HAL
archives-ouvertes.fr

Effects of dietary polyphenols on metabolic syndrome features in humans: a systematic review

M. J. Amiot, C. Riva, A. Vinet

▶ To cite this version:

M. J. Amiot, C. Riva, A. Vinet. Effects of dietary polyphenols on metabolic syndrome features in humans: a systematic review. Obesity Reviews, Wiley, 2016, 17 (7), pp.573-586. 10.1111/obr.12409 . hal-01785583

HAL Id: hal-01785583
https://hal-amu.archives-ouvertes.fr/hal-01785583

Submitted on 4 May 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives| 4.0 International License

doi: 10.1111/obr.12409

Obesity Comorbidity/Nutrition

Effects of dietary polyphenols on metabolic syndrome features in humans: a systematic review

M. J. Amiot,[1,2,3] C. Riva[4] and A. Vinet[4]

[1]Unité Mixte de Recherche (UMR) 'Nutrition, Obesity and Risk of Thrombosis', Institut National de la Recherche Agronomique, Paris, France, [2]Institut National de la Santé et de la Recherche Médicale, Paris, France, [3]Aix-Marseille Université, Marseille, France, and [4]LaPEC, EA4278, Université d'Avignon, Avignon, France

Received 19 October 2015; revised 16 February 2016; accepted 16 February 2016

Address for correspondence: Marie Josèphe Amiot, UMR 1062 INSERM/1260 INRA/ Aix-Marseille Université, UMR NORT: Nutrition Obésité et Risque Thrombotique, Faculté de Médecine de la Timone, 27 Boulevard Jean Moulin, 13385 Marseille Cedex 05, France. E-mail: marie-josephe.amiot-carlin@univ-amu.fr

Summary

Dietary polyphenols constitute a large family of bioactive substances potential beneficial effect on metabolic syndrome (MetS). This review summarizes the results of clinical studies on patients with MetS involving the chronic supplementation of a polyphenol-rich diet, foods, extracts or with single phenolics on the features of MetS (obesity, dyslipidemia, blood pressure and glycaemia) and associated complications (oxidative stress and inflammation). Polyphenols were shown to be efficient, especially at higher doses, and there were no specific foods or extracts able to alleviate all the features of MetS. Green tea, however, significantly reduced body mass index and waist circumference and improved lipid metabolism. Cocoa supplementation reduced blood pressure and blood glucose. Soy isoflavones, citrus products, hesperidin and quercetin improved lipid metabolism, whereas cinnamon reduced blood glucose. In numerous clinical studies, antioxidative and anti-inflammatory effects were not significant after polyphenol supplementation in patients with MetS. However, some trials pointed towards an improvement of endothelial function in patients supplemented with cocoa, anthocyanin-rich berries, hesperidin or resveratrol. Therefore, diets rich in polyphenols, such as the Mediterranean diet, which promote the consumption of diverse polyphenol-rich products could be an effective nutritional strategy to improve the health of patients with MetS. © 2016 The Authors. Obesity Reviews published by John Wiley & Sons Ltd on behalf of World Obesity

Keywords: Blood pressure, dyslipidemia, insulin resistance, weight management.

obesity reviews (2016) **17**, 573–586

Introduction

With abdominal obesity reaching epidemic proportions (1), there are increased risks of cardiovascular morbidity and mortality via complex interrelationships with unfavourable metabolic consequences. Metabolic syndrome (MetS) is a clustering of cardio-metabolic risk factors, including abdominal obesity, insulin resistance, dyslipidemia and hypertension and is a key phenotype leading to atherogenic and diabetogenic profiles (2,3). MetS depends on many parameters such as age, gender, ethnicity, socioeconomic status and the definition used to identify MetS. The rapidly growing prevalence of MetS, and the increased cardiovascular risks it entails, is a major public health concern (4).

Global strategies initially approach the treatment of MetS by focussing on lifestyle changes, including diet and physical activity. This is followed by pharmacological intervention. Diets recommending increased fruit and vegetable consumption over a long-term period are very attractive and efficient in inducing health benefits (5,6). The Mediterranean diet, rich in plant-derived products, was shown to prevent MetS (7,8). Its beneficial effects are related to the high content of bioactive compounds, monounsaturated and polyunsatured fatty acids and polyphenols (9).

© 2016 The Authors. Obesity Reviews published by John Wiley & Sons Ltd on behalf of World Obesity

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Epidemiological studies associated an increased consumption of polyphenol-rich foods and beverages with a reduction of cardiovascular diseases (10–12). Among polyphenol-rich foods and beverages, tea received particular attention and meta-analysis enlightened that a higher intake of green or black tea is associated with a lower risk of stroke (13) and type 2 diabetes (14). There is large body of evidence attributing anti-obesity, anti-diabetic, anti-hypertensive, anti-hyperlipidemic and anti-inflammatory effects to polyphenols (15).

The present review summarizes the results of clinical studies on the chronic supplementation of polyphenol-rich diet, foods, extracts and molecules in features of MetS. Molecular and physiological mechanisms are discussed. As MetS is characterized by an altered oxidative/antioxidant status and by subclinical chronic inflammation, both of which are responsible for the development of atherosclerosis, we review the impact of polyphenol supplementation on these associated complications.

Metabolic syndrome: definition and associated complications

As reviewed by Kassy et al. (16), a number of definitions of MetS have been published by different organizations. These include the World Health Organization, the National Cholesterol Education Program Adult Treatment Panel III, the International Diabetes Federation and the American Heart Association/National Heart, Lung, and the Blood Institute. The definition of MetS was standardized (17). A person has MetS when three or more of the following five cardiovascular risk factors have been diagnosed: (i) central obesity (waist circumference: men ≥ 102 cm; women ≥ 88 cm); (ii) elevated triglycerides ($\geq 150\,mg\,dl^{-1}$); (iii) diminished high-density lipoprotein (HDL) cholesterol (men $< 40\,mg\,dl^{-1}$; women $< 50\,mg\,dl^{-1}$) (or treated for dyslipidemia); (iv) systemic hypertension ($\geq 130/\geq 85$ mm Hg) (or treated for hypertension); and (v) elevated fasting glucose ($\geq 100\,mg\,dl^{-1}$) (or treated for hyperglycaemia).

