

**Supplement Table S3.** Prebiotics/probiotics/synbiotics and immune and metabolic outcomes.

outcome(s) of interest	estimated summary effect (95% CI)	number of studies / total studies	number of intervention group or total participants	Heterogeneity ( <i>I</i> <sup>2</sup> , %)	the first author + year of publication	Intervention	Duration of Intervention/follow-up	study design	populations	outcome comparison	meta-analysis metric	type of effect model	publication bias	
total cholesterol concentrations after prebiotic supplementation	-0.25 (-0.48 to -0.02)	9	313	14.4	BESERRA B 2015[1]	prebiotic OR fructo-oligosaccharide OR fructooligosaccharide OR galacto-oligosaccharide OR galactooligosaccharide OR inulin OR lactulose OR FOS OR GOS OR Oligofructose OR synbiotic	NP	All RCTs	Overweight (body mass index ≥ 25 kg/m <sup>2</sup> ) or obese individuals	any versus none	SMD	random	No serious bias	
LDL-c concentrations after prebiotic supplementation	-0.2 (-0.44 to -0.00)	9	313	0.0										
triglycerides concentrations after synbiotics supplementation	-0.43 (-0.70 to 0.15)*	3	148	0.0										
fasting insulin after synbiotics supplementation	-0.39 (-0.75 to -0.02)	3	180	0.0										
triglycerides concentrations after prebiotic supplementation	-0.72 (-1.20 to -0.23)	9	313/513	32.7										
HDL-c concentrations after prebiotic supplementation	0.49 (0.01 to 0.97)	9	313/513	0.0										
diamine oxidase	-0.78(-0.93 to -0.63)	3	147/293	0.0	CHEN X R 2021[2]	early nutrition	enteral (EEN)	≥ 14 days	All RCTs	All met patients the	early enteral nutrition	MD	Random	No serious

D-lactic acid	-0.06(-0.07 to -0.05)	4	162/324	0.0		combined probiotics	with		criteria of severe stroke set by the fourth national Cerebrovascular Disease Conference, and were diagnosed by head CT and MRI; the onset was ≤3 days; Glasgow Coma Scale ≤9 points; gastrointestinal function was normal or basically normal. Exclusion criteria were: patients with previous history of gastrointestinal and metabolic diseases, malignant tumor and malnutrition; patients with severe heart, liver, and kidney failure.	(EEN) combined with probiotics versus EEN			bias
dysbacteriosis rate	0.17(0.07 to 0.41)	3	132/262	0.0							OR		
albumin	3.38(2.74 to 4.02)	15	637/1271	45.0							MD		
prealbumin	32.20(24.42 to 39.98)	7	302/601	44.0									
total protein	4.91(3.20 to 6.62)	7	336/672	77.0									
hemoglobin	9.62(7.92 to 11.32)	10	437/872	0.0									
immunoglobulin A	0.23(0.12 to 0.34)	4	144/280	20.0									
immunoglobulin G	0.33(0.21 to 0.45)	3	106/208	0.0									
immunoglobulin M	0.14(0.00 to 0.28)	4	147/290	46.0									
TC concentrations	-3.04(-4.88 to -1.21)mg/dL	12	767	45.9	YAN S 2019[3]	probiotics	6 weeks to 6 months	All RCTs	overweight or obesity was defined according to local standards	the probiotics vs. control groups	WMD	random	NP
LDL concentrations	-2.28(-3.60 to -0.96)mg/dL	11	737	36.9								fixed	
HDL concentrations	-0.26(-2.39 to 1.87)mg/dL*	12	767	95.5								random	
Triglyceride (TG) concentrations	-0.86(-2.54 to 0.83)17.0mg/dL*	11	726	17.0								fixed	
TC	-1.23(-3.52 to	5	NP	0.0		single probiotic						fixed	

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(TC)														
high-density lipoprotein cholesterol (HDL-c)	0.53 (-0.33 to 1.39)*	7	428	94.3										
low-density lipoprotein cholesterol (LDL-c)	-0.84 (-1.64 to -0.03)	7	428	93.4										
very-low-density lipoprotein cholesterol (VLDL-c)	-0.44 (-0.70 to -0.18)	4	235	0.0										
CRP	-0.63 (-1.37 to 0.10)*	9	558	93.9										
total anti-oxidant capacity (TAC)	0.04 (-0.75 to 0.83)*	3	82	83.9	DENG H Y 2020 [9]	Probiotic	12 weeks	All RCTs	Adult human participants who had a diagnosis of AD or MCI (aged over 18 y)	Probiotics versus placebo	SMD	random	NP	
total glutathione (GSH)	0.04 (-0.28 to 0.35)	3	82	44.1								fixed		
malondialdehyde (MDA)	-0.60 (-0.91 to -0.28)	3	82	0.0										
nitric oxide (NO)	-0.16 (-0.47 to 0.15)	3	82	4.4										
high-sensitivity C-reactive protein (hs-CRP)	-0.57(-0.95 to -0.20)	2	57	0.0										
Plasma ammonia concentration (at one month)	-5.55 (-10.67 to -0.42) μmol/L	5	179/357	56.0	DALAL R 2017 [10]	probiotics	at one month	randomised clinical trials	people with any grade of acute or chronic hepatic encephalopathy	probiotics in any dosage vs. placebo or no intervention, or with any other treatment in people with hepatic encephalopathy.	MD	random	NP	
Plasma ammonia concentration (at 2 months)	-5.11 (-14.56 to 4.34) μmol/L*	4	109/211	62.0			at 2 months							
Plasma ammonia concentration	-8.29 (-13.17, -3.41) μmol/L	10	357/705	79.0			follow-up: 1 month to 6 months							



