psycho	15.7800	[3.2202; 28.3398]	2.46	0.0138
Edu+Psycho	1.3499	[-0.9519; 3.6517]	1.15	0.2504
PA	2.8916	[0.1600; 5.6233]	2.07	0.0380
Psycho	-0.3766	[-3.6154; 2.8623]	-0.23	0.8197
Usual_care

Quantifying heterogeneity / inconsistency:

$\tau^2 = 4.9121$; $\tau = 2.2163$; $I^2 = 52.8\%$ [26.2%; 69.8%]

Tests of heterogeneity (within designs) and inconsistency (between designs):

	Q	d.f.	p-value
Total	52.98	25	0.0009
Within designs	40.14	19	0.0031
Between designs	12.84	6	0.0457

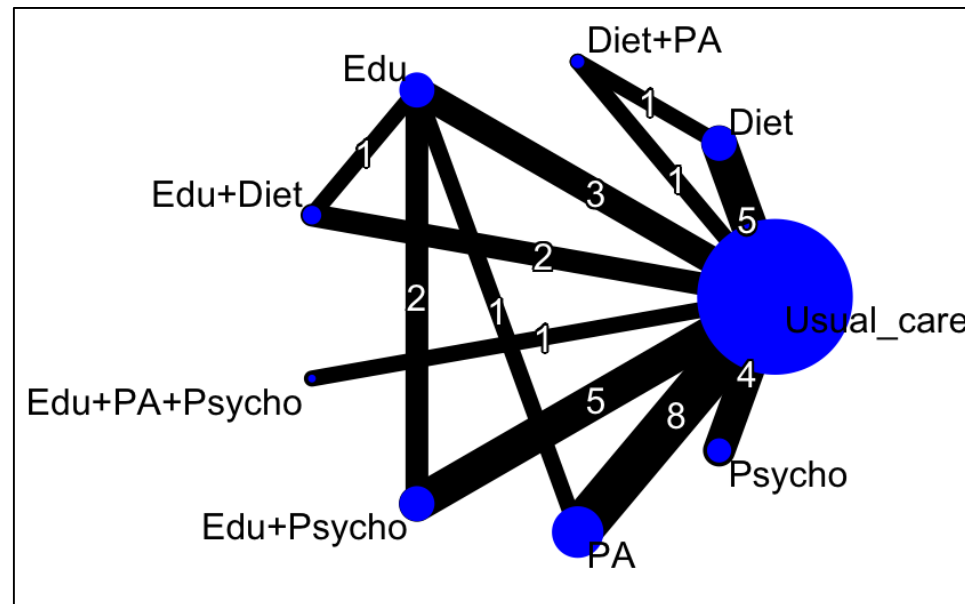


Figure: Network map for eGFR outcome

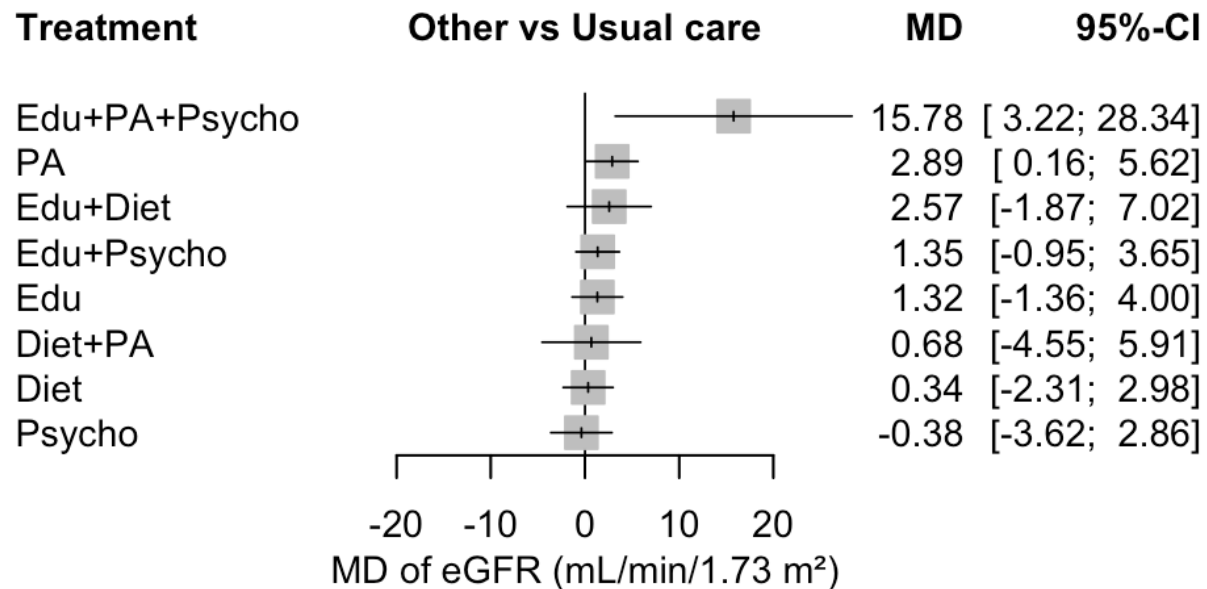


Figure: Forest plot for eGFR outcome (SNMA)

Steps of analysis

3. Component network meta-analysis

- Connected network => netcomb
- ```
cnma_eGFR <- netcomb(netSMI_eGFR, inactive =
"Usual_care", component = TRUE, add=FALSE)
```