Polyphenols: classes and dietary sources

Polyphenols are a large group of bioactive plant compounds displaying a wide variety of diverse structures which belong to two main classes: non-flavonoids (especially phenolic acids, stilbenes and lignans) and flavonoids which are characterized by the basic C6-C3-C6 skeleton (Table 1). The two aromatic rings within the flavonoid structure are linked by a heterocyclic ring, which differs in the degree of oxidation and leads to the following sub-classification: flavones, flavonols, isoflavones, flavanones, anthocyanins and flavanols, usually called catechins. In plant food products, the major forms are conjugated either with acid-alcohol or with glycosides. Moreover, polyphenols are also found as oligomers and polymers, usually called tannins. These are divided into hydrolysable tannins (derived from gallic and ellagic acids) and condensed tannins (derived from catechin and usually called procyanidins). The diversity and the complexity of phenolic compounds leads to difficulties in their quantification, but the mean total polyphenol intake in the French diet was estimated at $1193 \pm 510\,mg\,d^{-1}$, or $820 \pm 335\,mg\,d^{-1}$ when expressed as aglycone equivalents (18) and ranged from $584\,mg\,d^{-1}$ for Greek women and $1786\,mg\,d^{-1}$ for Danish men (19). The main dietary sources associated with the main phenolic structures are reported in Table 1.

Effects of polyphenols and associated mechanisms on the main features of metabolic syndrome

Central obesity

As reported in Table 2, numerous clinical interventions have investigated the effects of polyphenol-rich intake on anthropometric variables, weight, body mass index (BMI), waist circumference and body fat mass in MetS subjects. Clearly, clinical studies pointed towards significant beneficial effects of green tea on BMI (21–28) and waist circumference (21,24–28). In a study by Basu et al. (22), 35 MetS subjects were randomly assigned to three groups (1): control, (2) green tea (beverage) and (3) green tea extract given for 8 weeks. Subjects who consumed green tea (beverage or extract) decreased significantly their body weight (-2.5 ± 0.7 in green tea beverage and -1.9 ± 0.6 kg in green tea extract compared with controls) and BMI (-0.9 ± 0.3 in green tea beverage and -0.7 ± 0.2 kg in green tea extract compared with controls) without changes in body fat and waist circumference. Nagao et al. (21) have previously confirmed a significant reduction of body weight, BMI, waist circumference and body fat mass in men who took a green tea extract compared with the control group. As caffeine was adjusted in both groups, the authors evidenced the role of catechin-polyphenols in the green tea extract. In the trial conducted by Suliburska et al. (26), 12 weeks of green tea extract supplementation resulted in decreases in BMI and waist circumference in men, even when the dose of catechins was around three times lower than that tested in the trial conducted by Nagao et al. (21). Interestingly, green tea catechin consumption also enhanced exercise-induced changes ($\geq 180\,min\,week^{-1}$ moderate intensity exercise, including ≥ 3 supervised sessions per week) in abdominal fat in overweight and obese adults compared with the control beverage group (least squares mean [95%CI]: -7.7 [-11.7, -3.8] vs. -0.3 [-4.4, 3.9] in catechin and control groups respectively) (29). Green tea, which is unfermented and mainly consumed in Asia, is rich in catechins, especially in (-)-epigallocatechin 3-O-gallate (EGCG), the major phenolic compound, (-)-epigallocatechin, (-)-epigallocatechin 3-O-gallate,

© 2016 The Authors. Obesity Reviews published by John Wiley & Sons Ltd on behalf of World Obesity

Table 1 Polyphenolic classes and their main dietary sources

Class	Sub-class	Main dietary sources
Non-flavonoids	Hydroxycinnamic acids	Fruits: blueberry, cranberry, pear, cherry (sweet), apple, orange, grapefruit, cherry juice, apple juice, lemon, peach and cider Vegetables: potato, lettuce and spinach Others: coffee and tea
	Hydroxybenzoic acids	Fruits: strawberry, raspberry, grape juice (black/green) and pomegranate juice
	Stilbenes	Fruits: grapes and rhubarbOthers: red wine and peanuts
	Lignans	Cereals: rye, wheat, oat, barley and soybeanFruits: apricots and strawberries Vegetables: broccoli and cabbageOthers: nuts and seeds,
Flavonoids	Flavones	Fruits: celery and olives Vegetables: hot peppers and celery hearts,Spices and herbs: parsley, oregano, rosemary and thyme
	Flavonols	Fruits: apples, apricots, grapes, plums, bilberries, blackberries, blueberries, cranberries, olive elderberries, currants, cherries, blackcurrant juice, apple juice and ginkgo biloba Vegetables: capers, celery, chives, onions, red onions, dock leaves, fennel, hot peppers, cherry tomatoes, spinach, sweet potato leaves, turnip (green), endive, leek, lettuce, celery, broccoli, Hartwort leaves and kaleLegumes: beansCereals: buckwheat Spices and herbs: dill weedOthers: red wine, tea (green, black), tea (black beverage) and cocoa powder
	Isoflavones	Fruits: grape seed/skinLegumes and derived products: soybean, soy nuts, soy flour/bread, tofu, miso, soy milk and tofu yogurt
	Flavanones	Citrus fruits and juices: lemon, lime orange, orange, grapefruit and tangerineSpices and herbs: peppermint
	Anthocyanidins	Fruits: blackberries, black currant, blueberries, black grape, elderberries, strawberries, cherries, plums, cranberry, pomegranate juice and raspberry Others: red wine
	Flavanols	Fruits: apples, apricots, grapes, peaches, nectarines, pears, plums, raisins, raspberries, cherries, blackberries, blueberries and cranberries Others: red wine, tea (green, black), chocolate (dark, milk), white wine and cocoa
Tannins	Procyanidins (Condensed tannins)	Fruits: grape (dark/light) seed/skin, apple juice, strawberries, raspberries, walnuts, muscadine grape, peach, blackberry (juices/jams/jellies) and plum Legumes: chick pea, black-eyed peas and lentils, Others: red wine, white wine, cocoa, chocolate, oak-aged red wine, tea, cider, tea and coffee
	Ellagitannins (hydrolysable tannins)	Fruits: pomegranate

© 2016 The Authors. Obesity Reviews published by John Wiley & Sons Ltd on behalf of World Obesity

Table 2 Effects on cardiometabolic features of polyphenol-rich intake given to subjects with metabolic syndrome

