Relative efficacy of prehabilitation interventions and their components: systematic review with network and component network meta-analyses of randomised controlled trials

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Introduction

- >300 million surgeries performed worldwide each year
- 20% of surgical patients
  - Postoperative complications
  - Impaired functional recovery
- **Prehabilitation**
  - a process undertaken in advance of surgery to actively preparing patients for surgery
    - which has the specific intent of improving an individual's functional, physiologic, cognitive and/or mental health status through targeted interventions.

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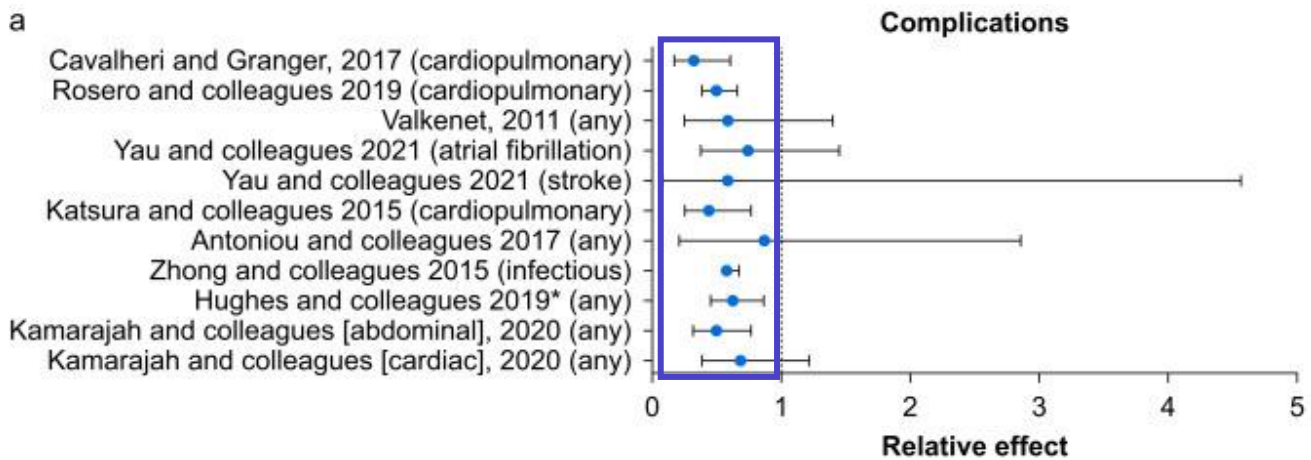
Review Article

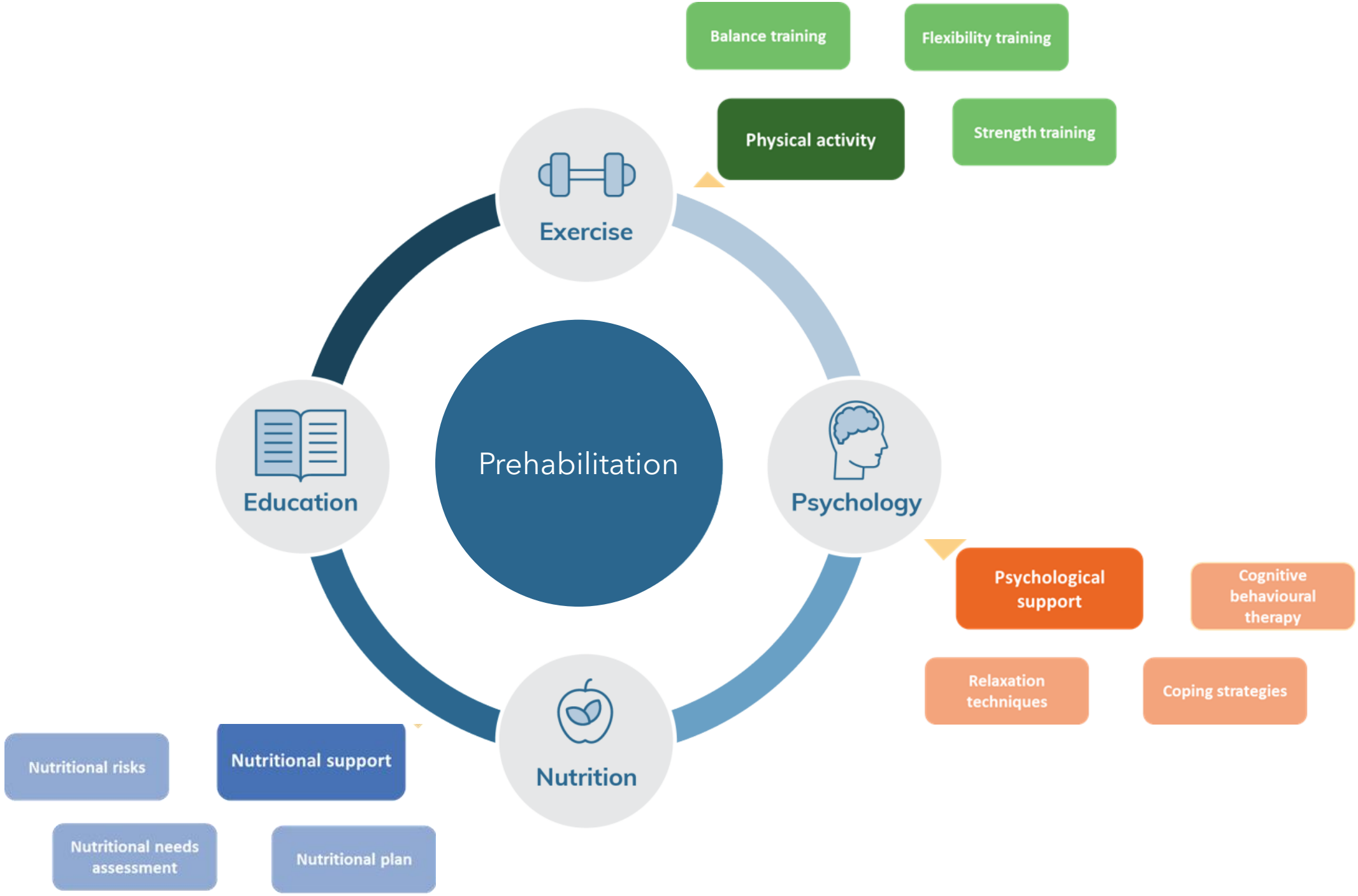
CLINICAL PRACTICE

Prehabilitation in adult patients undergoing surgery: an umbrella review of systematic reviews

Daniel I. McIsaac[1,2,3,*,†], Marlyn Gill[4], Laura Boland[5], Brian Hutton[1,3], Karina Branje[1,2], Julia Shaw[1,2], Alexa L. Grudzinski[1], Natasha Barone[6], Chelsia Gillis[7] on behalf of the Prehabilitation Knowledge Network[‡]



Prehabilitation may have protective effects in reducing complications


Balance training
Flexibility training
Physical activity
Strength training
Exercise
Education
Prehabilitation
Psychology
Psychological support
Cognitive behavioural therapy
Relaxation techniques
Coping strategies
Nutrition
Nutritional risks
Nutritional support
Nutritional needs assessment
Nutritional plan

