Effects of dietary patterns on biomarkers of inflammation and immune responses: A systematic review and meta-analysis of randomized controlled trials

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Online Supplementary Material

Supplemental Table 1. Mean differences [95% CI] in biomarker concentrations from intervention trials following a Mediterranean diet, according to potential sources of heterogeneity

Sources		CRP		IL-6		IL-8		TNF-α		IL-1β		E-selectin		IFN-γ
	n[a]	(mg/L)	n	(pg/mL)	n	(pg/mL)	n	(pg/mL)	n	(pg/mL)	n	(ng/mL)	n	(pg/mL)
Age														
< 60 years	5	-1.52 [-3.29, 0.24]	3	-1.69 [-4.74, 1.35]	2	-6.38 [-23.82, -11.05]	1	-3.53 [-4.14, -2.92]	1	-0.52 [-0.75, -0.29]	2	-4.05 [-9.22, 1.11]	1	-1.53 [-1.79, -1.27]
≥ 60 years	6	-0.63 [-1.75, 0.49]	5	-0.83 [-0.85, -0.81]	3	-0.77 [-2.34, 0.80]	3	-0.97 [-1.72, -0.22]	2	-0.18 [-0.66, 0.30]	1	0.67 [-1.01, 2.35]	2	-4.01 [-13.37, 5.35]
P-group difference[b]		0.40		0.58		0.53		<0.01		0.21		0.09		0.60
Sex														
Female (< 50%)	4	-1.39 [-2.62, -0.17]	3	-0.51 [-1.05, 0.02]	1	-0.02 [-0.16, -0.12]	0		0		1	-0.80 [-5.99, 4.39]	3	
Female (≥ 50%)	6	-0.10 [-0.13, -0.07]	5	-1.43 [-3.41, 0.55]	4	-1.99 [-2.91, -1.07]	4		3		2	-2.74 [-9.46, 3.98]	0	
P-group difference		0.04		0.38		<0.01		-		-		0.65		-
Geographic region														
Americas	2	-0.57 [-2.75, 1.61]	2	-2.51 [-5.94, 0.93]	2	-6.38 [-23.82, 11.05]	1	-3.53 [-4.14, -2.92]	1	-0.52 [-0.75, -0.29]	1	-6.19 [-8.14, -4.24]	1	-1.53 [-1.79, -1.27]
Asia	0		0		0		0		0		0		0	
Europe	5	-1.85 [-3.02, -0.67]	4	-0.38 [-0.70, -0.07]	2	-3.64 [-18.68, 11.40]	3	-0.97 [-1.72, -0.22]	2	-0.18 [-0.66, 0.30]	2	0.53 [-1.07, 2.13]	3	-4.01 [-13.37, 5.35]
Oceania	4	-0.09 [-0.55, 0.37]	2	-0.83 [-0.85, -0.81]	1	-0.02 [-0.16, -0.12]	0				0		0	