Polyphenols	Exposition/day duration	Participants N (Male)age	BMI	WC	BP	LDL-C	HDL-C	TG	BG	IR	Oxidative markers	Inflammatory markers	Other markers	References
Diet rich in foods and beverages with a high content of polyphenols PP	2.9 mg PP8 weeks	86 (33) 35–70 years	ns	ns	ns	ns	ns	↓	ns	↓	Urinary 8-isoprostane ns	na		20
Green tea	Extract (690 mg catechins) 12 weeks	32 (32) 24–46 years	↓	↓	na	ns	ns	ns	ns	ns	↓ MDA	leptin ns, PAI-1 ns	↓ body fat mass and subcutaneous fat aera	21
	4 cups (928 mg catechins) or extract (870 mg catechins) 8 weeks	35 (8) 42.8 years	↓	ns	ns	↓	ns	ns	ns	na	↓ MDA, ↓HNE ↑ plasma antioxidant, ↑ GSH	adiponectin nsCRP ns, IL6 ns, IL1-β ns, leptin ns	↓Large very LDL TG ↓HDL TGVCAM-1 ns, ICAM-1 ns	22,23
	1000 mg Puerh tea (capsules)	90 (41) 18–70 years	↓	↓	ns	↓	ns	↓	↓	na	↓ MDA, ↑ SOD	↓ CRP, ↓ IL6, ↑ IL10	↓ apoB-100	24
	3 g (3 sachets) 2 months	4560 years	↓	↓	na	ns	ns	ns	ns	na				25
	Extract (208 mg EGCG) 12 weeks	46 (46) 30–60 years	↓	↓	ns	↓	ns	↓	ns	na	↑ antioxidant level,	na	↑ Zn, ↑ Mg, ↓ Fe	26
	Greenselect Phytosome, (300 mg) 24 weeks	100 (49) 46.5 years	↓	↓	↓	↓	↑	↓	↓	na	↓ Plasma free radicals	na		27
	999 mg Puerh tea extract (capsules) 3 months	70 59.2 years	↓	↓	na	ns	ns	ns	ns	na				28
(+ exercise)	Extract (625 mg catechins) 12 weeks	128 (67) 21–65 years	↓	↓	ns	ns	ns	↓	na	na	na	na	↓ body fat mass and subcutaneous fat	29
Black tea	Puerh tea (1.5 g d^{-1}) 3 months	70 (40)	ns ↓(M)	na	ns	↓	ns	ns	ns	na	na	na	na	30
Cocoa	eq 902 mg flavanols 6 weeks	49 (18), 18–65 years	ns	ns	↓	ns	ns	ns	↓	↓	Fat oxidation ns	na		31
	same conditions than above +exercise	49 (18), 18–65 years	ns	ns	↓	ns	ns	ns	↓	↓	↑ Fat oxidation	na	↓ body fat↓ abdominal body fat ↑ endothelial function	31
Cocoa	beverage (701 mg vs. 22 mg catechins) 7 d	21 (14) 54.9 years	na	na	↓	na	na	na	na	na	na	na	↑ endothelial function	32
	idem + pre-exercise	40 (40)	na	na	na	na	na	na	↓	na	↓F_2-isoprostane	IL6 ns	leucocytes ns	33

© 2016 The Authors. Obesity Reviews published by John Wiley & Sons Ltd on behalf of World Obesity

Table 2. (Continued)

Polyphenols	Exposition/day duration	Participants N (Male)age	BMI	WC	BP	LDL-C	HDL-C	TG	BG	IR	Oxidative markers	Inflammatory markers	Other markers	References
(+ myo-inositol + soy isoflavones)	30 mg cocoa polyphenols 6 months	30 (0) 56 years	ns	ns	ns	ns	↑	↓	↓	na	na	↓visfatin, ↓resistin adiponectin ns	↓ bone specific alkaline phosphatase	34
Berries	500 g strawberries 8 weeks	30 (2) 47 years	ns	ns	ns	↓	ns	ns	ns	na	↓ox-LDL, ↓TBARS, ↓MDA	na	↑ Small LDL particlesICAM-1 ns, ↓ VCAM-1	22,23
	300 mg aronia extract 2 months	25	↓	ns	↓	↓	↑	↓	↑	na	↑ SOD, ↑ GPX ↓CA, ↓TBARS	CRP ns	↓ endothelin↑ fibrinogen	35
	480 mL cranberry juice 8 weeks	3652 years	na	na	ns	ns	ns	ns	ns	na	↑ plasma antioxidant capacity, ↓ox-LDL,↓ MDA, ↓HNE	CRP ns, IL6 ns	na	23
	Berries (bilberry BB and sea buckthorn) 8 weeks	80 (0) 44.2 years	↓	↓	na	na	na	na	↓	↓	na	↓TNFα ↑adiponectin for BB	↓ $GHbA_{1c}$ ↓ VCAM-1	36
	Smoothie blueberry 6 weeks	32 (5) 54 years	ns	ns	ns	ns	ns	ns	ns	↓	na	CRP ns, TNFα ns MCP-1 ns		37
	grape powdereq 252 g grape 8 weeks	24 (24) 30–70 years	ns	ns	↓	ns	ns	ns	ns	na	na	↑ IL10, ↑ adiponectin in men without dyslipidemia	↑ endothelial function	33,38,51
Citrus	Citrus-based juice (300 mL)	53 (24) 50–65 years	na	na	na	↓	↓	ns	ns	na	↓ox-LDL	↓ CRP	↓ homocysteine	52
Cinnamon	Cinnulin PF® 12 weeks	22 (11) 46 years	na	na	↓	ns	ns	ns	↓	na	na	na	↓ body fat mass	53
	1.5 g 12 weeks	4045 years	na	na	na	↓	ns	↓	↓	↓	na	↓ hs-CRP	↓ total cholesterol	54
Soy isoflavones Daidzein D, genistein G	soy-based meal 12 weeks	100 (20) 35–65 years	↓	↓	ns	↓	ns	na	na	na	na	na	↓ body fat mass	55
S-equol* (metabolite of isofavone * effect in equol non producers)	5 mg equol+0.8 mg D+1 mg G+2.2 mg glycitein 12 weeks	54(16) 59.4 years	ns	↓	ns	↓	ns	ns	↓	na	na	CRP ns, adiponectin nsleptin ns	↓ HbA1c↑ aortic stiffness (cardio-ankle vascular index)	56
Genistein	36 mg 3/6 months	12 (0) 18–32 years	ns	ns	na	↓	ns	ns	ns	ns	na	na	↓ total cholesterol	57
Quercetin	150 mg 6 weeks	96 (42) 45 years	na	na	↓	↓	↓	ns	ns	na	↓ox-LDL	↓TNFα, CRP ns		58