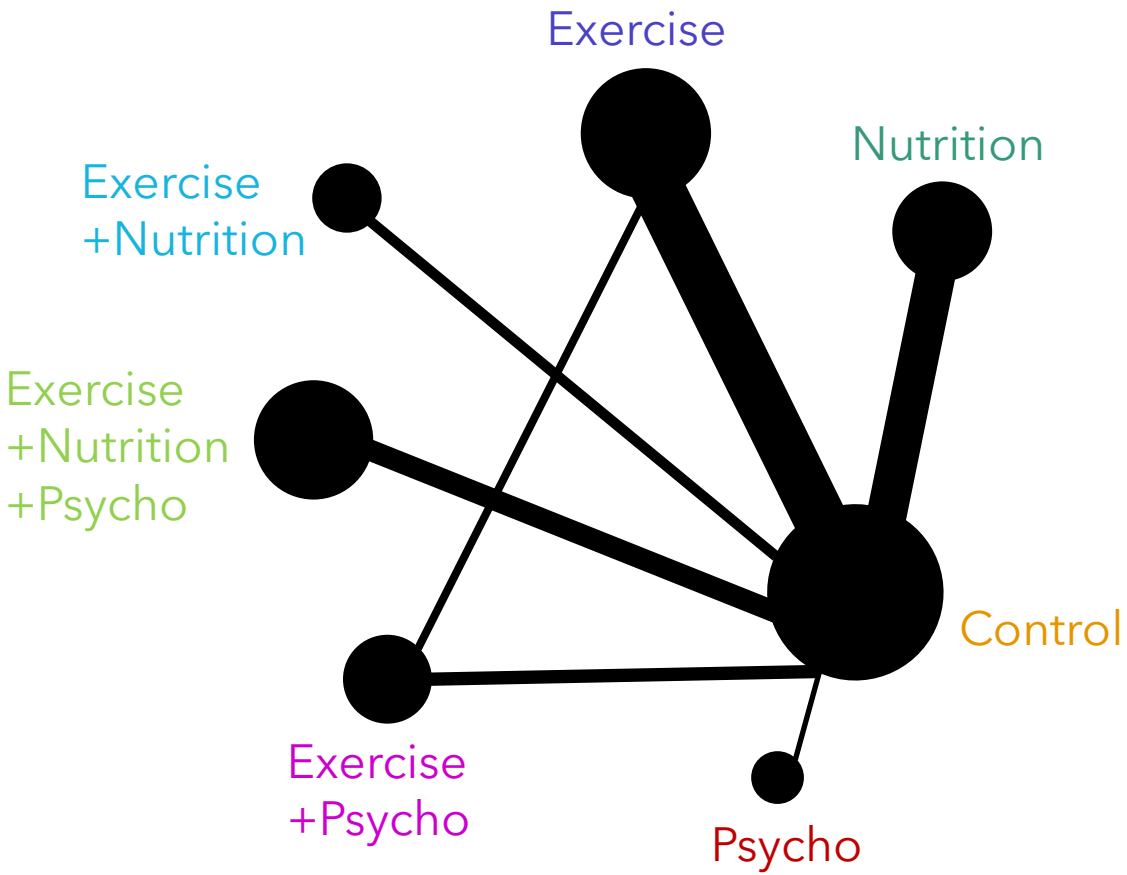
Previous reviews

Single prehabilitation

Year	Author		P	I	C
2018	Maemelo et al	SRMA	Patients undergoing non-urgent cardiovascular surgical intervention	Exercise prehabilitation	Standard care
2022	Falz et al	SRMA	Patients who have received surgical therapy of colon and rectal cancer	Exercise prehabilitation	Standard care
2023	Clifford et al	SRMA	Adults undergoing major surgery	Exercise prehabilitation (HIIT)	Standard care
2019	Hughes et al	SRMA	Patients undergoing major abdominal surgery	Exercise ± Nutrition prehabilitation	Standard care
2023	Punnoose et al	SRMA	Patients undergoing orthopedic surgery	Multimodal prehabilitation	Standard care
2025	Wang et al	SR**NMA**	Patients undergoing digestive system cancer surgery	Nutritional prehabilitation Exercise prehabilitation Psychosocial prehabilitation Multimodal prehabilitation	Standard care

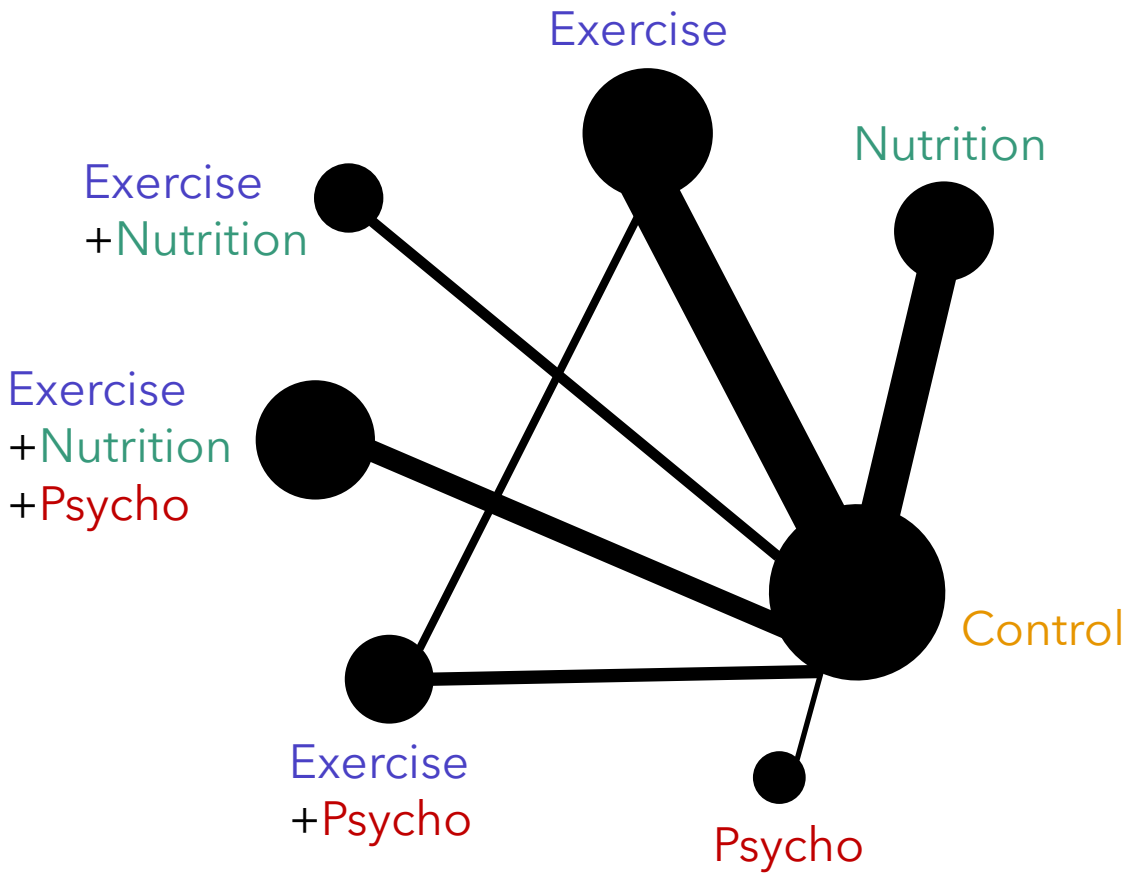
Multimodal prehabilitation
(pool heterogeneous interventions together)

Standard NMA



Compare multiple interventions
Which <u>intervention</u> work?

Component NMA



Decomposition of multicomponent intervention
Which <u>component</u> work?

Standard NMA

Exercise + Nutrition
Exercise + Nutrition + Psycho
Exercise
Nutrition
Exercise + Psycho
Psycho
Control

Intervention effects

Component NMA

Exercise
Nutrition
Psycho
Control

Component effects

Rationale

- Previous reviews typically estimate one effect for
  - a single prehabilitation
  - pool heterogeneous interventions together
    - Lack of clarity regarding which components, or combination of components, are efficacious in improving critical outcomes
- **Standard NMA** allow estimation of separate effects for specific combinations of components
  - not align with the multicomponent nature of prehabilitation interventions
- **Component NMA** (cNMA) allow estimation of separate effects for individual components

Objective

- To estimate the relative efficacy of different prehabilitation components
- To identify which prehabilitation components and combinations of components were most likely to improve critical postoperative outcomes in adults preparing for surgery

PICO

P	Adults preparing for major elective surgery
I	Prehabilitation interventions
C	Usual care
O	Primary: Postoperative complications Secondary: Length of stay, HRQoL, Physical recovery
S	RCT

Search strategy

- 7 Databases
  - Ovid
  - Medline
  - Embase
  - CINAHL
  - PsycINFO
  - Web of Science
  - Cochrane CENTRAL Register of Controlled Trials
- Until 25 October 2023

Criteria

Inclusion criteria

- Adults (>18 years) undergoing elective surgery
- Prehabilitation intervention
  - vs comparator intervention
  - vs standard care
- RCT

Exclusion criteria

- Studies that evaluated isolated preoperative risk factor management
- Prehabilitation intervention was for fewer than seven days

Intervention

- No universal definition of prehabilitation exists
- Define based on descriptions of prehabilitation provided in the literature
  - **Exercise**
    - eg, aerobic, strength or flexibility focused interventions
  - **Nutrition**
    - eg, advice, supplementation or other interventions to improve oral or enteral macro or micronutrient intake
  - **Cognitive**
    - eg, interventions to improve or maintain cognitive function
  - **Psychosocial**
    - eg, interventions to improve mood, affect or motivation
  - **Multimodal intervention**
- No limitations on duration, location or supervisory approaches