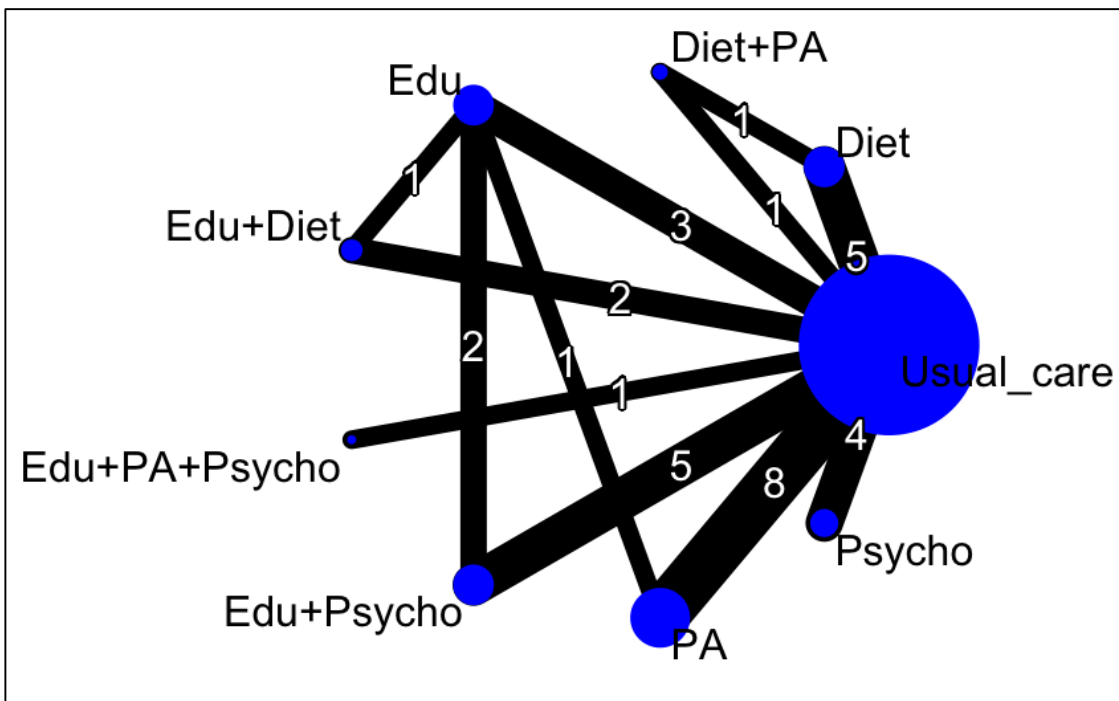


Figure: Network map for eGFR outcome

Incremental effect for existing combinations:

|               | iMD    | 95%-CI            | z    | p-value |
|---------------|--------|-------------------|------|---------|
| Diet+PA       | 2.9919 | [ 0.1424; 5.8414] | 2.06 | 0.0396  |
| Edu+Diet      | 1.8422 | [-0.9229; 4.6073] | 1.31 | 0.1916  |
| Edu+PA+Psycho | 4.4365 | [ 1.2748; 7.5982] | 2.75 | 0.0060  |
| Edu+Psycho    | 1.6308 | [-0.3732; 3.6348] | 1.59 | 0.1107  |

Incremental effect for components:

|        | iMD     | 95%-CI            | z     | p-value |
|--------|---------|-------------------|-------|---------|
| Diet   | 0.1862  | [-1.9064; 2.2788] | 0.17  | 0.8616  |
| Edu    | 1.6560  | [-0.5288; 3.8408] | 1.49  | 0.1374  |
| PA     | 2.8057  | [ 0.4608; 5.1506] | 2.35  | 0.0190  |
| Psycho | -0.0252 | [-2.1351; 2.0847] | -0.02 | 0.9813  |

Quantifying heterogeneity / inconsistency:

$\tau^2 = 4.3121$ ;  $\tau = 2.0766$ ;  $I^2 = 51.9\%$  [26.9%; 68.3%]

Heterogeneity statistics:

|                | Q     | df | p-value |
|----------------|-------|----|---------|
| Additive model | 60.27 | 29 | 0.0006  |
| Standard model | 52.98 | 25 | 0.0009  |
| Difference     | 7.29  | 4  | 0.1214  |

# Steps of analysis

## 3. Component network meta-analysis

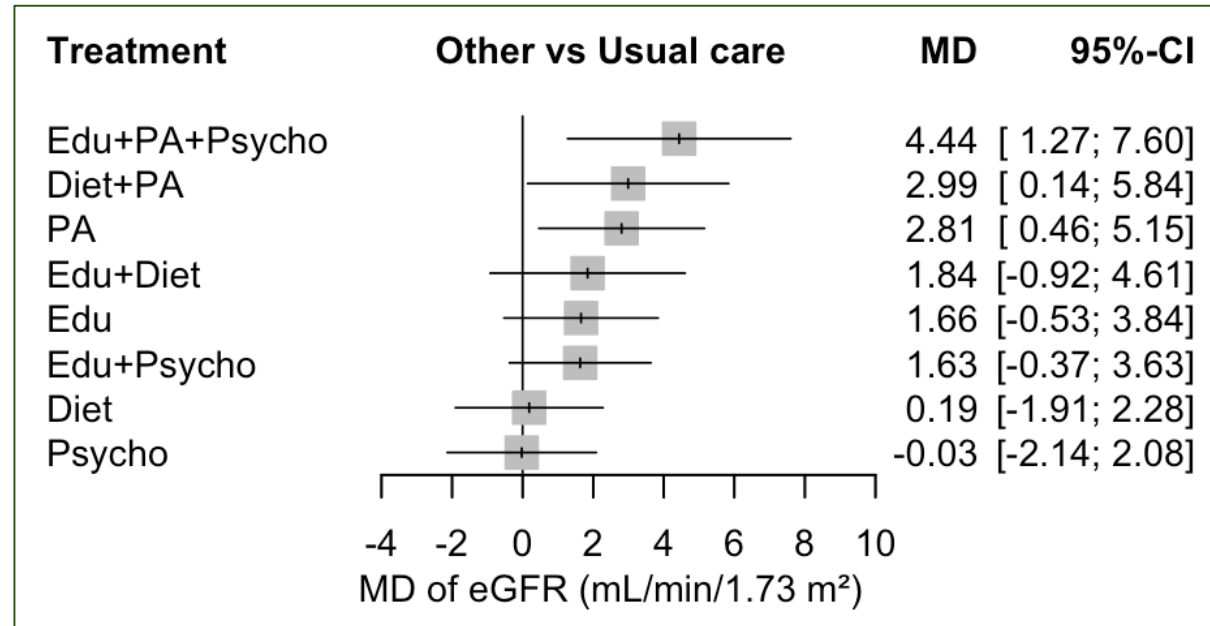


Figure: Forest plot for eGFR outcome (CNMA)

Results of **observed** monocomponents and combinations (**8** out of 15 interventions).