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IgA	0.24 (-0.09 to 0.57)*	4		14.0												0.729
IgA secretion rate	4.21 (-8.35 to 16.77)*	3		13.8												0.208
The efficacy of syn and probiotics on hs-CRP	-0.58 (-0.79 to -0.37)	8	359	0.0	ASKARI G 2021[21]	Synbiotic probiotics	or NP	clinical trials	age >12 years old and disease duration between 2 and 20 years	Vs. Control group	SMD	rando m				0.195
IL-10	-0.12 (-2.11 to 1.87) pg/ml*	5	184	93.9							WMD					0.660
IL-6	-7.79 (-13.81 to -1.77) pg/ml	6	214	91.9												0.191
TNF- $\alpha$	-1.05 (-2.01 to -0.10) pg/ml	5	184	85.2												0.102
ESR: Erythrocyte Sedimentation Rate	3.05 (-7.60 to 13.7) mm/h*	3	90	71.5												0.450
GSH: Glutathione	1311 (-55.68 to 81.91) $\mu$ mol/L	4	222	88.8												0.099
MDA: Malondialdehyde	-0.36 (-0.68 to -0.04)	5	268	41.0							SMD					0.058
TAC	0.08 (-0.16 to -0.32)	5	268	0.0												0.286
HOMA-IR	-0.71 (-1.05 to -0.37)	4	222	0.0							WMD					0.133
HOMA- $\beta$	-15.18 (-22.08 to -8.28)	3	174	0.0												0.096
serum creatinine	0.08 (-0.13 to 0.28) mg/dL*	5	126	0.0	JIA L P 2018[22]	probiotics	1-6 momths	All RCTs	adult chronic kidney disease (CKD) patients	probiotics vs controls	MD	rando m	NP			
blood urea	-1.38 (-9.26 to 6.50)*	3	164	0.0												
p-cresyl sulfate	-0.57 (-0.99 to -0.14)	3	125	25.0							SMD					
hemoglobin	0.21 (-0.48 to 0.91)*	3	93	20.0							MD					



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LDL-c	-6.60 (-14.41 to 1.21) mg/dL*	7		52.7										0.69
HDL-c	0.27 (-2.80 to 3.34) mg/dL*	7		75.7										0.89
cortisol	-0.28 (-0.65 to 0.09)*	3	NP	0.0	AS'HABI A 2020 [32]	probiotics (supplement or food)	2-20 weeks	All RCTs	athletes	Vs. control	SMD	random	0.20	
HDL- C	2.51 (1.04 to 6.05) mg/dL	6		50.3									0.25	
LDL-C	-4.06 (-14.70 to 6.58) mg/dL*	3		0.0									0.98	
TC	-5.99 (-10.83 to -6.04) mg/dL	6		67.5									0.70	
TG	-32.26 (-60.44 to -4.08) mg/dL	6		93.0									0.48	
serum calcium levels	3.82 (1.05 to 6.59)	4	NP	98.0	EJTAHED H 2021[33]	probiotic	NP	clinical trial	adults	Vs. control diets	SMD	Random	No serious bias	
serum phosphorus levels	1.14 (-0.44 to 2.73)*	4		96.1										
parathyroid hormone (PTH)	-5.35 (-9.83 to -0.86)	3		98.2										
urinary calcium	4.85 (1.16 to 8.53)	3		97.6										
CRP	-0.60 (-0.98 to -0.23)	7	342	64.0	MCLOUGHLIN R F 2017[34]	prebiotics, delivered orally, intravenously, or perrectum (enema)	2-12 weeks	All RCTs	human participants of any age and sex	vs. placebo or control	SMD	random	NP	
IL-6	0.35 (-0.84 to 0.13)*	6	313	75.0										
TNF-α	-0.49 (-1.20 to 0.22)*	4	219	84.0										
postprandial ghrelin	-71.66 (-148.83 to 5.50) pg/ml*	3	NP	84.6	DA SILVA BORGES D 2020[35]	prebiotic synbiotic	or NP	clinical trials	overweight or obesity diagnosis (BMI ≥ 25 kg/m²), (3)	Vs. control	WMD	random	NP	

										adults and older adults (≥ 18 y)					
levels of	-0.24 (-0.69 to 0.21)*	7	NP	82.7	QU H 2019[36]	microbiota-driven therapy (probiotic, prebiotic or symbiotic)	14-180 days	the study described a randomized, controlled, parallel or crossover trial	healthy elderly individuals with age>60 years	vs. placebo	SMD	random	0.37		
IL-6	-0.13 (-0.74 to 0.49)*	6		90.7									0.26		
IL-10	1.00 (-0.15 to 2.15)*	6		96.3									0.20		
CRP	-1.28 (-2.62 to 0.06)*	4		96.2									NP		
IL-8	-0.03 (-0.67 to 0.61)*	4		88.0											
CRP	0.02 (-0.32 to 0.36)*	3	135	0.0	ZHU H F 2020[37]	treated with microecological preparations (probiotics, prebiotics, synbiotics, or a combination of two preparations)	15 days to 6months	All RCTs	obese adults (age ≥18 years) who had undergone bariatric surgery (a type of surgery was not restricted)	Vs. placebo or conventional treatment	SMD	Random	NP		
IL-6	-0.10 (-0.81 to 0.61)*	3	135	0.0								random			
TNF-α	-0.29 (-0.64 to 0.05)*	3	135	0.0								fixed			

\* No statistical significance; CI, confidence interval; RCT, randomized controlled trial; RR, relative risk; HR, hazard ratio; MD, mean difference; SMD, standard mean difference; WMD, weighted mean difference; OR, odds ratio; NA, not available; NP, not published.

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