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A systematic review and meta-analysis of randomized controlled trials exploring the role of inter-individual variability on the effect of flavanols on insulin and HOMA-IR

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Meta-analyses of randomised controlled trials (RCTs) report that polyphenol-rich diets can modulate a range of cardiometabolic biomarkers, with increasing evidence that inter-individual factors (e.g. age, BMI, or ethnicity) contribute toward the variability in the response to the bioactive[1,2]. This systematic review and meta-analysis assessed the effect of flavanols from cocoa, apple and tea on fasting insulin and HOMA-IR and explored the role of inter-individual variability.

PubMed and Web of Science databases were searched from inception to October 2017 (PROSPERO reg. CRD42016033878). The effect of flavanols supplementation on insulin and HOMA-IR was estimated using a random effects meta-analysis model and reported as standardised mean difference (SMD) and 95%CI. Subgroup analyses (Q tests; multivariate meta-regression) focused on baseline BMI, gender, age, and geographical location to explore the role of inter-individual variability.

Out of 1409 studies identified, 31 RCTs were included for insulin (n = 1792) and 21 RCTs for HOMA-IR (n = 1152). Low heterogeneity was found between studies (insulin $I^2 = 0\%$, $p = 0.98$; HOMA-IR $I^2 = 5.9\%$, $p = 0.38$) with evidence of low publication bias. Flavanol-rich interventions (2–26 weeks; 88 to 1344 mg flavanols/day) decreased both insulin (SMD −0.25, 95% CI −0.33; −0.16) and HOMA-IR (SMD −0.26; 95% CI −0.36, −0.16). Results were consistent across subgroups (Q tests) with lack of effect in subgroups with BMI<25 or male subjects only; multivariate meta-regression showed that baseline BMI (overweight versus lean, coef. −1.07; 95% CI −2.03, −0.08; p = 0.03) and study location (Asia versus other sites, coef. 0.94; 95% CI 0.03,1.84; p = 0.04) impacted on the effect on HOMA-IR significantly. There was no impact of age, gender, baseline BMI or geographical location on the effect on insulin.

Factor	Subgroup	Insulin (95% CI)	Q value	(n, N)	HOMA-IR (95% CI)	Q value	(n, N)
Age	<50 years	−0.21 (−0.36, −0.05)	Q bet 0.276 p = 0.6	(15, 662)	−0.34 (−0.54, −0.14)	Q bet 0.62 p = 0.43	(13, 522)
	>50 years	−0.26 (−0.36, −0.15)		(24, 1373)	−0.22 (−0.35, −0.10)		(14, 630)
	All	−0.24 (−0.33, −0.15)			−0.25 (−0.36, −0.15)		
Gender	Male	−0.12 (−0.40, 0.15)	Q bet 1.46, p = 0.48	(3, 14)	N/A		
	Female	−0.21 (−0.37, −0.04)		(9, 475)	−0.09 (−0.28, 0.09)	N/A	(7, 372)
	All	−0.25 (−0.33, −0.16)					
Baseline BMI (kg/M$^{2)}$	<25	−0.2 (−0.44, 0.03)	Q bet 1.67 p = 0.4	(4, 156)	−0.10 (−0.42, 0.22)	Q bet 2.4 p = 0.29	(2, 98)
	25–30	−0.31 (−0.34, −0.16)		(13, 898)	−0.32 (−0.46, −0.19)		(12, 653)
	>30	−0.19 (−0.33, −0.05)		(12, 696)	−0.23 (−0.43, −0.04)		(12, 401)
	All	−0.25 (−0.33, −0.16)			−0.27 (−0.38, −0.17)		
Geographical location	Asia	−0.19 (−0.33, −0.04)	Q bet 1.01 p = 0.79	(13, 748)	−0.20 (−0.34, −0.05)	Q bet 2.27 p = 0.51	(8, 496)
	USA	−0.27 (−0.52, −0.02)		(5, 213)	−0.29 (−0.63, 0.06)		(6, 106)
	Europe	−0.29 (−0.42, −0.16)		(21, 731)	−0.36 (−0.53, −0.19)		(10, 434)
	Other	−0.33 (−0.69, 0.05)		(3, 100)	−0.29 (−0.74, 0.17)		(3, 100)
	All	−0.25 (−0.33, −0.16)			−0.27 (−0.37, −0.17)		

Values are showed in SMD (95%CI). n, number of trials; N, number of participants.

Flavanols from tea, apple and cocoa were effective in modulating insulin and HOMA-IR. Inter-individual variability in the response was limited in contrast to previous studies[1,2]. This could be partly explained by the small number of trials reporting data for specific subgroups, and the broad range of doses and duration tested among the studies.

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2. González-Sarrías A, Combet E, Pinto P *et al. Nutrients*. 2017;**9**(7):746.

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