© 2016 The Authors. Obesity Reviews published by John Wiley & Sons Ltd on behalf of World Obesity

Table 2. (Continued)

Polyphenols	Exposition/day duration	Participants N (Male)age	BMI	WC	BP	LDL-C	HDL-C	TG	BG	IR	Oxidative markers	Inflammatory markers	Other markers	References
													↓ BP in apo ε3/ε3 genotype	41
Hesperidin	500 mg 3 weeks	28 (15) 52 years	ns	ns	ns	↓	↓	ns	↓	↓	na	↓ CRP, ↓ serum amyloid ↓ soluble E-selectin	↑ endothelial function	59
Epigallocatechin gallate	800 mg 8 weeks	88 (88) 40–65 years	ns	ns	↓	ns	ns	ns	ns	ns	na	na		60
Resveratrol	Longevinex (eq 100 mg resveratrol) 3/6 months	34	ns	ns	ns	ns	ns	ns	ns	ns	na	hsCRP ns, IL-6 ns	↑ endothelial function	61
	2 weeks	11 28–55 years	na	na	na	na	na	ns	ns	ns	na	na	↓ apoB-100 and apoB-48 production	62
	500 mg 3 months	24	↓	↓	na	na	na	na	↓	↓	na	na	↓ fat mass	63
	150 mg 4 weeks	45 (25) 61 years	ns	ns	↓	ns	ns	ns	ns	ns		CRP ns, IL-6 ns, TNF α ns, E-and P-selectin ns, ICAM-1 ns, VACAM-1 ns		64
Resveratrol R+ Epigallocatechin gallate E	200 mg R + 282 mg E3 d	18 (9) 33 years	na	na	na	na	na	na	na	na		na	↑ fasting and postprandial energy expendure in men	65

BMI, body mass index; BP, blood pressure; BG, blood glucose; EGCG, epigallocatechin gallate ; ↓↑, significant augmentation or diminution; ns, not significant; IR, insulin resistance; LDL-HDL-C, low and high density lipoprotein cholesterol; na, not assayed or not reported; MDA, malonyl dialdehyde ; SOD, superoxide dismutase; hs CRP, highly sensitive C-reactive protein; TNF, tumour necrosis factor ; MCP, monocyte chemoattractant protein; HbA_{1c} , glycated haemoglobin A1c, ICAM, intercellular adhesion molecule; TG, triglycerides; VCAM, vascular cell adhesion molecule; WC, waist circumference.

© 2016 The Authors. Obesity Reviews published by John Wiley & Sons Ltd on behalf of World Obesity

(-)-epicatechin, (+)-gallocatechin, but also in 5-O-galloylquinic acid, and 5-caffeoylquinic acid and diverse flavonols (66,67). However, the trial conducted with 800 mg of EGCG had no significant effect on BMI and waist circumference (68) even though its beneficial effects were demonstrated in experimental studies in animal models, as reported by Legeay et al. (69). These diverging results could be because of the dose, but also because green tea has other polyphenolic compounds, as previously reported, and their mixture could be more efficient than the single EGCG. The combination of catechin-polyphenols and caffeine with green tea was demonstrated to stimulate thermogenesis lead to increased 24 h energy expenditure and fat oxidation in humans (70), by mechanisms attributed to their actions on different molecular pathways: via inhibiting the phosphodiesterase-induced degradation of cAMP, and inhibiting catechol O-methyltransferase, an enzyme that degrades norepinephrine (71). Tea polyphenols may stimulate cellular energy expenditure that could reduce body-weight gain and suppress the expression of fatty acid synthase (72). Intake of Puerh tea (fermented) for 3 months was also associated with a slight reduction of body weight (−2.05 kg) and BMI (−0.73), but only in men and without the improvement of other metabolic parameters (30). Fermented tea commonly named black tea, which is largely consumed in Western countries, contains the same compounds than green tea, but with lower amounts of catechins, because of their oxidation during fermentation step. Theafavins and thearubigins, which result from the oxidation of flavanols, are other major polyphenols in black tea (66,67). This quantitative and qualitative composition could explain the less pronounced effects of black tea compared with green tea. Interestingly, Yang et al. (73) hypothesized two types of effect, which could explain the biological differences between teas. The first one concerns the decrease of macronutrient absorption at intestine level leading to the reduction of caloric intake by polyphenols; the aflavins and thearubigins of black tea could be particularly involved. The second mechanism may involve bioavailable polyphenols, which, by their action on AMP-activated protein kinase activation, could decrease gluconeogenesis and fatty acid synthesis, increase catabolism and consequently, reduce body weight. While trials evidenced the beneficial action of tea on anthropometric parameters, cocoa-drink with a high dose of flavanols did not affect body composition (31) nor augment the effect of exercise on body composition (31). The addition of myositol and soy isoflavones to cocoa supplementation also had no effect. Berry supplementation with strawberries (74), cranberries (75) or blueberry smoothies (37) did not change weight or body composition in MetS subjects. However, decreased weight and waist circumference were reported after bilberry supplementation in overweight-obese women (delta changes calculated by the subtraction of wash out value from the value obtained at the end of the supplementation were −0.2 kg for body weight and −1.2 cm for waist circumference) (36). One explanation of those differences may be because of the level of anthocyanidin between these berries. Supplementation of citrus-based juice, known to be rich in vitamin C and flavanones (especially hesperidin), had also no effect on anthropometric parameters (52). Studies by Ziegenfuss et al. (53) in pre-diabetic men and women and Askari et al. (54) in non-alcoholic fatty liver disease patients conducted on cinnamon supplementation did show a significant decrease in body weight and waist circumference, whereas soy isoflavone supplementation had a beneficial effect on both these anthropometric parameters compared with the control group (55). MetS subjects in the 12-week soy isoflavone supplementation and control MetS were followed up at 4-week intervals and seen at screening, at 4, 8 and 12 weeks. The treatment group had significant greater losses of body weight at week 12 (−7.1 vs. −2.5 kg in experimental and control groups) and body fat at weeks 8 and 12 compared with controls (−3.0 vs. −1.7 kg and −4.3 vs. −1.4 kg in experimental and control groups at weeks 8 and 12 respectively) (55). The beneficial effect was heightened after 12 weeks. Decreased waist circumference was only significant after 12 weeks. Weight reduction has been also observed in a group of diabetic patients where three meals per day were replaced with a soy meal (76). Another study compared weight loss in obese men and women after soy or casein meals (77), but there was no difference in weight loss and body composition between both protein meals. Thus, the role of soy isoflavones in weight management remains questionable even if in rodents, isoflavone administration decreased fat accumulation (78). Interestingly, the effect of equol, a key metabolite of soy daidzin, was tested in non-equol producers corresponding to people who cannot convert daidzin into S-equol through their intestinal bacterial flora (56). In fact, great interindividual variability in the ability to produce equol from soy isoflavone (79) was found. Usui et al. (56) have shown a significant beneficial effect of S-equol supplementation on the waist circumference of non-equol producers displaying MetS, although a significant reduction was also observed in the placebo group because of one patient with a strong waist circumference reduction. When taking phenolic molecules only, there was no effect in different studies conducted with genistein (57), quercetin (58), hesperidin (59), EGCG (60) and resveratrol for most of the trials (61,62,64). However, one trial with 500 mg of resveratrol during 3 months produced significant decreased anthropometric features (body weight, BMI, fat mass and waist circumference) than baseline values (63). This was certainly because of the high dose given compared with the previous studies (61,62,64). The combination of two polyphenols, resveratrol and EGCG also had no effect on BMI and waist circumference (65), but the authors reported a significant rise in fasting and postprandial energy expenditure in men. While no changes have been reported using resveratrol in most of the previously mentioned intervention studies, Konings et al. (80) have found a beneficial effect on the adipose tissue function after administering resveratrol to 11 obese men for 30 d. Thus,