### 3. Component network meta-analysis

| Interventions      | Observed from trials?               |
|--------------------|-------------------------------------|
| Edu                | <input checked="" type="checkbox"/> |
| Diet               | <input checked="" type="checkbox"/> |
| PA                 | <input checked="" type="checkbox"/> |
| Psycho             | <input checked="" type="checkbox"/> |
| Edu+Diet           | <input checked="" type="checkbox"/> |
| Edu+PA             | <input type="checkbox"/>            |
| Edu+Psycho         | <input checked="" type="checkbox"/> |
| Diet+PA            | <input checked="" type="checkbox"/> |
| Diet+Psycho        | <input type="checkbox"/>            |
| PA+Psycho          | <input type="checkbox"/>            |
| Edu+Diet+PA        | <input type="checkbox"/>            |
| Edu+Diet+Psycho    | <input type="checkbox"/>            |
| Diet+PA+Psycho     | <input type="checkbox"/>            |
| Edu+PA+Psycho      | <input checked="" type="checkbox"/> |
| Edu+Diet+PA+Psycho | <input type="checkbox"/>            |

#### Identify unobserved combinations

```
unobserved_comb_name <- c("Diet+Psycho",
"Edu+PA", "PA+Psycho", "Edu+Diet+PA",
"Edu+Diet+Psycho", "Diet+PA+Psycho",
"Edu+Diet+PA+Psycho")
```

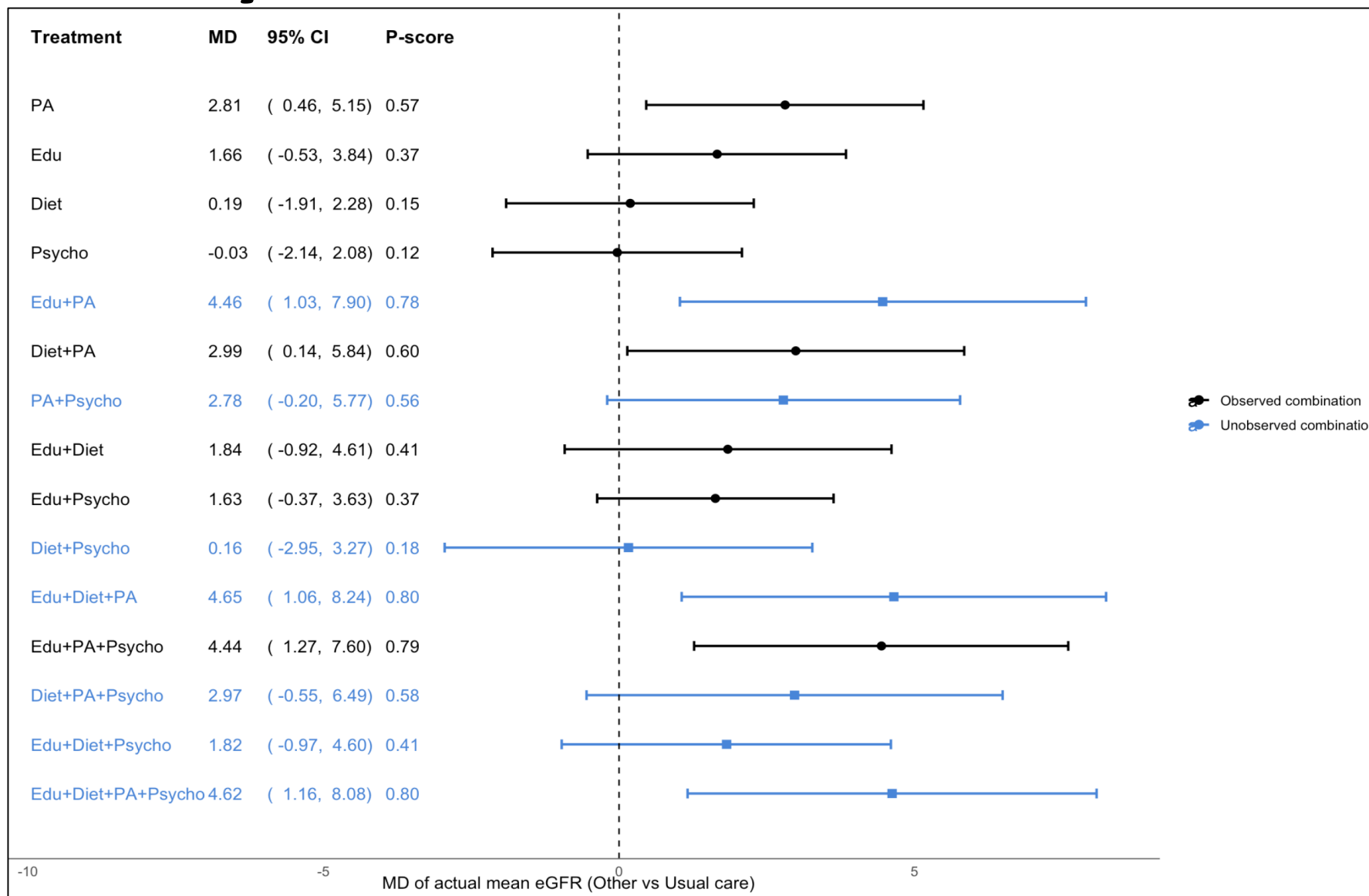
#### Estimate TEs of unobserved combinations

```
cnma_unobserved_eGFRend <-
netcomplex(cnma_eGFR, unobserved_comb_name)
```