Outcome

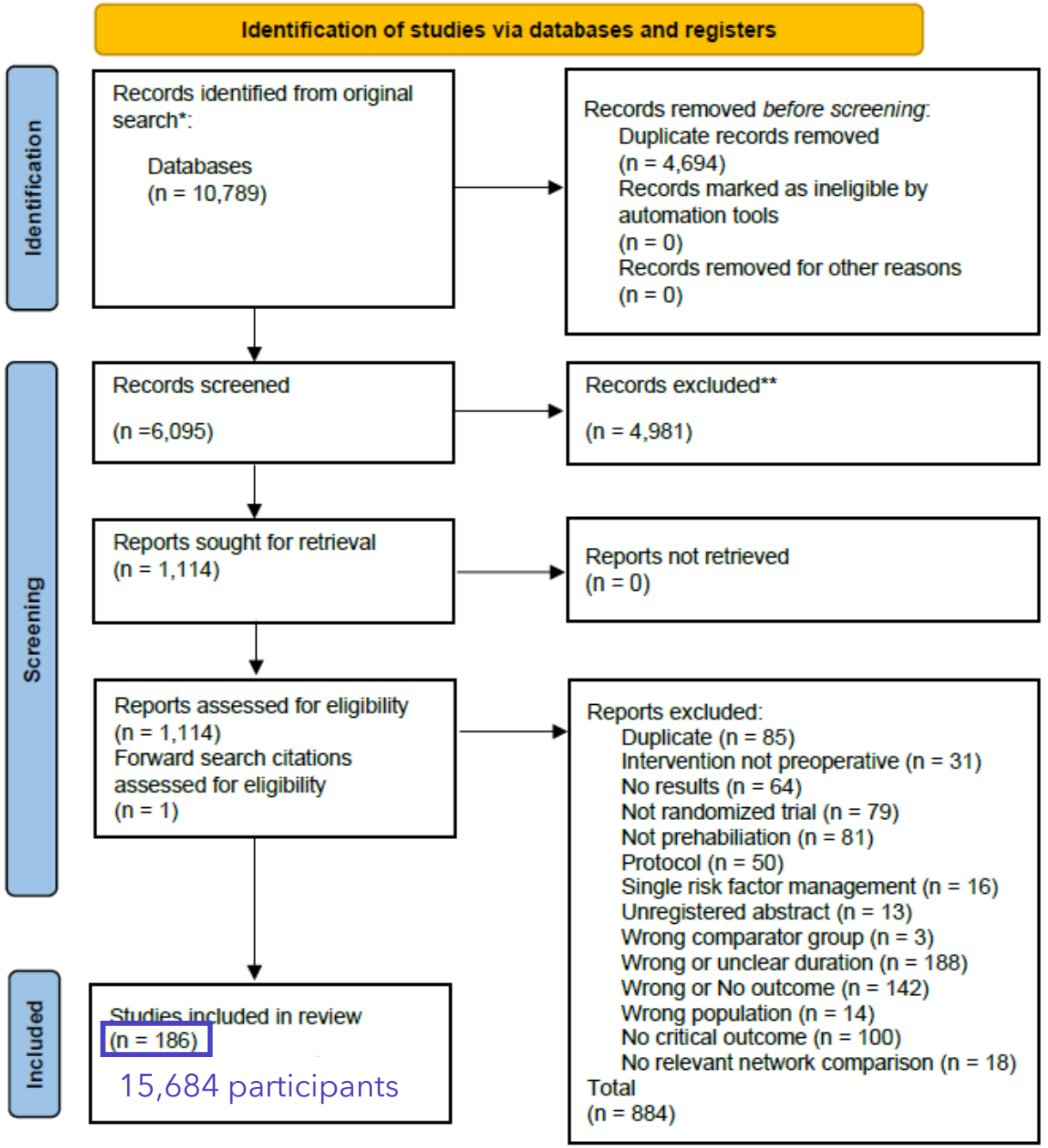
- Postoperative complications *- Binary*
- Length of hospital stay (LOS) *- Continuous*
- Health related quality of life (HRQoL) *- Continuous*
- Physical recovery *- Continuous*

Data syntheses and analyses

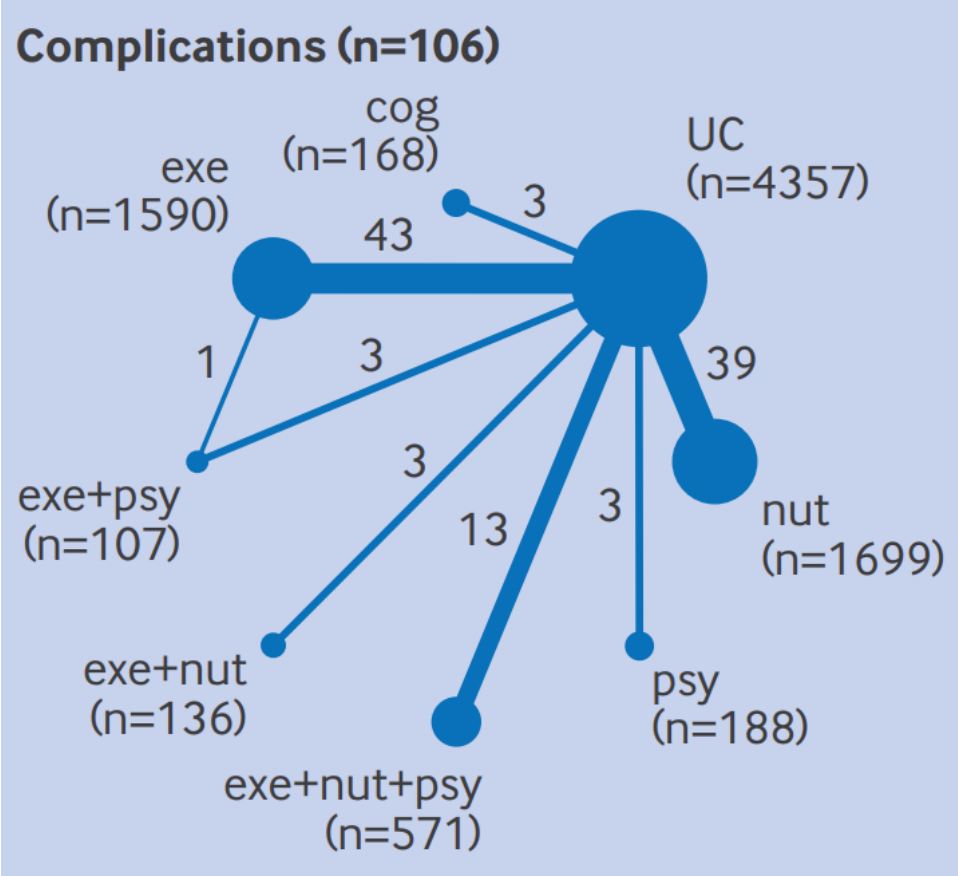
- **Standard NMA** or Treatment level NMA
- **Component NMA** (cNMA)
- Frequentist random-effects network meta-analysis models
- All analyses were performed in R statistical software

Data syntheses and analyses

Network connectivity	Network diagram
Transitivity	Box plot
Consistency	Global test (design-by-treatment interaction test) Local test (comparison of direct and indirect treatment effect)
Heterogeneity	Calculate I^2, Estimate τ^2 (between-study variance) *Explore evidence of heterogeneity by network meta-regression*
Treatment ranking	P score
Small study effect (Publication bias)	Contour-enhanced funnel plot
Sensitivity analysis	Restriction of NMAs to studies judged to be at overall low risk of bias


Identification of studies via databases and registers
Identification
Records identified from original search*:
Databases
(n = 10,789)
Records removed *before screening*:
Duplicate records removed
(n = 4,694)
Records marked as ineligible by automation tools
(n = 0)
Records removed for other reasons
(n = 0)
Screening
Records screened
(n =6,095)
Records excluded**
(n = 4,981)
Reports sought for retrieval
(n = 1,114)
Reports not retrieved
(n = 0)
Reports assessed for eligibility
(n = 1,114)
Forward search citations assessed for eligibility
(n = 1)
Reports excluded:
Duplicate (n = 85)
Intervention not preoperative (n = 31)
No results (n = 64)
Not randomized trial (n = 79)
Not prehabiliation (n = 81)
Protocol (n = 50)
Single risk factor management (n = 16)
Unregistered abstract (n = 13)
Wrong comparator group (n = 3)
Wrong or unclear duration (n = 188)
Wrong or No outcome (n = 142)
Wrong population (n = 14)
No critical outcome (n = 100)
No relevant network comparison (n = 18)
Total
(n = 884)
Included
Studies included in review
(n = 186)
15,684 participants