© 2016 The Authors. Obesity Reviews published by John Wiley & Sons Ltd on behalf of World Obesity

resveratrol supplementation resulted in a modification of adipose tissue morphology with a decrease in adipocyte size. Furthermore, the authors reported a down-regulation of Wnt and Notch signalling pathways, suggesting an increased adipogenesis.

Blood pressure: diastolic and systolic

Given that hypertension is one of the main cardiovascular risk factors in the patients with MetS, its management could be achieved by adopting a healthy lifestyle including a higher intake of fruit, vegetables and whole cereals, all known rich sources of fibres and polyphenols. However, the role of polyphenols on the blood pressure of patients with MetS remains difficult to isolate. When considering a diet naturally rich in polyphenols (close to 3 g d^{-1}) blood pressure was unchanged (20) and when focussing on specific foods or beverages, tea had no effect while cocoa lowered blood pressure (31,34). While cocoa supplementation decreased diastolic blood pressure (DBP) (−1.6 mm Hg) and systolic blood pressure (SBP) (−1.2 mm Hg) in the high-flavanol cocoa MetS group, these changes were independent of exercising (31). Berry et al (32) conducted a randomized, double-blind, cross-over trial to test the acute effects of cocoa flavanols on blood pressure responsiveness to exercise. Area under the curve for DBP response to exercise was significantly lower in high-flavanol (701 mg) than low-flavanol cocoa (22 mg) (743 ± 1098 vs. 2359 ± 822 mm Hg.s respectively) in 21 patients with borderline/mild hypertension, whereas there was no change in SBP and mean arterial pressure. Although the best dose and food matrix were not well established, it seems that a high dose of flavanols was required to obtain a beneficial effect on blood pressure. The study conducted by D'Anna et al. (34) with 30 mg of cocoa flavanols had no effect on blood pressure even with the addition of soy isoflavones. To strengthen dose–effect role, a two-month polyphenol-rich olive oil diet led to a significant decrease in SBP (−7.91 mm) and DBP (−6.65 mm Hg) in 24 young women with high-normal BP or stage 1 essential hypertension (81). The meta-analysis performed by Petrone et al. (82) including 23 randomized and control trials was consistent with a beneficial effect of dark chocolate and cocoa products on endothelial function and thus on blood pressure. Following berry supplementation (strawberry, cranberry, bilberry, sea buckthorn or blueberry), blood pressure remained unchanged in MetS subjects apart from chokeberry (Aronia melanocarpa), which lowered both DBP and SBP after 2 months (37). Grape polyphenol extract also produced an improvement in blood pressure with a mean decrease of 5 mm Hg in SBP. Although modest, this change was nevertheless clinically significant. Indeed, a reduction in DBP of 2 mm Hg has been calculated to reduce the risk of stroke and CHD by 15 and 6% respectively (83). Cinnamon was also shown to improve blood pressure (53), whereas citrus-based juice supplementation still had no effect (52). In terms of the flavonoid tested, soy isoflavones (55) and hesperidin (59) were not effective, whereas a daily intake of 150 mg of quercetin for 6 weeks had a beneficial effect on blood pressure (58). These effects were more pronounced in younger MetS adults aged 25–50 years compared with the whole group and to (pre)-hypertensive MetS subjects defined as SBP ≥ 120 or DBP ≥ 80 mmHg. DBP decreased after 8 weeks of EGCG treatment (−2.5 mmHg) in patients with MetS (60). There was no change of blood pressure in 34 MetS individuals who consumed resveratrol for 6 months (61), whereas DBP increased following 150 mg of daily resveratrol intake for 4 weeks (84). All the results of intervention studies point towards the ability of dietary polyphenols to improve endothelial dilatory function associated with increased bioavailability of nitric oxide (NO) as was shown for cocoa flavanols (85). The enhancing effect of dietary polyphenols on the endothelial synthesis of NO was reported in an intervention sub-study of 200 high cardiovascular risk participants conducted as part of the Predimed trial : effects of Mediterranean diet on the primary prevention of cardiovascular disease, in which a Mediterranean diet enriched with extra virgin olive oil or nuts were beneficial on blood pressure (86).

Dyslipidemia

Based on catechin-polyphenol consumption, green tea supplementation was shown to improve lipid profile by reducing significantly LDL-cholesterol in trials conducted by Basu et al. (22), Chu et al. (24), Suliburska et al. (26) and Belcaro et al. (27) and/or triglycerides in trials undertaken by Chu et al. (24), Suliburska et al. (26) and Belcaro et al. (27) and Maki et al. (29). Furthermore, no significant effect was observed for HDL cholesterol, although Basu et al. (22) reported an upwards trend. Other studies found no improvement in lipid profile using green tea (21,25,28) and cocoa (31). However, the combination of cocoa polyphenols with soy isoflavones and myoinositol was efficient on triglycerides level (34). It should be noted that Di Renzo et al. (87) recently showed that regular consumption of dark chocolate had a beneficial effect on HDL cholesterol and lipoprotein ratios in women with normal weight obese syndrome. Among berries, only strawberries and chokeberries improved serum lipids (35,74). Twenty-seven middle-aged MetS subjects with high BMI (mean 37.5 kg m^{-2}) were given 50 g d^{-1} of freeze-dried strawberries for 8 weeks (74). This resulted in 10% and 11% reductions in total cholesterol and LDL cholesterol respectively, whereas it had no effect on triglycerides, HDL cholesterol or very LDL cholesterol levels. An important result was a 14% decrease in small LDL particle concentrations which are specifically atherogenic (74). In the trial conducted by Broncel et al. (35) enrolling 25 MetS subjects, administering aronia extract significantly reduced total cholesterol, LDL-cholesterol and