**Combine the results of observed and unobserved interventions.**

# Steps of analysis

## 3. Component network meta-analysis



**Figure:** Forest plot of all interventions for eGFR outcome (CNMA)

**How to interpret the results?**

# Interpret the results

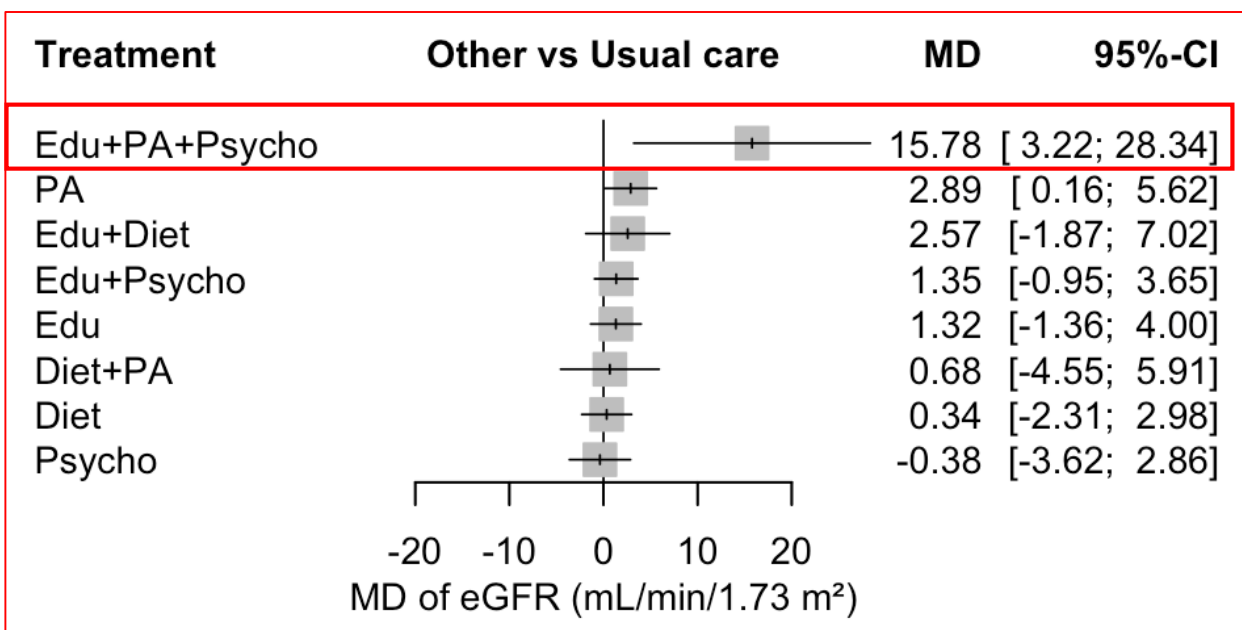


Figure: Forest plot for eGFR outcome (**SNMA**)

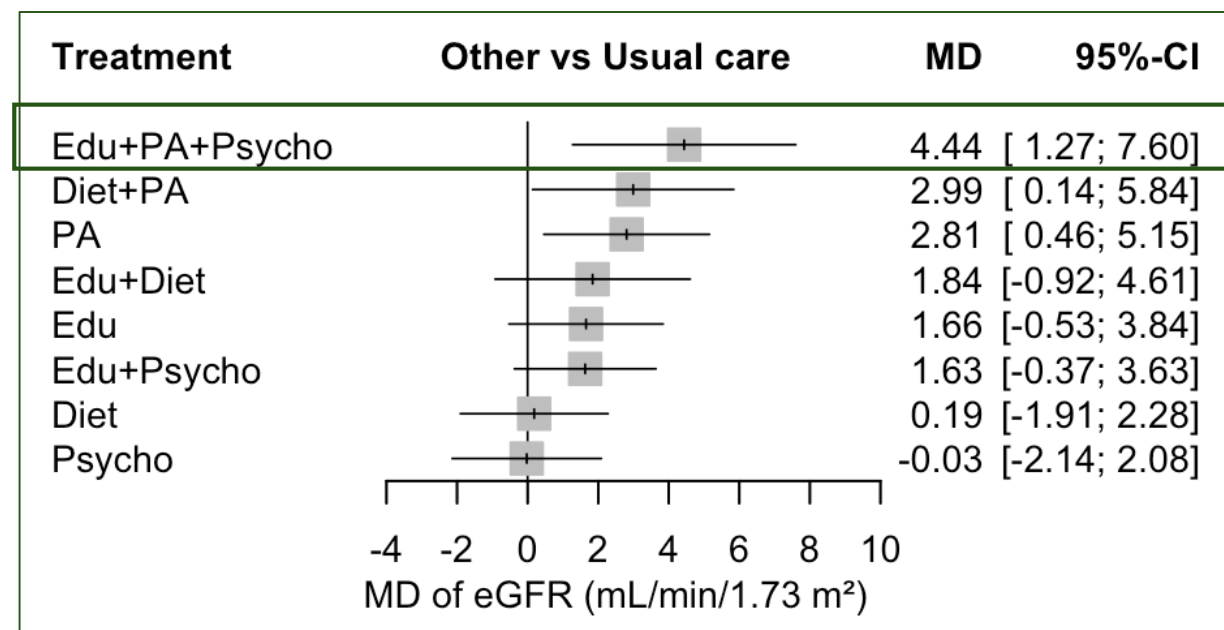


Figure: Forest plot for eGFR outcome (**CNMA**)

- TE of Edu+PA+Psycho **reduced** from 15.78 (SNMA) to 4.44 (CNMA) with a **narrower 95% CI** (1.27; 7.60).
  - The CIs from CNMA were narrower than those from SNMA.
  - In addition to Edu+PA+Psycho and PA, CNMA showed that Diet+PA significantly improved eGFR compared with Usual care.
- ➔ CNMA provided **more precise** and **explainable** results