Outcome: **Complication**

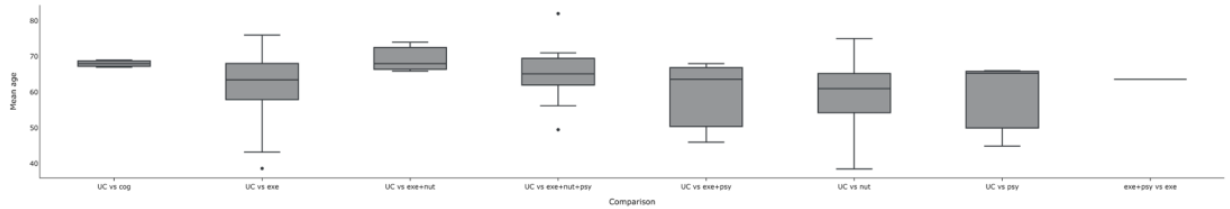


Consistency assumption

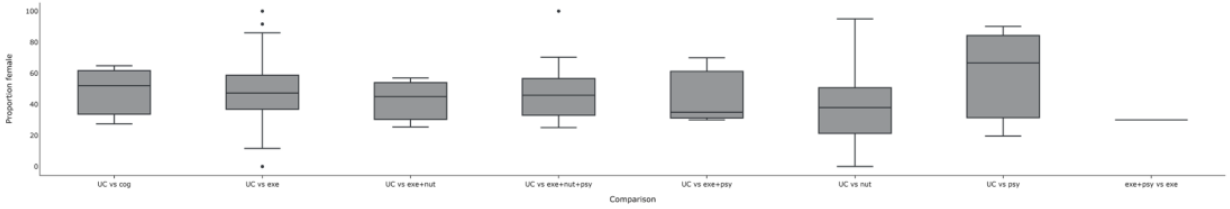
- No inconsistency was observed in the NMA globally (design-by-treatment interaction model: p = 0.18)

Outcome: **Complication**

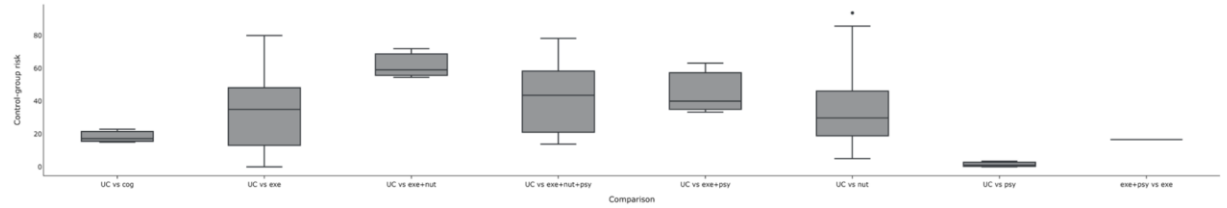
Age



% Female



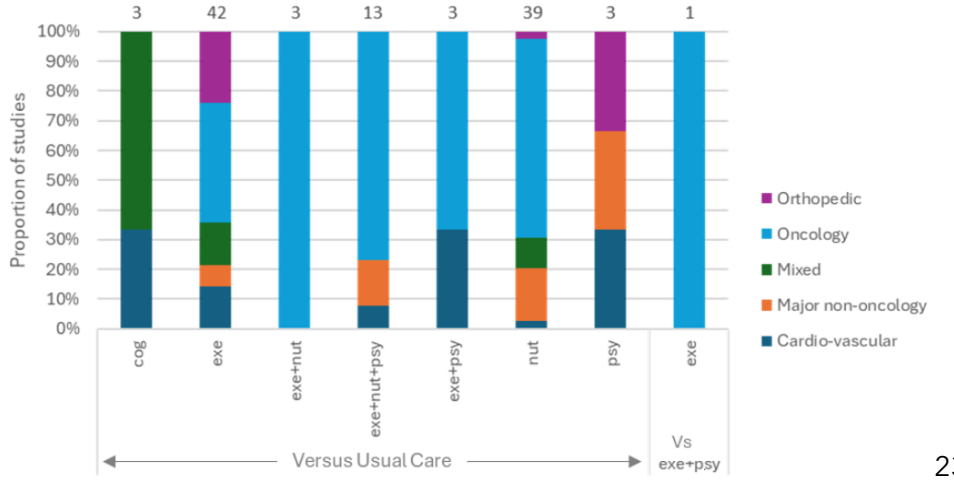
Control group risk



Transitivity assumption

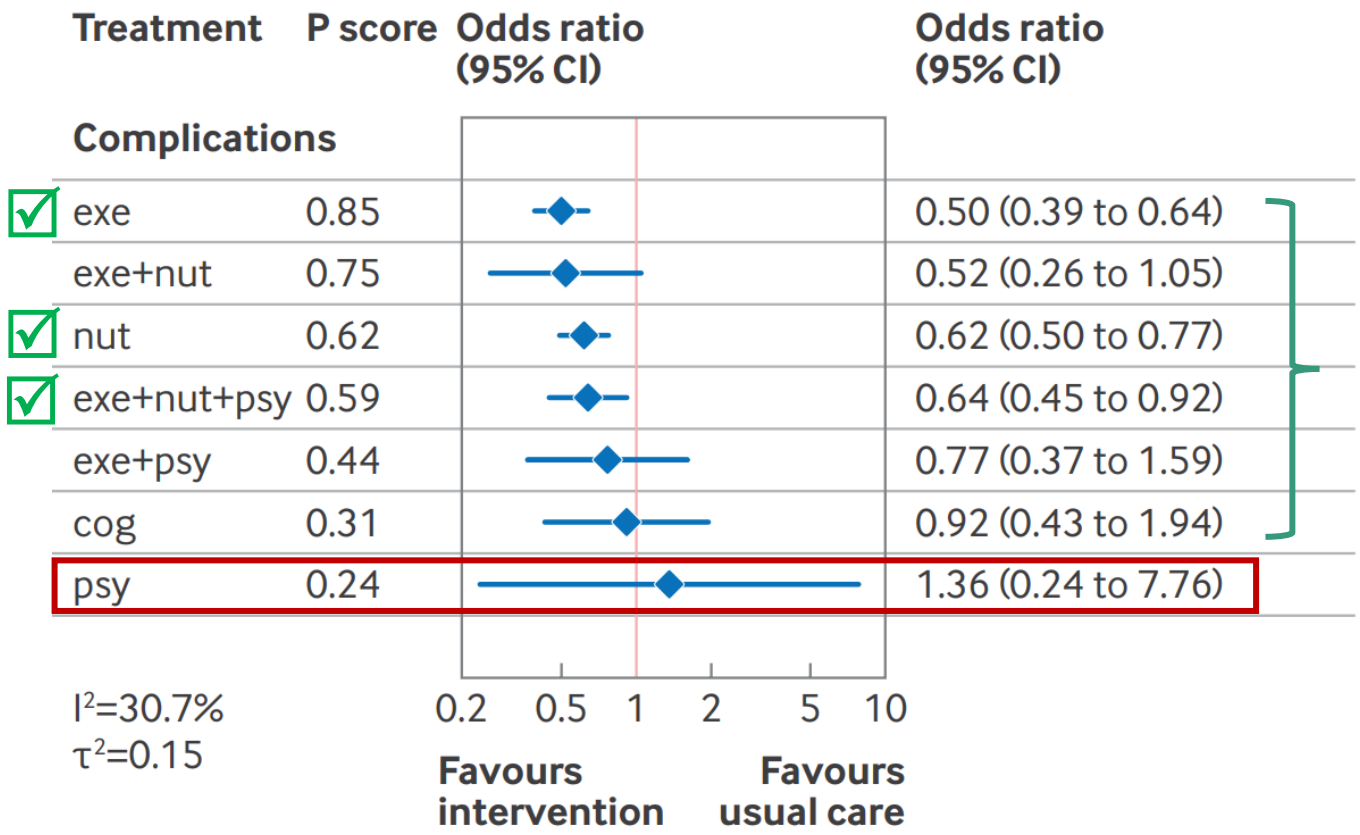
- Minor difference
- Some variability

Surgery type



Outcome: **Complication**

Treatment level NMA (standard NMA)



Directionally **reduced the odds of complications** compared with usual care

Isolated psychosocial prehabilitation

Outcome: **Complication**

Component NMA

Test the additive assumption

by comparing the difference in Cochrane's Q-statistics of the additive cNMA model and the standard NMA model