© 2016 The Authors. Obesity Reviews published by John Wiley & Sons Ltd on behalf of World Obesity

triglycerides after two months, whereas HDL-cholesterol did not change significantly. No significant changes in serum lipids were found for other berries such as cranberries (75), blueberries (37), bilberries, sea buckthorn (36) and grape powder (38). Considering these trials, it is difficult to understand the beneficial role of anthocyanins in lipid improvement because strawberries and cranberries displayed the lowest anthocyanin contents among the berries tested whereas chokeberries and bilberries had the highest levels (39). However, strawberries were reported to have the highest content of total polyphenols among fruit consumed in France (40), suggesting the action of other phenolic structures. The dose and the food matrix could influence the bioavailability of polyphenols and their effect on lipid metabolism (39). Two studies on cinnamon supplementation gave different results on lipid profile (53,54). Interestingly, isoflavone, flavone or flavanone supplementation pointed towards improved lipid profiles (55–59). A reduction of LDL-cholesterol was observed in MetS subjects following isoflavone supplementation with a soy-based meal (55) or a 30 mg genistein administration (57) or administering S-equol to non-equol producers (56). Egert et al. (58) reported the effect of a 6-week supplementation with quercetin ($150\,mg\,d^{-1}$) given to 93 MetS subjects with little difference in serum lipid levels. Reanalysis of their data suggested that those subjects with specific apolipoprotein-E genotypes had differential lipid responses to quercetin (41). Flavanone supplementation, with 300 mL citrus juice or hesperidin at $500\,mg\,d^{-1}$ for three weeks, showed a significant reduction in total cholesterol and LDL cholesterol (59). Resveratrol was shown to be inactive on lipid metabolism. However, resveratrol has been reported to decrease triglyceride-rich lipoprotein apoB100 and apoB48 concentrations (62). Considering all the results, catechin-polyphenols of tea and flavonoids could contribute to a beneficial effect on lipid metabolism. The mechanisms at intestinal level would be the reduction effect of polyphenols on lipid availability, cholesterol absorption and chylomicron secretion. It has been reported that polyphenols could constrain the digestion of fats by inhibiting the pancreatic lipases (42). Moreover, impaired lipid availability in hepatocytes by polyphenols seems to contribute to reduced hepatic very LDL secretion. Polymeric catechins, namely proanthocyanidins, were shown to be able to suppress the expression of miR-33a and miR-122 (43). MiR-33a and miR-122 are two key regulators of lipid metabolism in the liver corresponding to the ATP-binding cassette transporter ABCA1 targets genes, fatty acid synthase and peroxisome proliferator-activated receptor PPARβ/δ respectively (44).

Blood glucose and insulin resistance

With regards to fasting glucose and/or insulin resistance, clinical studies of polyphenol supplementation have reported controversial results. Neither green tea nor EGCG treatment in patients with MetS had an effect on insulin sensitivity, secretion or glucose tolerance and on insulin resistance in the majority of clinical trials, apart from those conducted by Vieira Senger et al. (25) and Belcaro et al. (27). By contrast, cocoa products were reported to have a beneficial effect on glycaemia. Decreased insulin resistance assessed by HOMA2 (−0.31%) was observed in high-flavanol cocoa (902 mg) supplementation in obese individuals (31), highlighting the dose-dependent effect of polyphenols on blood glucose changes. Acute dark chocolate consumption prior to prolonged exercise also enhanced insulin sensitivity compared with chocolate consumption alone (33). Berry consumption gave conflicting results; fasting glucose was unchanged after strawberry (74) and cranberry (75) supplementation but was lower after a sea buckthorn diet (36). Using a hyperinsulinemic euglycemic clamp with a blueberry diet, Stull et al. (37) reported improved insulin sensitivity without any change in body weight, suggesting that bioactive blueberry substances had a direct effect on increasing whole-body insulin action. Concerning citrus-juice (52), fasting glucose was unchanged while hesperidin supplementation improved glycemia and insulin resistance (59). Cinnamon-extract supplementation for 12 weeks reduced fasting glucose in 22 MetS subjects (53). This decrease was confirmed in a trial conducted by Askari et al. (54). Single phenolic molecule tested on patients with MetS had no effect apart from hesperidin, as previously mentioned, and high doses of resveratrol (500 mg) in the 3-month trial carried out by Méndez-del Villa et al. (63). Dose–effect may partly explain the lack of results in numerous trials. Polyphenols, as reviewed by Hanhineva et al. (45), could act on different targets such as the intestine, by inhibiting glucose absorption via the sodium-dependent glucose transporter SGLT1, the pancreas, by protecting β-cells from glucotoxicity, the liver by suppressing glucose release from liver storage and peripheral tissues by improving glucose uptake via the glucose transporter GLUT4. These mechanisms could explain the inverse association between a higher consumption of berries and the risk of type 2 diabetes as reported in a prospective study by Mursu et al. (46).

Associated complications

Oxidative stress

Because polyphenols are poorly absorbed and extensively metabolized, their antioxidant effects are attributed to the regulation of redox enzymes by reducing reactive oxygen species production from mitochondria, NADPH oxidases and uncoupled endothelial NO synthase in addition to multiple up-regulated antioxidant enzymes (47). Moreover data supporting the oxidative stress-reducing effects of polyphenols was promising in reducing plasma isoprostanes and thiobarbituric acid-reacting substances (TBARS), malonyl dialdehyde (MDA), 4-hydroxy nonenal (HNE) or oxidized

© 2016 The Authors. Obesity Reviews published by John Wiley & Sons Ltd on behalf of World Obesity

low-density lipoprotein (ox-LDL). Not all clinical trials reported significant reductions in oxidative stress in MetS subjects, especially for those carried out using a single phenolic compound. While green tea beverages or extract supplementations were shown to induce antioxidative responses in MetS subjects enrolled in several clinical trials (23,24,26,27), this did not apply to cocoa products. Among berries, strawberry, aronia and cranberry treatments reduced lipid oxidation (lower Ox-LDL, lower TBARS or lower MDA) and improved antioxidant status (increased superoxide dismutase and a 47% increase in plasma antioxidant capacity) in MetS individuals (35,75). As reported by Sivaprakasipallai et al. (48), the higher the baseline ox-LDL was, the greater the decrease in ox-LDL with a high dose of grape seed extract. Six months of citrus juice supplementation also induced lower ox-LDL. Egert et al. (41) used quercetin supplementation and reported decreased ox-LDL in apoE3 and apoE4 groups of Mets subjects. As ox-LDL was involved in the initiation and progression of atherosclerosis, polyphenols may thus represent natural dietary sources of potent antioxidants to improve the antioxidative status in Mets subjects.