P-group difference		0.02		0.01		0.69		<0.01		0.21		<0.01		0.60
Health status														
CVD	4	-0.75 [-2.90, 1.40]	1	-0.45 [-1.30, 0.40]	0		0		0		0		0	
MetS	5	-1.40 [-2.90, 0.10]	5	-1.19 [-2.96, 0.57]	3	-1.98 [-2.87, -1.09]	3	-2.10 [-3.92, -0.28]	2	-0.41 [-0.77, -0.04]	3		3	
Healthy	1	-0.40 [-1.13, 0.33]	0		0		0		0		0		0	
Diabetes	1	-0.78 [-1.45, -0.11]	0		0		0		0		0		0	
Other	0		2	-0.83 [-0.85, -0.81]	2	-3.50 [-23.23, 16.23]	1	-0.68 [-1.70, 0.34]	1	-0.32 [-1.16, 0.52]	0		0	
P-group difference		0.67		0.63		0.88		0.18		0.85		-		-
Obesity														
< 30 kg/m^2	4	-1.1 [-2.39, 0.16]	3	-0.83 [-0.85, -0.81]	2	-0.82 [-2.21, 0.58]	1	-1.50 [-2.75, -0.25]	1	-0.11 [-0.19, -0.03]	1	0.67 [-1.01, 2.35]	1	-9.40 [-15.93, -2.87]
≥ 30 kg/m^2	7	-0.95 [-2.40, 0.51]	4	-1.33 [-3.81, 1.15]	2	-2.34 [-3.33, -1.35]	2	-2.31 [-5.13, 0.52]	1	-0.52 [-0.75, -0.29]	2	-4.05 [-9.22, 1.11]	1	-1.53 [-1.79, -1.27]
P-group difference		0.87		0.69		0.08		0.61		<0.01		0.09		0.02
Duration														
< 6 months	7	-0.32 [-0.76, 0.12]	5	-1.45 [-2.87, -0.03]	4	-1.28 [-3.61, 1.05]	2	-2.14 [-4.93, 0.66]	2	-0.51 [-0.73, -0.28]	2	-4.05 [-9.22, 1.11]	2	-0.66 [-2.37, 1.06]
≥ 6 months	4	-1.82 [-3.29, -0.35]	3	-0.54 [-0.93, -0.15]	1	-1.61 [-2.55, -0.67]	2	-1.31 [-2.42, -0.20]	1	-0.11 [-0.69, 0.47]	1	0.67 [-1.01, 2.35]	1	-9.40 [-15.93, -2.87]
P-group difference		0.06		0.23		0.80		0.59		0.21		0.09		0.01
< 1 year	8	-0.29 [-0.68, 0.09]	7	-1.14 [-2.23, -0.04]	4	-1.28 [-3.61, 1.05]	2	-2.14 [-4.93, 0.66]	2	-0.51 [-0.73, -0.28]	2	-4.05 [-9.22, 1.11]	2	-0.66 [-2.37, 1.06]
≥ 1 year	3	-2.34 [-3.85, -0.83]	1	-0.62 [-1.09, -0.15]	1	-1.61 [-2.55, -0.67]	2	-1.31 [-2.42, -0.20]	1	-0.11 [-0.69, 0.47]	1	0.67 [-1.01, 2.35]	1	-9.40 [-15.93, -2.87]
P-group difference		<0.01		0.39		0.80		0.59		0.21		0.09		0.01
Study design														
Crossover	3	-0.10 [-0.13, -0.07]	1	-4.20 [-4.73, -3.67]	1	-2.35 [-3.34, -1.36]	1	-3.53 [-4.14, -2.92]	1	-0.52 [-0.75, -0.29]	1	0.53 [-1.07, 2.13]	1	-4.01 [-13.37, 5.35]
Parallel	8	-1.45 [-2.54, -0.37]	7	-0.58 [-0.88, -0.28]	4	-0.82 [-2.45, 0.80]	3	-0.97 [-1.72, -0.22]	2	-0.18 [-0.66, 0.30]	2	-6.19 [-8.14, -4.24]	2	-1.53 [-1.79, -1.27]
P-group difference		0.01		<0.01		0.12		<0.01		0.21		<0.01		0.60

Weight loss														
In both groups	3	-0.96 [-1.51, -0.41]	2	-0.14 [-0.58, 0.29]	0	-	2	-0.61 [-3.00, 1.78]	0		1	-0.80 [-5.99, 4.39]	0	
Intervention	2	-2.26 [-5.51, 0.98]	4	-0.83 [-0.85, -0.81]	3	-8.39 [-27.91, 11.13]	2	-1.01 [-1.80, -0.22]	1	-0.32 [-1.16, 0.52]	0		1	0.22 [-0.08, 0.52]
Control	1	0.25 [-0.68, 1.18]	0		0	-	0		0		0		0	
None	4	-0.91 [-2.81, 0.99]	1	-4.20 [-4.73, -3.67]	1	-2.35 [-3.34, -1.36]	1	-3.53 [-4.14, -2.92]	1	-0.52 [-0.75, -0.29]	1	-6.19 [-8.14, -4.24]	1	-1.53 [-1.79, -1.27]
P-group difference		<0.01		<0.01		<0.01		<0.01		0.65		0.06		<0.01

[a]Number of studies in each subgroup; [b]P- significance of subgroup difference

Abbreviations: CRP, C-reactive protein; CVD, cardiovascular disease; MetS, metabolic syndrome

Supplemental Table 2. Mean difference [95% CI] in CRP concentrations from intervention trials following a DASH diet and Vegetarian/vegan diet, according to potential sources of heterogeneity