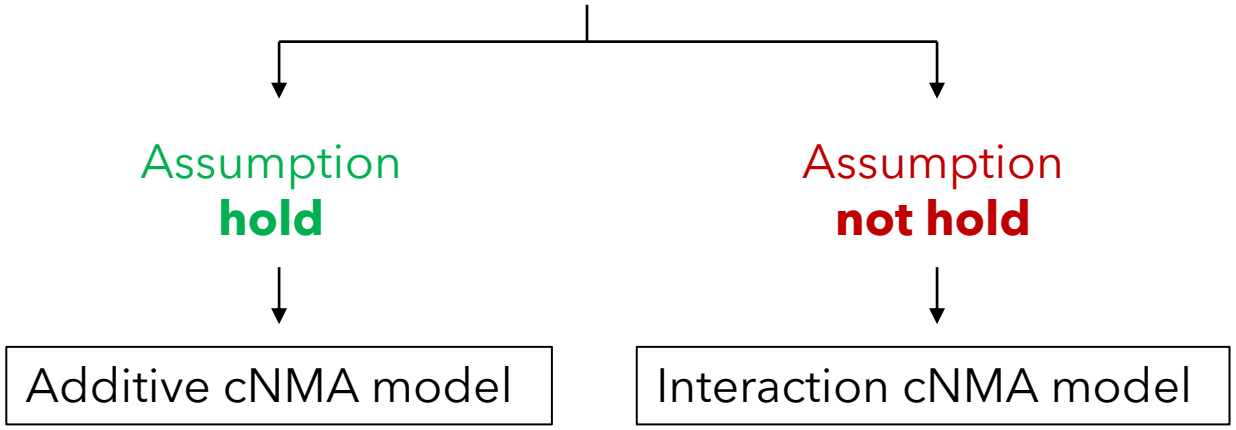
Model	Model statistics		Difference with Standard NMA		
	Q-statistic	df	Q_{diff}	df_{diff}	p-value$_{diff}$*
Standard NMA	144.20	100			
Additive cNMA model	147.72	103	3.52	3	0.3182

The additive assumption **holds** because the p-value of the difference in Q-statistics between the additive and standard NMA models is > 0.1116

Outcome: **Complication**

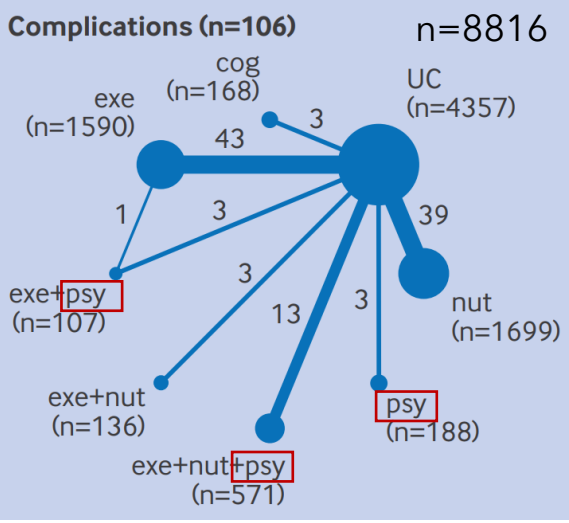
Component NMA

Test the additive assumption
by comparing the difference in Cochrane's Q-statistics of the additive cNMA model and the standard NMA model



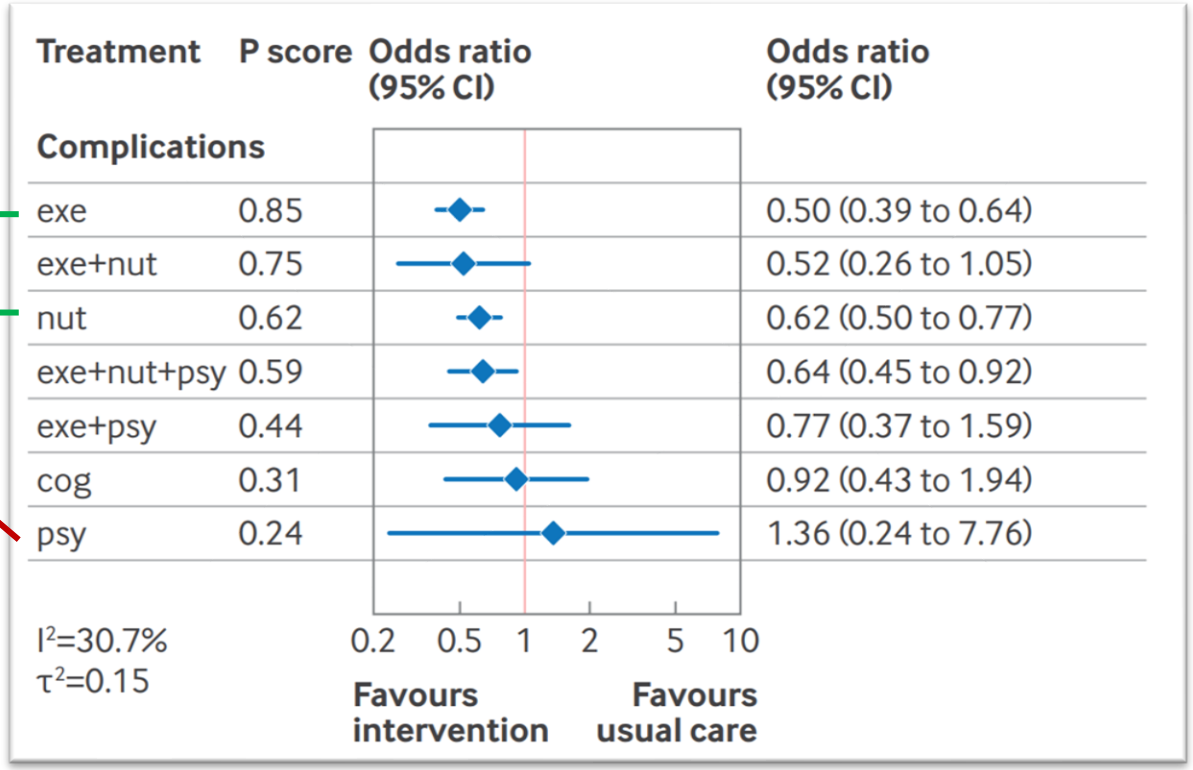
Outcome: **Complication**

Component NMA – *Additive cNMA analysis*



	Component	OR (95% CI)
☑	Exercise	0.53 (0.42 to 0.66)
☑	Nutrition	0.66 (0.54 to 0.81)
☑	Psychosocial	1.75 (1.17 to 2.61)
	Cognitive	0.91 (0.43 to 1.92)

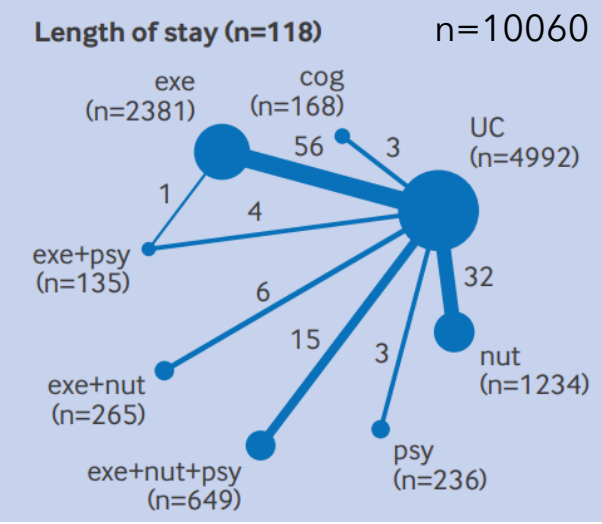
Standard NMA



More precise intervention effects
(use evidence from all studies that share the same component)

Outcome: **Length of stay**

Treatment level NMA (standard NMA)



Treatment	P score	Mean difference (95% CI)	Mean difference (95% CI)
Length of stay			
☑ exe+psy	0.97		-2.44 (-3.85 to -1.04)
exe+nut	0.71		-1.22 (-2.54 to 0.10)
☑ nut	0.67		-0.99 (-1.49 to -0.48)
☑ exe	0.63		-0.93 (-1.27 to -0.58)
exe+nut+psy	0.42		-0.53 (-1.19 to 0.13)
psy	0.32		-0.26 (-1.53 to 1.02)
cog	0.12		0.36 (-1.04 to 1.76)

I^2=83.2%
τ^2=1.07

-4 -3 -2 -1 0 1 2

Favours intervention | Favours usual care

Directionally **reduced length of stay** compared with usual care

Isolated cognitive prehabilitation

Outcome: **Length of stay**

Component NMA

Test the additive assumption

by comparing the difference in Cochrane's Q-statistics of the additive cNMA model and the treatment-level NMA model

