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► To cite this version:

N. Alshammari, S. A. Palma-Duran, G. Jiang, A. Gonzalez-Sarrias, P. Pinto, et al.. 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. 2018 Spring Conference on Nutrient-Nutrient Interaction, Mar 2018, NA, France. 10.1017/s0029665118000344 . hal-02062457

HAL Id: hal-02062457

<https://hal.science/hal-02062457>

Submitted on 2 Jun 2020

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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 I² = 0%, p = 0.98; HOMA-IR I² = 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)
Baseline BMI (kg/M ²)	All	-0.25 (-0.33, -0.16)	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	-0.2 (-0.44, 0.03)		(4, 156)	-0.10 (-0.42, 0.22)		(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.

1. Pinto P & Santos C. *Eur J Nutr.* 2017;**56**(4):1393–1408.
2. González-Sarriás A, Combet E, Pinto P *et al.* *Nutrients.* 2017;**9**(7):746.