# Interpret the results

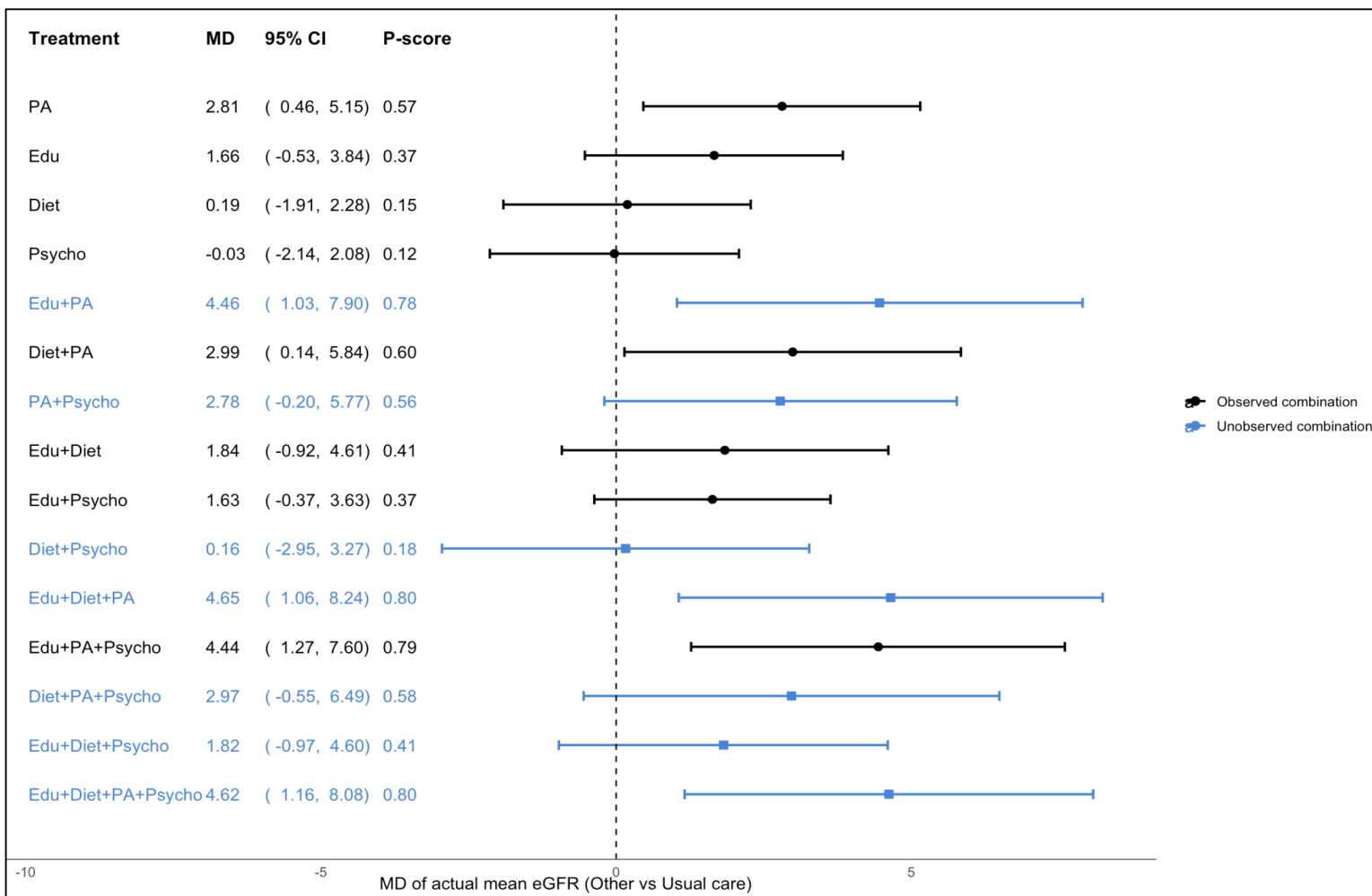


Figure: Forest plot of all SMIs for eGFR outcome (CNMA)

- PA was the only mono-component SMI that significantly improved eGFR.

## Among two-component SMIs:

- Adding Edu and Diet to PA increased the TE compared with Edu+PA alone.

## Among three-component SMIs:

- Adding Diet to Edu+PA also increased the TE compared with Edu+PA alone.
- Adding Psycho to Edu+PA and Edu+Diet+PA did not yield any additional effect.

**Additional outcomes**

# Systolic blood pressure (SBP)

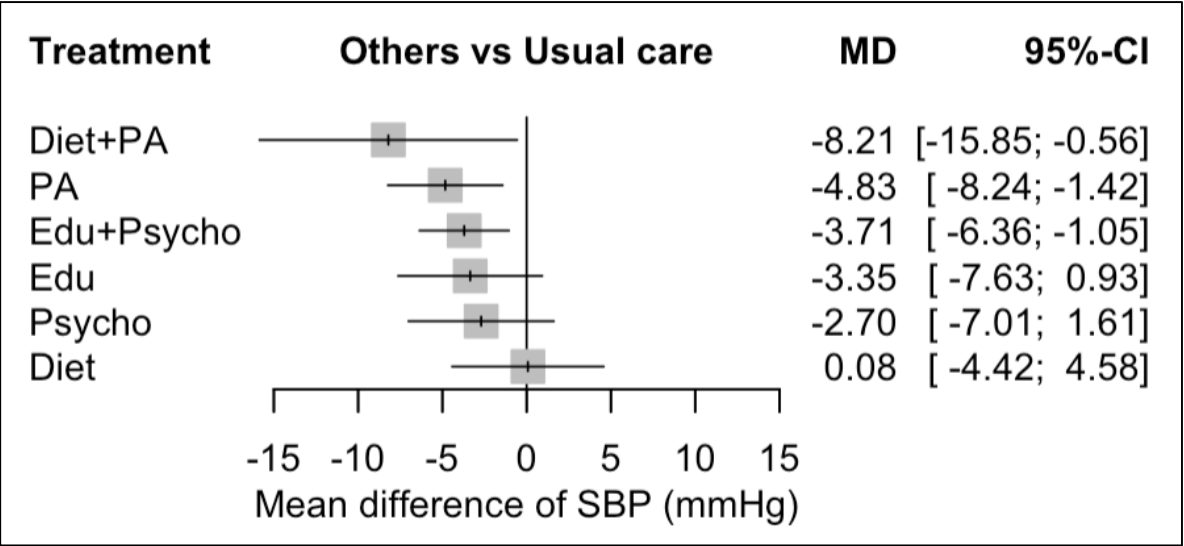
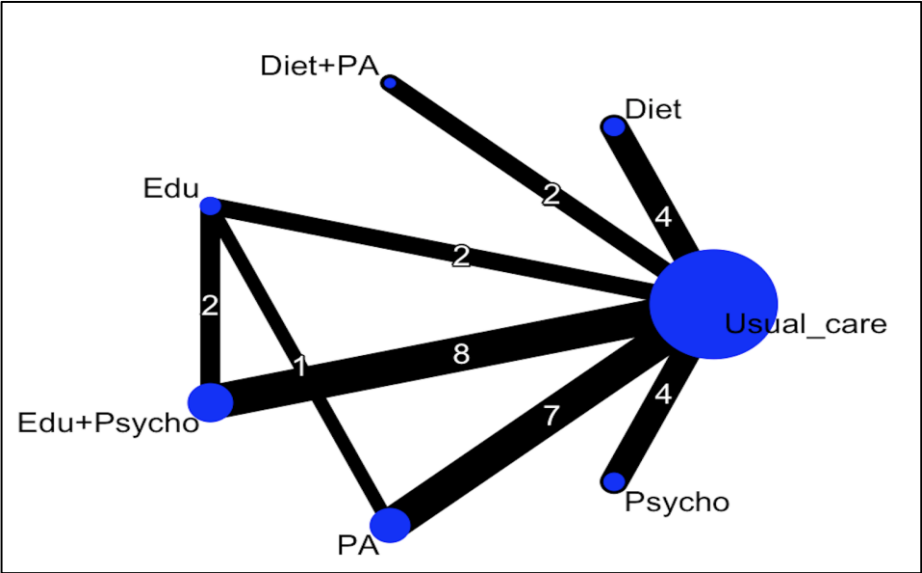