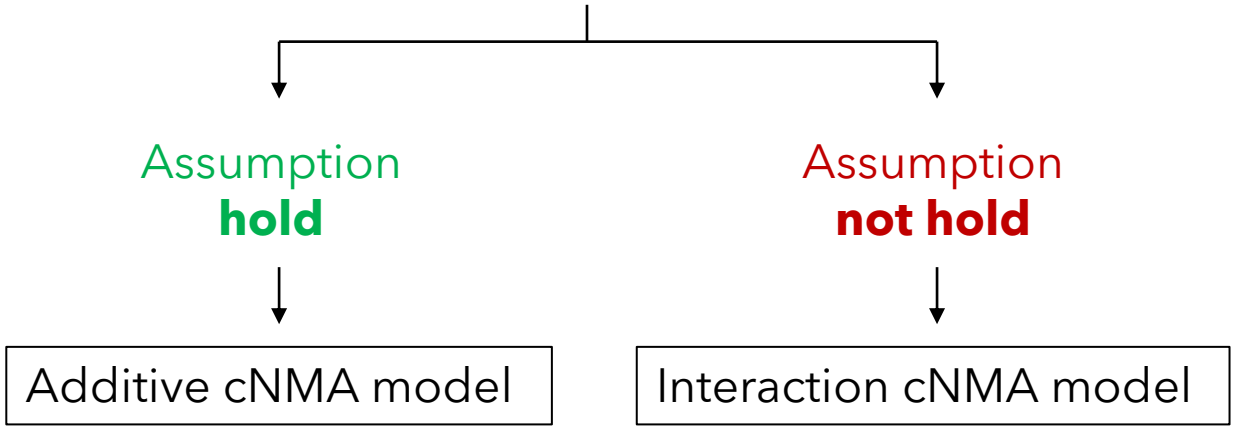
Model	Model statistics		Difference with Standard NMA		
	Q-value	df	Q_{diff}	df_{diff}	p-$value_{diff}$*
Standard NMA	670.64	112			
Additive cNMA model	685.21	115	14.56	3	0.0022

The additivity assumption is **not met** because the p-value of the difference in Q-statistics between the additive and standard NMA models is < 0.1116

Outcome: **Length of stay**

Component NMA

Test the additive assumption
by comparing the difference in Cochrane's Q-statistics of the additive cNMA model and the standard NMA model



Outcome: **Length of stay**

Component NMA

Model	Model statistics		Difference with Standard NMA			Difference with Additive model		
	Q-value	df	Q_{diff}	df_{diff}	p-$value_{diff}$*	Q_{diff}	df_{diff}	p-$value_{diff}$*
Standard NMA	670.64	112						
Additive cNMA model	685.21	115	14.56	3	0.0022			
First-order interaction models								
1) exe*nut	684.61	114	13.97	2	0.0009	-0.595	1	0.4403
2) exe*psy	683.80	114	13.16	2	0.0014	-1.410	1	0.2350
3) exe*nut*psy	679.01	114	8.37	2	0.0153	-6.203	1	0.0128

Model 3 (exe*nut*psy) reduces the Q-statistic significantly compared to the additive model ($p < 0.1573$)

Outcome: **Length of stay**

Component NMA

Model	Model statistics		Difference with Standard NMA			Difference with Additive model			Difference with previous nested model with lowest Q		
	Q-value	df	Q_{diff}	df_{diff}	p-$value_{diff}$*	Q_{diff}	df_{diff}	p-$value_{diff}$*	Q_{diff}	df_{diff}	p-$value_{diff}$*
Standard NMA	670.64	112									
Additive cNMA model	685.21	115	14.56	3	0.0022						
First-order interaction models											
1) exe*nut	684.61	114	13.97	2	0.0009	-0.595	1	0.4403			
2) exe*psy	683.80	114	13.16	2	0.0014	-1.410	1	0.2350			
3) exe*nut*psy	679.01	114	8.37	2	0.0153	-6.203	1	0.0128			
Second-order interaction models											
4) exe*nut + exe*psy	683.80	113	13.16	1	0.0003	-1.410	2	0.4940	0	1	1.0000
5) exe*nut + exe*nut*psy	672.13	113	1.49	1	0.2222	-13.08	2	0.0014	-6.88	1	0.0087
6) exe*psy + exe*nut*psy	677.61	113	6.97	1	0.0083	-7.59	2	0.0224	-1.40	1	0.2367
7) exe*nut + exe*psy + exe*nut*psy (i.e., full interaction model)	670.64	112	0	0	1.0000	-14.56	3	0.0022			

Model 5 (exe*nut + exe*nut*psy) further reduces the Q-statistic significantly compared to Model 3 ($p < 0.1573$)

Model 5 is preferred because it has a better fit than all other models.

Outcome: **Length of stay**

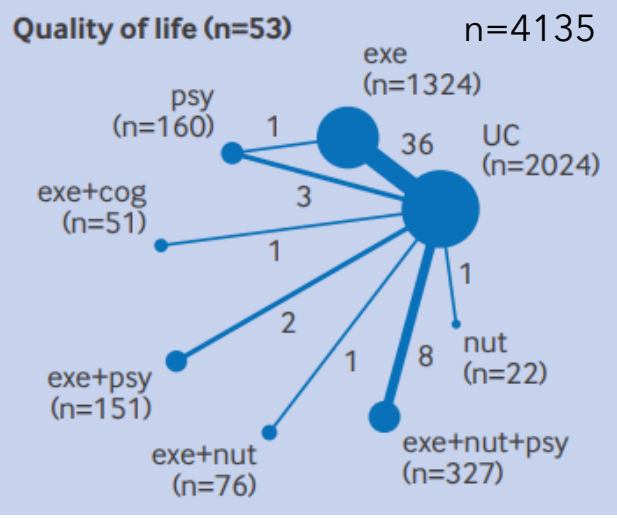
Component NMA – Interaction model (Model 5)

	Component	Mean Difference (95%CI)
☑	**Exercise**	-0.96 (-1.30 to -0.61)
☑	**Nutrition**	-0.99 (-1.49 to -0.48)
	Psychosocial	-0.82 (-1.76 to 0.13)
	Cognitive	0.36 (-1.04 to 1.76)
☑	**Exercise*Nutrition**	1.52 (0.86 to 2.71)
	Exercise*Nutrition*Psychosocial	1.51 (-0.25 to 3.26)

Exercise and **nutrition** components significantly reduced length of stay

The incremental effects of the **exercise** and **nutrition** components were reduced in the other's presence (=the reduction in length of stay was not as large as their sum)

Outcome: **HRQoL**



Treatment level NMA

Treatment	P score	Mean difference (95% CI)	Mean difference (95% CI)
Quality of life			
☑ exe+nut+psy	0.85		3.48 (0.82 to 6.14)
nut	0.75		3.28 (-5.03 to 11.60)
☑ exe	0.62		2.29 (0.96 to 3.62)
exe+psy	0.59		1.31 (-3.36 to 5.98)
exe+nut	0.44		0.59 (-5.92 to 7.11)
exe+cog	0.31		0.00 (-6.86 to 6.86)
psy	0.24		-0.77 (-4.59 to 3.05)

I^2=60.0%
τ^2=0.09

-10 -5 0 5 10 15

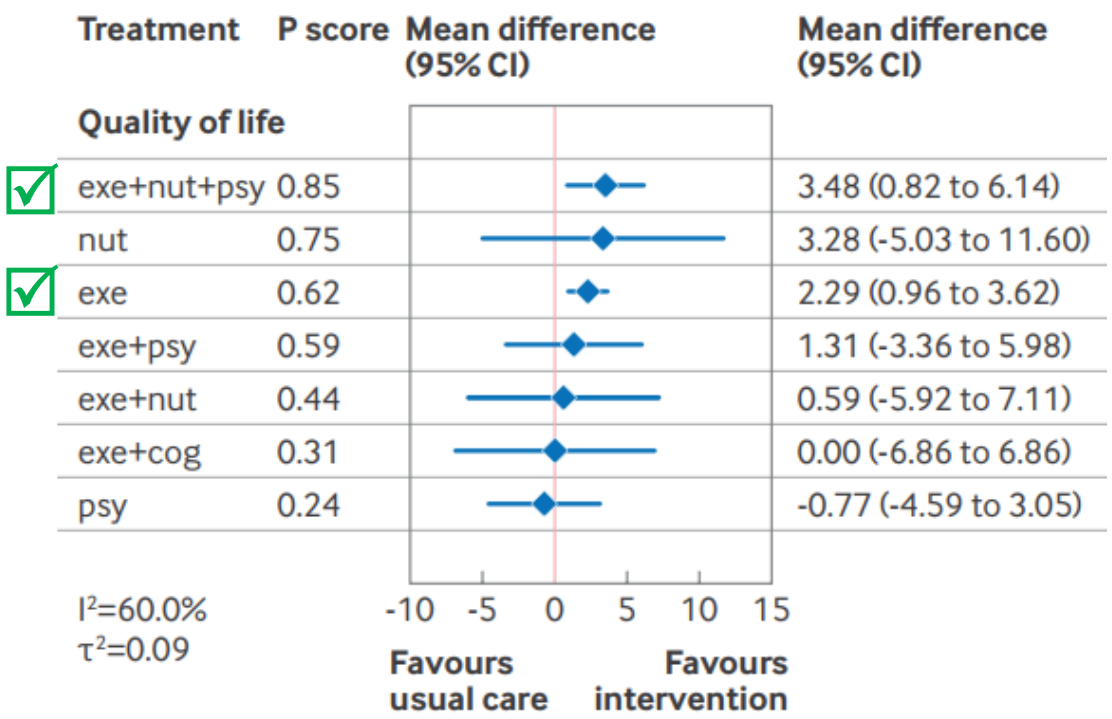
Favours usual care **Favours intervention**