Sources	DASH		Vegetarian/vegan	
		CRP		IL-6
	n[a]	(mg/L)	n	(mg/L)
Age				
< 60 years	4		2	-1.04 [-2.32, 0.24]
≥ 60 years	0		2	-0.20 [-0.74, 0.34]
P-group difference[b]		-		0.23
Sex				
Female (< 50%)	2	-0.06 [-0.12, 0.01]		-0.04 [-0.29, 0.21]
Female (≥ 50%)	2	-1.11 [-1.76, -0.46]		-2.10 [-4.41, 0.21]
P-group difference		<0.01		0.08
Geographic region				
Americas	1	0.00 [-0.28, 0.28]	2	-0.04 [-0.29, 0.21]
Asia	2	-1.11 [-1.76, -0.46]	0	
Europe	1	-0.06 [-0.13, 0.01]	2	-2.10 [-4.41, 0.21]
P-group difference		<0.01		0.08
Health status				
CVD	1	-0.06 [-0.13, 0.01]	1	-0.20 [-0.74, 034]
Healthy	1	0.00 [-0.28, 0.28]	2	-0.69 [-2.03, 0.65]
Other	2	-1.11 [-1.76, -0.46]	1	-4.00 [-7.43, -0.57]
P-group difference		<0.01		0.09
Obesity				
< 30 kg/m^2	3	-0.09 [-0.32, 0.13]	2	-0.69 [-2.03, 0.65]
≥ 30 kg/m^2	1	-1.43 [-2.45, -0.41]	2	-1.71 [-5.35, 1.94]
P-group difference		0.01		0.61
Duration				
< 6 months	3	-0.68 [-1.59, 0.23]	3	-0.54 [-1.59, 0.52]
≥ 6 months	1	-0.06 [-0.13, 0.01]	1	-4.00 [-7.43, -0.57]
P-group difference		0.18		0.06
< 1 year	4		4	
≥ 1 year	0		0	
P-group difference		-		-
Weight loss				
In both groups	0		1	-0.20 [-0.74, 0.34]
Intervention	3	-0.69 [-1.57, 0.19]	2	-4.00 [-7.43, -0.57]
Control	0		0	
None	1	0.00 [-0.28, 0.28]	2	-0.69 [-2.03, 0.65]
P-group difference		0.01		0.09

[a]Number of studies in each subgroup; [b]P- significance of subgroup difference
Abbreviations: CVD, cardiovascular disease; DASH, Dietary Adherence to Stop Hypertension; MetS, metabolic syndrome

Supplemental Table 3. Sensitivity analysis – Pooled estimates including shorter follow-up measurements of respective studies

		Number studies with shorter follow-up	**Mean difference [95% CI]**	I^2
Mediterranean	CRP (mg/L)	3	-0.91 [-1.99, 0.16]	98%
	IL-6 (pg/mL)	3	-1.04 [-1.93, -0.15]	96%
	IL-8 (pg/mL)	3	-1.21 [-2.56, 0.14]	85%
	TNF-α (pg/mL)	1	-1.79 [-3.52, -0.07]	88%
	IL-1β (pg/mL)	1	-0.32 [-0.62, -0.02]	74%
	E-selectin (ng/mL)	1	-2.30 [-7.35, 2.76]	93%
	IFN-γ (pg/mL)	1	-1.08 [-2.76, 0.59]	97%
DASH	CRP (mg/L)	0	NA	NA
Vegetarian/vegan	CRP (mg/L)	1	-0.86 [-1.88, 0.15]	96%

Abbreviations: CRP, C-reactive protein

Supplemental Table 4. Estimates from multivariable meta-regression for Mediterranean diet and C-reactive protein

Variable	ß-coefficient (SE)	*P*-value
Study size	-0.003 (0.001)	<.0001
Sex	0.009 (0.013)	0.494
Duration	-0.012 (0.002)	<.0001
BMI	-0.135 (0.129)	0.295
Age	0.006 (0.029)	0.829

Supplemental Figure 1. Funnel plots for Mediterranean diet interventions and C-reactive protein in (A) all studies included in the meta-analysis and (B) including the imputed studies from the trim-and-fill procedure