Figure: Forest plot for SBP outcome (SNMA)

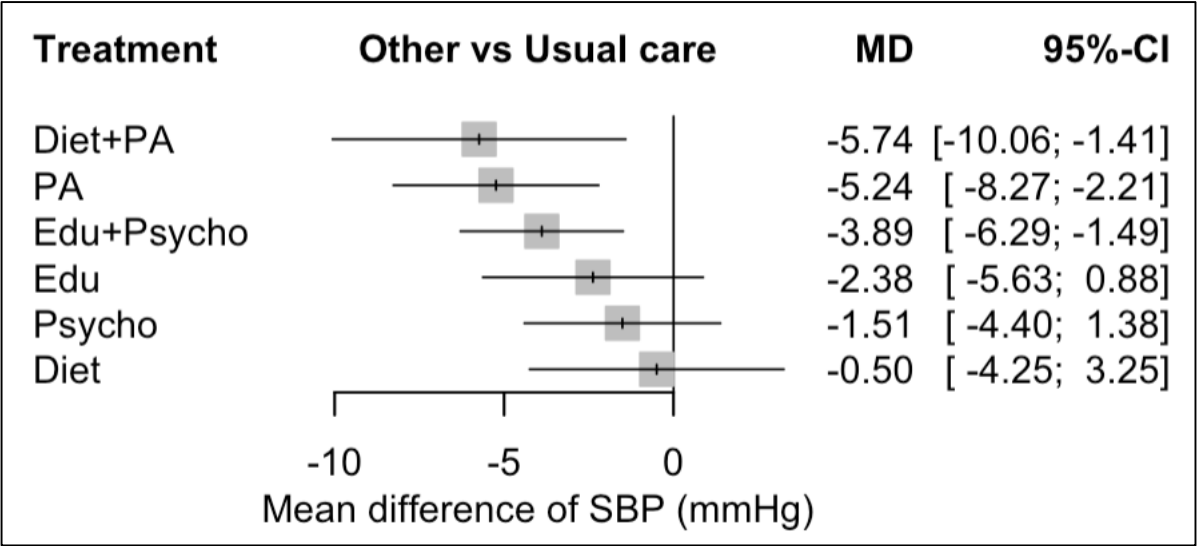


Figure: Forest plot for SBP outcome (CNMA)