Directionally **improved HRQoL** compared with usual care

Exercise + Cognitive prehabilitation
Isolated psychosocial prehabilitation

Outcome: **HRQoL**

Treatment level NMA



Component NMA

Model	Model statistics		Difference with Standard NMA		
	Q-value	df	Q_{diff}	df_{diff}	p-$value_{diff}$*
Standard NMA	115.08	46			
Additive cNMA model	119.51	49	4.44	3	0.2179

no evidence suggested violation of additivity assumption

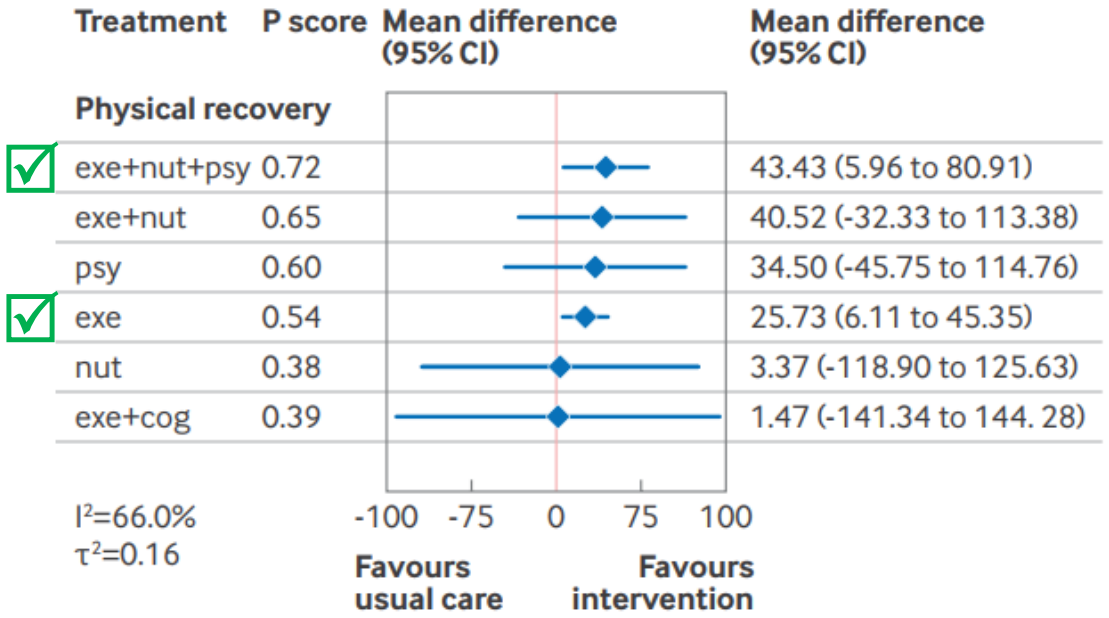
Additive cNMA analysis

Component	Standardized Mean Difference (95%CI)
Exercise	0.22 (0.10 to 0.35)
Nutrition	0.14 (-0.18 to 0.46)
Psychosocial	-0.04 (-0.30 to 0.22)
Cognitive	-0.22 (-0.90 to 0.46)

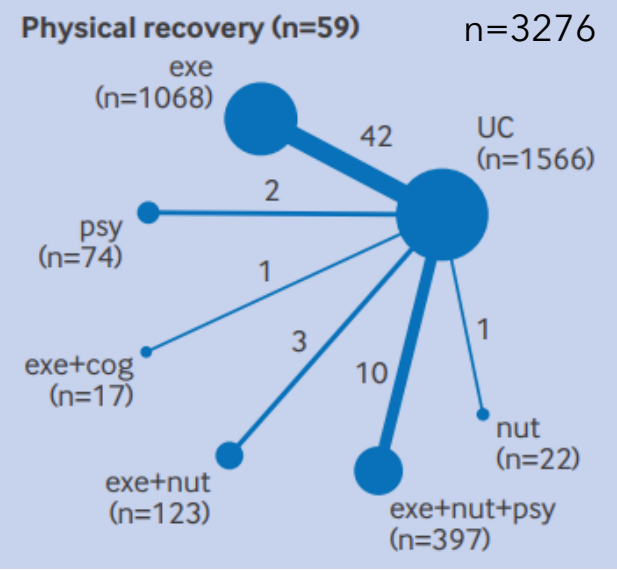
Only **exercise** was associated with a statistically significant improvement in HRQoL

Outcome: **Physical recovery**

Treatment level NMA

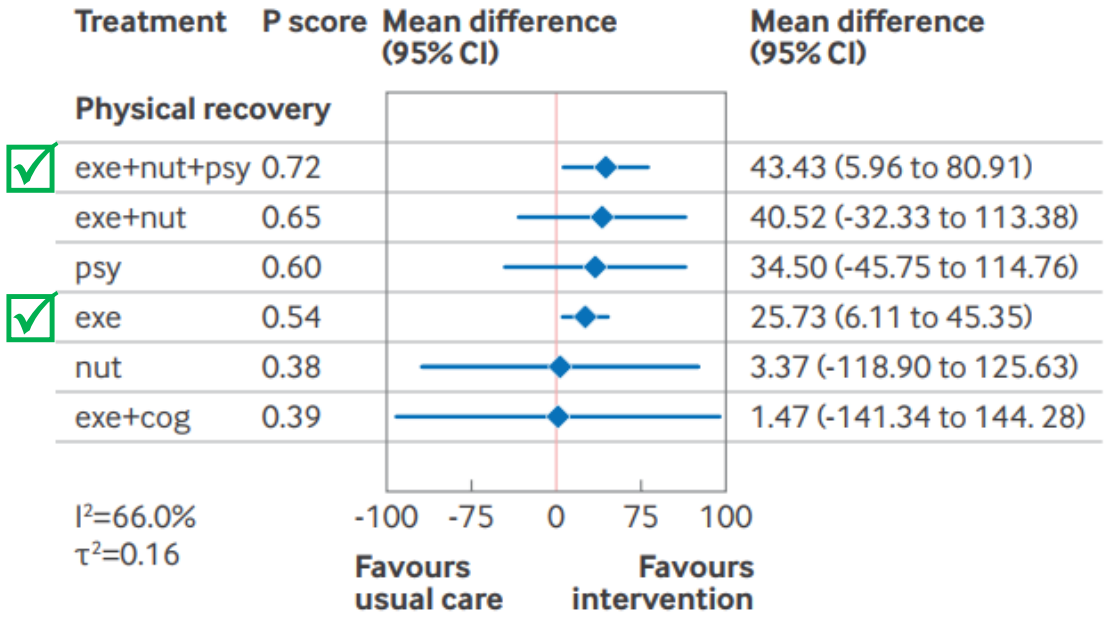


All interventions directionally **improved physical recovery** compared with usual care



Outcome: **Physical recovery**

Treatment level NMA



Component NMA

Model	Model statistics		Difference with Standard NMA		
	Q-value	df	Q_{diff}	df_{diff}	p-value$_{diff}$*
Standard NMA	156.06	53			
Additive cNMA model	156.62	53	0.57	2	0.7522

no evidence suggested violation of additivity assumption

Additive cNMA analysis

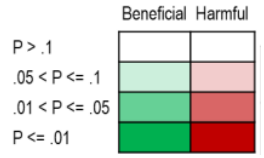
Component	Standardized Mean Difference (95%CI)
Exercise	0.21 (0.05 to 0.37)
Nutrition	0.02 (-0.41 to 0.44)
Psychosocial	0.15 (-0.28 to 0.58)
Cognitive	-0.20 (-1.35 to 0.95)

Only **exercise** was associated with a statistically significant improvement in physical recovery