Inflammation

Visceral obesity is characterized by chronic local and systemic inflammation. It seems well established that a rise in pro-inflammatory cytokines may be connected to enlarged adipose tissue and increased risk of coronary disease. A polyphenol-rich diet is currently recommended as having a beneficial impact on inflammation (9,49). However, results from various clinical trials conducted on patients with MetS reported no overall effect on the most common inflammation biomarkers following polyphenol supplementation. As a systemic inflammation marker, highly sensitive C-reactive protein (CRP) stimulates the production of other inflammatory cells and reduces the expression of endothelial nitric oxide synthase (eNOS). No significant change was noted after green tea supplementation (except in the trial conducted by Chu et al. (24)), cranberries (75), aronia (35), blueberries (37), quercetin (58) and resveratrol (61,64). Following citrus-based juice and hesperidin supplementation, CRP was significantly decreased and was associated to improved endothelial function in MetS individuals (59). Concerning the circulatory tumour -necrosis factor (TNF-α) associated inflammation, while blueberries (37) and grapes (38) did not produce any change in TNF-α, bilberries and sea buckthorn (36) or quercetin (41) significantly reduced its level. Furthermore, no study in MetS subjects reported changes in interleukin-6 (IL-6) following green tea, cranberry or grape supplementation (23,38,75). It has been suggested that the lack of changes may be because of the baseline inflammatory value and/or that the anti-hypertensive treatment usually received by the patients may explain the absence of additional effects due its anti-inflammatory effects (23). However, it is interesting to note an increased anti-inflammatory cytokines (IL-10 and adiponectin) production after 4 weeks of grape supplementation (38), 6 months of citrus juice supplementation (52) or after regular consumption of dark chocolate (87). As regards to these controversial findings, the higher dose of polyphenols or the adaptation of lifestyle with the greater physical activity may influence adiposity, turning to be one of the better anti-inflammatory strategies for patients with MetS.

Vascular dysfunction

MetS is associated with endothelial-dependent and endothelial-independent dysfunction, affecting both the macrovascular and microvascular systems (50). As reported in Table 2, some clinical interventions have investigated the effects of polyphenol-rich intake on vascular dysfunction in MetS subjects. Clearly, clinical trials pointed towards significant beneficial effects of polyphenols on endothelial dysfunction (31,32,51,59) and adhesion modulation (36,74). In fact, supplementation of cocoa-drink with a high dose of flavanols improved flow mediated dilation, an established measure of endothelial function, acutely (2 h post-dose) by 2.4% and chronically (over 12 weeks) by 1.6% in patients with MetS (31). Grape polyphenols also increased flow-mediated dilation in 25 MetS subjects (51). Following oral hesperidin administration (500 mg once daily for three weeks), flow mediated dilation increased in MetS subjects ($10.26 + 1.19$ vs. $7.78 + 0.76\%$, $p = 0.02$) (59). In 34 MetS individuals, resveratrol consumption for 6 months improved flow-mediated dilation (61). According to vasoconstriction effect, administering aronia extract during 2 months in 25 MetS subjects significantly reduced plasma endothelin-1 (35). Moreover, vascular cell adhesion molecule (VCAM and/or intercellular adhesion molecule [ICAM]) decreased after berries supplementation, for strawberries (74) or buckthorn (36). However, green tea intervention did not affect VCAM and ICAM (22). Several mechanisms, mostly based on *in vitro* studies, have been described to explain the protective effects of polyphenols on endothelium and vascular smooth muscle cells. Polyphenols increase the production of vasodilatory substances such as NO and endothelium-derived hyperpolarizing factor by stimulating the phosphorylation of Akt, AMP kinase and eNOS, prevent ROS-mediated degradation of NO by decreasing the expression of NADPH oxidase, blunt vasoconstrictive and pro-inflammatory responses (47).

Conclusions and future directions

Cross-over and randomized controlled trials in MetS subjects with single phenolic compound or specific food/beverage/extract do not provide strong evidence for the promising protective effects of polyphenols on cardiovascular diseases as reported in numerous animal and cell studies. Different factors could be involved: (i) the

© 2016 The Authors. Obesity Reviews published by John Wiley & Sons Ltd on behalf of World Obesity