# Systolic blood pressure (SBP)

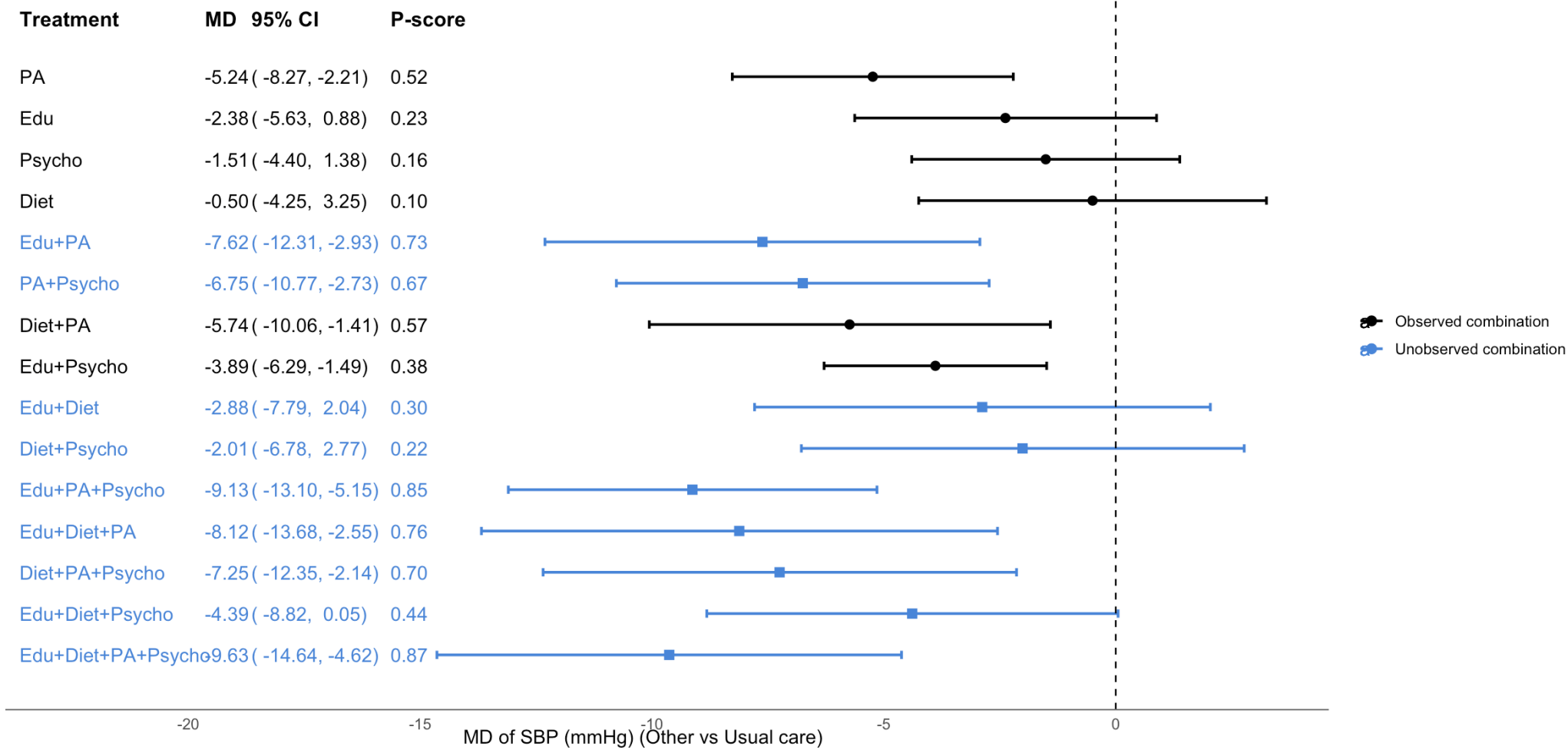


Figure: Forest plot of all SMIs for SBP outcome (CNMA)

# Diastolic blood pressure (DBP)

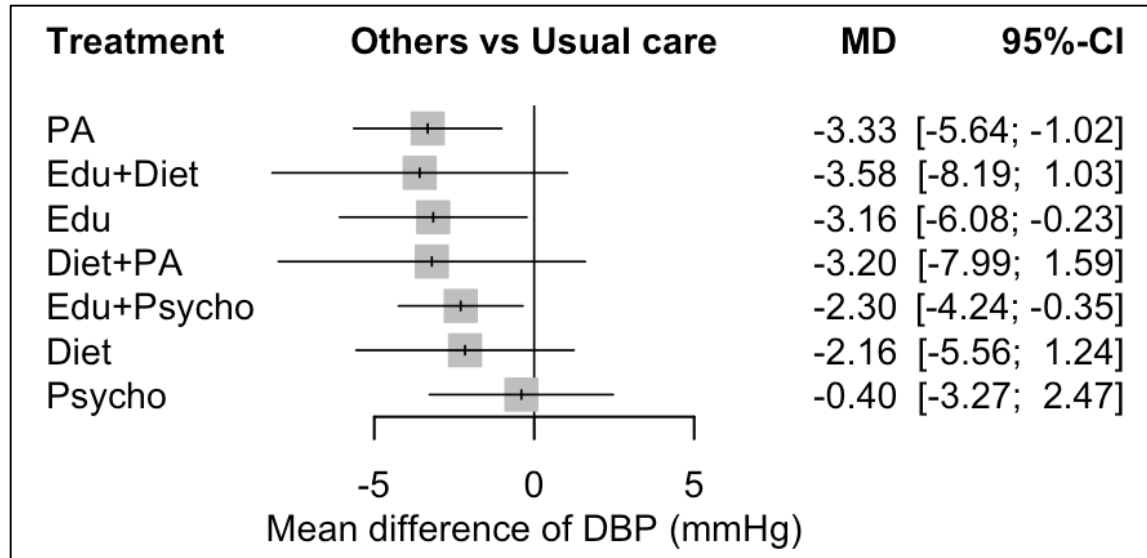
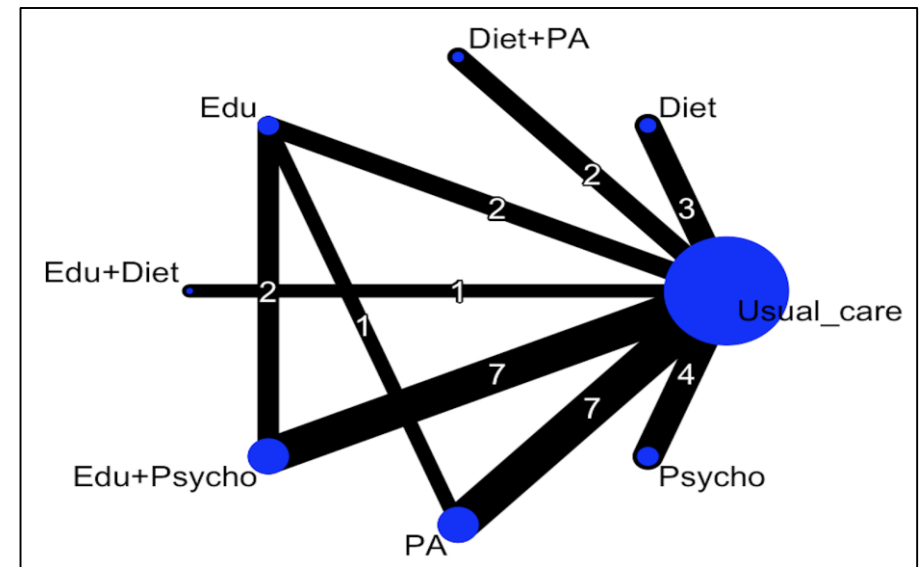


Figure: Forest plot for DBP outcome (SNMA)