Summary of NMA results

Standard NMA

	Treatment vs Usual care	Complications All studies (n = 106)	LOS All studies (n = 118)	QOL All studies (n = 53)	Physical recovery All studies (n = 56)
unimodal	Exercise	0.50 (0.39 to 0.64)	-0.93 (-1.27 to -0.58)	0.23 (0.10 to 0.36)	0.20 (0.05 to 0.36)
unimodal	Nutrition	0.62 (0.50 to 0.77)	-0.99 (-1.49 to -0.48)	0.33 (-0.50 to 1.16)	0.03 (-0.95 to 1.01)
unimodal	Psychosocial	1.36 (0.24 to 7.76)	-0.26 (-1.53 to 1.02)	-0.08 (-0.46 to 0.30)	0.28 (-0.37 to 0.92)
unimodal	Cognitive	0.92 (0.43 to 1.94)	0.36 (-1.04 to 1.75)	NA	NA
multimodal	Exercise + nutrition	0.52 (0.26 to 1.05)	-1.22 (-2.54 to 0.10)	0.06 (-0.59 to 0.71)	0.32 (-0.26 to 0.91)
multimodal	Exercise + psychosocial	0.77 (0.37 to 1.59)	-2.44 (-3.85 to -1.04)	0.13 (-0.34 to 0.60)	NA
multimodal	Exercise + nutrition + psychosocial	0.64 (0.45 to 0.92)	-0.53 (-1.19 to 0.13)	0.35 (0.08 to 0.61)	0.35 (0.05 to 0.65)
multimodal	Exercise + cognitive	NA	NA	-0.00 (-0.69 to 0.69)	0.01 (-1.13 to 1.15)



Component NMA

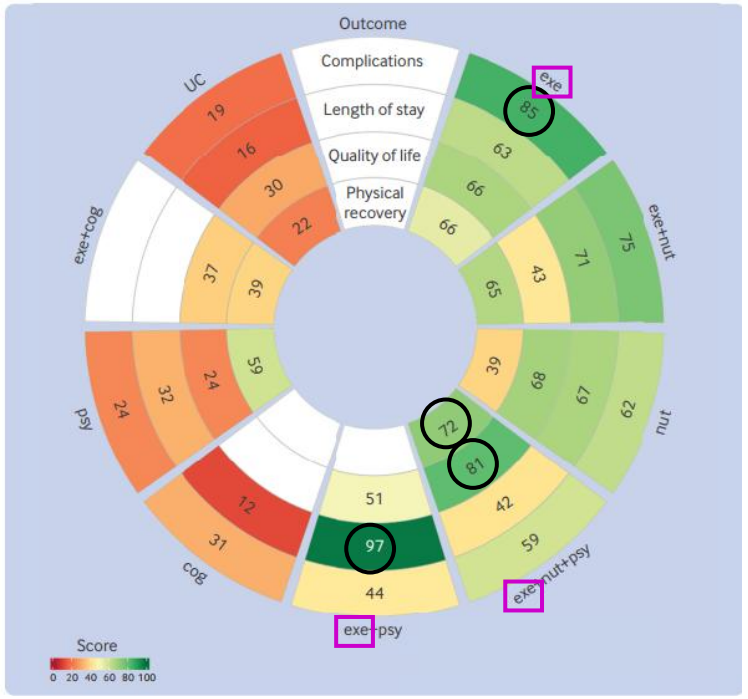
Component	Complications OR (95% CI)	LOS MD (95% CI)	QOL SMD (95% CI)	Physical recovery SMD (95% CI)
Exercise	0.53 (0.42 to 0.66)	-0.96 (-1.30 to -0.61)	0.22 (0.10 to 0.35)	0.21 (0.05 to 0.36)
Nutrition	0.66 (0.54 to 0.81)	-0.99 (-1.49 to -0.48)	0.14 (-0.18 to 0.46)	0.02 (-0.40 to 0.44)
Psychosocial	1.75 (1.17 to 2.61)	-0.82 (-1.76 to 0.13)	-0.04 (-0.30 to 0.22)	0.15 (-0.27 to 0.57)
Cognitive	0.91 (0.43 to 1.92)	0.36 (-1.04 to 1.76)	-0.22 (-0.90 to 0.46)	-0.19 (-1.33 to 0.94)
Interaction				
Exercise * nutrition	NA	0.72 (-0.73 to 2.18)	NA	NA
Exercise * nutrition * psychosocial	NA	1.51 (-0.25 to 3.26)	NA	NA

Exercise was the only component to improve all critical outcomes in a statistically significant manner

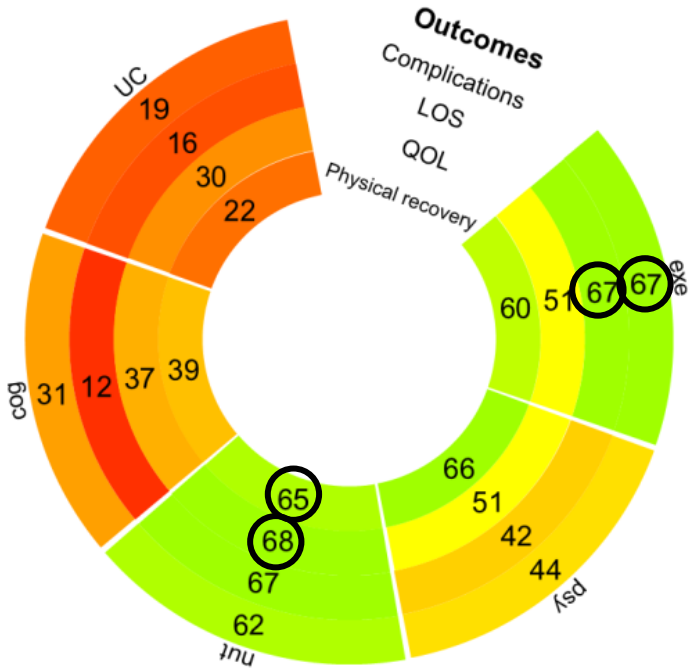
Treatment rankings – Rank heat plot

based on P scores ranking

Standard NMA



Component NMA



Sensitivity analysis - *by risk of bias*

Treatment level NMA

	Beneficial	Harmful
P > .1		
.05 < P <= .1		
.01 < P <= .05		
P <= .01		

	Primary outcome			
	Complications		LOS	
Effect estimate	OR (95% CI)		MD (95% CI) [days]	
Treatment vs Usual care	**All studies (n = 106)**	**Low/Unclear ROB (n = 36)**	**All studies (n = 118)**	**Low/Unclear ROB (n = 36)**
Exercise	0.50 (0.39 to 0.64)	0.50 (0.32 to 0.77)	-0.93 (-1.27 to -0.58)	-0.60 (-1.30 to 0.11)
Nutrition	0.62 (0.50 to 0.77)	0.56 (0.40 to 0.78)	-0.99 (-1.49 to -0.48)	-1.45 (-2.30 to -0.59)
Psychosocial	1.36 (0.24 to 7.76)	1.05 (0.06 to 19.01)	-0.26 (-1.53 to 1.02)	-0.67 (-3.22 to 1.88)
Cognitive	0.92 (0.43 to 1.94)	NA	0.36 (-1.04 to 1.75)	NA
Exercise + nutrition	0.52 (0.26 to 1.05)	0.56 (0.21 to 1.50)	-1.22 (-2.54 to 0.10)	0.00 (-2.63 to 2.63)
Exercise + psychosocial	0.77 (0.37 to 1.59)	NA	-2.44 (-3.85 to -1.04)	NA
Exercise + nutrition + psychosocial	0.64 (0.45 to 0.92)	0.80 (0.42 to 1.51)	-0.53 (-1.19 to 0.13)	-0.09 (-1.34 to 1.15)
Exercise + cognitive	NA	NA	NA	NA

Exclusion of high risk of bias trials

← Estimates for **exercise** and **nutrition**
← prehabilitation were robust.

Conclusion

- Prehabilitation benefits adults preparing for surgery
  - moderate effect sizes in reducing complications
  - clinically meaningful improvements in LOS, HRQoL, and physical recovery
- The strongest evidence supports **isolated exercise** and **nutritional** prehabilitation, as well as **multicomponent interventions including exercise**.

Discussion

- Prehabilitation's efficacy (Pool results) may be heterogenous
  - Surgery type
  - Age
  - Different timing of outcome ascertainment
  - Intervention duration
- Heterogeneity within pooled components (Within-component interventions)
  - Different types of exercise programs were all pooled as exercise interventions
    - eg, aerobic, strength, inspiratory muscle training
- Data for HRQoL and physical recovery were sparse.
  - Limited to provide robust estimates of their efficacy

Complication	106/8816
LOS	118/10060
HRQoL	53/4135
Physical recovery	59/3276