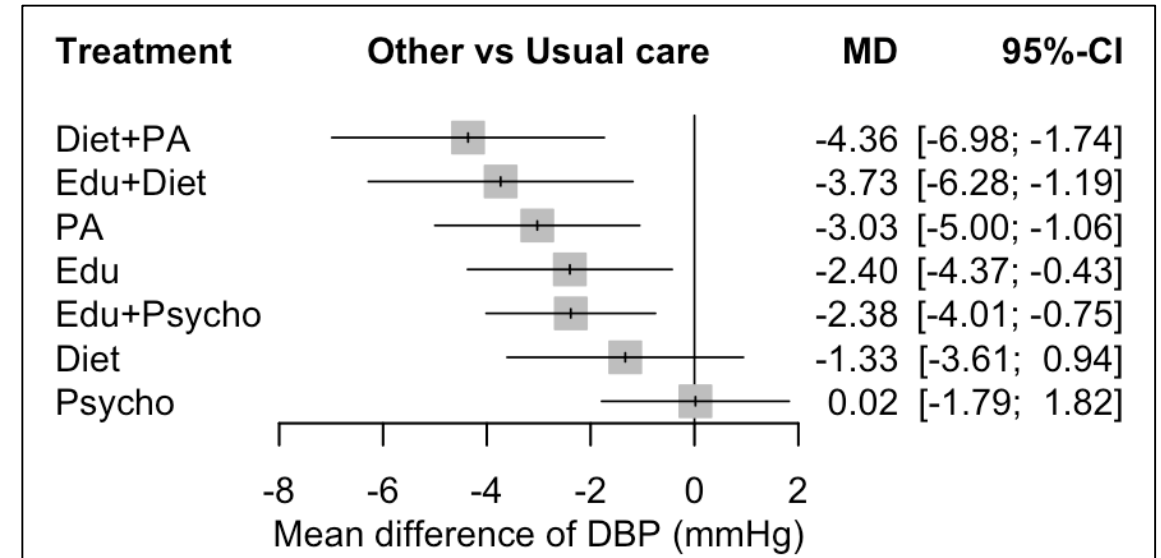
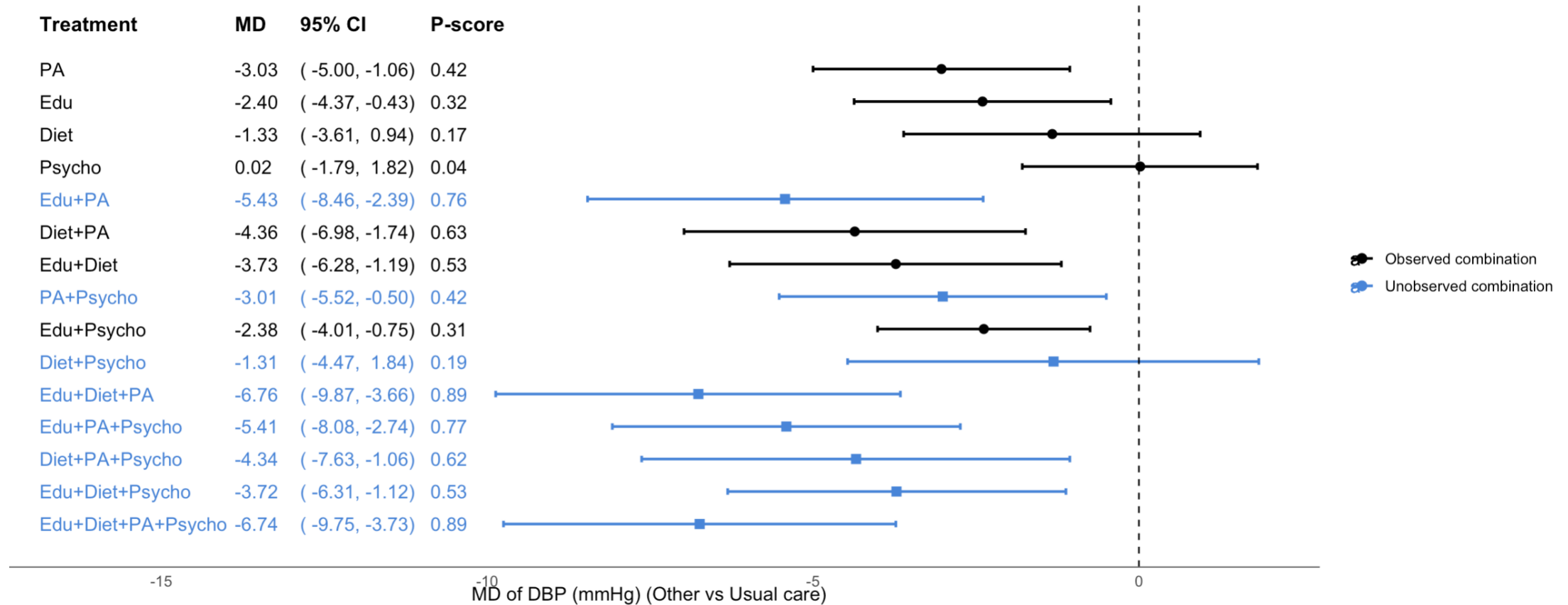


Figure: Forest plot for DBP outcome (CNMA)

# Diastolic blood pressure (DBP)



**Figure:** Forest plot of all SMIs for DBP outcome (CNMA)

# Checking additive assumption

| Outcomes | Q (df) (Heterogeneity statistics) |                       |                        |
|----------|-----------------------------------|-----------------------|------------------------|
|          | CNMA (Additive model)             | SNMA (Standard model) | Difference             |
| eGFR     | 60.27 (29)                        | 52.98 (25)            | 7.29 (4)<br>p = 0.1214 |
| SBP      | 58.54 (25)                        | 55.99 (23)            | 2.56 (2)<br>p = 0.2783 |
| DBP      | 70.68 (24)                        | 62.20 (21)            | 8.47 (3)<br>p = 0.0372 |

# For more information

1. Tsokani S, Seitidis G, Mavridis D. Component network meta-analysis in a nutshell. *BMJ Evid Based Med*. 2023 Jun;28(3):183-186. doi: 10.1136/bmjebm-2021-111906. Epub 2022 Jul 27. PMID: 35896417.
2. Welton NJ, Caldwell DM, Adamopoulos E, Vedhara K. Mixed treatment comparison meta-analysis of complex interventions: psychological interventions in coronary heart disease. *Am J Epidemiol*. 2009 May 1;169(9):1158-65. doi: 10.1093/aje/kwp014. Epub 2009 Mar 3. PMID: 19258485.
3. Rücker G, Schwarzer G. Reduce dimension or reduce weights? Comparing two approaches to multi-arm studies in network meta-analysis. *Stat Med*. 2014 Nov 10;33(25):4353-69. doi: 10.1002/sim.6236. Epub 2014 Jun 18. PMID: 24942211.
4. Rücker G, Petropoulou M, Schwarzer G. Network meta-analysis of multicomponent interventions. *Biom J*. 2020 May;62(3):808-821. doi: 10.1002/bimj.201800167. Epub 2019 Apr 25. PMID: 31021449; PMCID: PMC7217213.
5. Petropoulou M, Rücker G, Weibel S, Kranke P, Schwarzer G. Model selection for component network meta-analysis in connected and disconnected networks: a simulation study. *BMC Med Res Methodol*. 2023 Jun 14;23(1):140. doi: 10.1186/s12874-023-01959-9. PMID: 37316775; PMCID: PMC10268445.

**Thank you for your attention!**

**Discussion**