characteristics of the selected MetS population under study; (ii) insufficient statistical power; (iii) inadequate treatment duration, (iv) the use of suboptimal dosages and (v) low bioavailability supplementation with a single molecule; and (vi) improper administration of micronutrients relative to meal ingestion. However, the present review highlights that polyphenols, usually at higher doses, could have a beneficial effect on the main features of MetS through different actions on (i) anthropometric features with tea (green and black); (ii) blood pressure with cocoa; (iii) lipid metabolism with green tea and soy isoflavones, citrus products/flavanones with quercetin; and (iv) blood glucose with cocoa and cinnamon. Because of the composition complexity of tea, cocoa, soy and citrus products, it is difficult to emphasize the bioactivity of a specific polyphenol. The more beneficial effect of a dietary polyphenol-rich plant product compared with a single molecule could be explained by the coexistence of diverse phenols molecules and other bioactive substances, which could (i) confer to a better chemical stability within the matrix, notably for highly oxidizable catechins and (ii) provide additive or synergistic effects. Mixture of phenolic compounds may have synergistic effects for certain functions, such as reported by Yang et al (73) for AMP kinase, which could be activated by other phenols than EGCG, such as resveratrol, curcumin or capasicin. Aside, because polyphenols are highly metabolized through the products of microbial breakage in the intestine or hepatic transformation, these are phenolic metabolites that reach target tissues, making the circulating pool of potential bioactive phenolic phytochemicals most distinct from the native molecules. The measurement of the phenolic metabolome in humans would point out which phenolic molecules are present in the plasma/urine of humans followed the intake of polyphenol-rich foods (green tea, cocoa, citrus, apple…) and should facilitate the provision of clearer evidence on the relations between food composition and risk of major chronic diseases such as cancer, cardiovascular diseases or diabetes and shed new light on the causes of such diseases (46). Moreover, some polyphenol supplementations may improve antioxidant and inflammatory status. With regard to all these results, it is difficult to establish the best dose and the ideal food matrix and mode of supplementation. Moreover, further research is needed to evaluate the possible preventive effects of a higher consumption of polyphenols by a combination of their diverse dietary sources (green tea, dark chocolate, berries, citrus fruits…). Because gut microbiota has been demonstrated to play a key role in the development of several pathologies (49), and, in particular, has been recently identified as a possible new cardiovascular disease risk factor (50), the role concerning the interaction of polyphenols with microbiota might be considered in the dietary management of MetS (51,88). It has been estimated that only 5–10% of total polyphenol intake is absorbed in the small intestine (88). The remaining polyphenols (90–95% of total polyphenol intake) may accumulate in the large intestinal lumen up to the millimolar range where, together with conjugates excreted into the intestinal lumen through bile, they are subjected to the enzymatic activities of the gut microbial community (88). Recent studies have in fact suggested that both the phenolic substrates supplied to gut bacteria through different dietary intake patterns and the aromatic metabolites produced may modulate and cause fluctuations in the composition of the microflora populations through selective prebiotic effects and antimicrobial activities against gut pathogenic bacteria (89–94) that could influence its involvement in health problems. Gut microbiota could therefore be an interesting target for exploring the potential role of polyphenols in metabolic balance and weight loss.

Acknowledgements

None.

Conflict of interest statement

No conflict of interest was declared.

No Funding

References

1. Grundy SM. Metabolic syndrome pandemic. *Arterioscler Thromb Vasc Biol* 2008; **28**: 629–636.
2. Ervin RB. Prevalence of metabolic syndrome among adults 20 years of age and over, by sex, age, race and ethnicity, and body mass index: United States, 2003–2006. *Natl Health Stat Report* 2009; **5**: 1–7.
3. Elks CM, Francis J. Central adiposity, systemic inflammation, and the metabolic syndrome. *Curr Hypertens Rep* 2010; **12**: 99–104.
4. Eckel RH, Alberti KGMM, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2010; **375**: 181–183.
5. Macready AL, George TW, Chong MF *et al.* Flavonoid-rich fruit and vegetables improve microvascular reactivity and inflammatory status in men at risk of cardiovascular disease—FLAVURS: a randomized controlled trial. *Am J Clin Nutr* 2014; **99**: 479–489.
6. Lichtenstein AH, Carson JS, Johnson RK *et al.* Food-intake patterns assessed by using front-of-pack labeling program criteria associated with better diet quality and lower cardiometabolic risk. *Am J Clin Nutr* 2014; **99**: 454–462.
7. Babio N, Bulló M, Salas-Salvadó J. Mediterranean diet and metabolic syndrome: the evidence. *Public Health Nutr* 2009; **12**: 1607–1617.
8. Esposito K, Marfella R, Ciotola M *et al.* Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *JAMA* 2004; **292**: 1440–1446.
9. Martínez-González MA, Salas-Salvadó J, Estruch R *et al.* Benefits of the Mediterranean diet: insights from the PREDIMED study. *Prog Cardiovasc Dis* 2015; **58**: 50–60.

© 2016 The Authors. Obesity Reviews published by John Wiley & Sons Ltd on behalf of World Obesity

10. Arts ICW, Hollman PCH. Polyphenols and disease risk in epidemiologic studies. *Am J Clin Nutr* 2005; **81**: 317S–325S.
11. Hooper L, Kroon PA, Rimm EB *et al.* Flavonoids, flavonoid-rich foods, and cardiovascular risk: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2008; **88**: 38–50.
12. Hollman PCH, Geelen A, Kromhout D. Dietary flavonol intake may lower stroke risk in men and women. *J Nutr* 2010; **140**: 600–604.
13. Arab L, Liu W, Elashoff D. Green and black tea consumption and risk of stroke: a meta-analysis. *Stroke* 2009; **40**: 1786–1792.
14. Jing Y, Han G, Hu Y, Bi Y, Li L, Zhu D. Tea consumption and risk of type 2 diabetes: a meta-analysis of cohort studies. *J Gen Intern Med* 2009; **24**: 557–562.
15. Cherniack EP. Polyphenols: planting the seeds of treatment for the metabolic syndrome. *Nutrition* 2011; **27**: 617–623.
16. Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: definitions and controversies. *BMC Med* 2011; **9**: 48.
17. Alberti KGMM, Eckel RH, Grundy SM *et al.* Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009; **120**: 1640–1645.
18. Pérez-Jiménez J, Fezeu L, Touvier M *et al.* Dietary intake of 337 polyphenols in French adults. *Am J Clin Nutr* 2011; **93**: 1220–1228.
19. Zamora-Ros R, Knaze V, Rothwell JA *et al.* Dietary polyphenol intake in Europe: the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Eur J Nutr* 2015.
20. Annuzzi G, Bozzetto L, Costabile G *et al.* Diets naturally rich in polyphenols improve fasting and postprandial dyslipidemia and reduce oxidative stress: a randomized controlled trial. *Am J Clin Nutr* 2014; **99**: 463–471.
21. Nagao T, Komine Y, Soga S *et al.* Ingestion of a tea rich in catechins leads to a reduction in body fat and malondialdehyde-modified LDL in men. *Am J Clin Nutr* 2005; **81**: 122–129.
22. Basu A, Sanchez K, Leyva MJ *et al.* Green tea supplementation affects body weight, lipids, and lipid peroxidation in obese subjects with metabolic syndrome. *J Am Coll Nutr* 2010; **29**: 31–40.
23. Basu A, Du M, Sanchez K *et al.* Green tea minimally affects biomarkers of inflammation in obese subjects with metabolic syndrome. *Nutrition* 2011; **27**: 206–213.
24. Chu S-L, Fu H, Yang J-X *et al.* A randomized double-blind placebo-controlled study of Pu'er tea extract on the regulation of metabolic syndrome. *Chin J Integr Med* 2011; **17**: 492–498.
25. Vieira Senger AE, Schwanke CHA, Gomes I, Valle Gottlieb MG. Effect of green tea (Camellia sinensis) consumption on the components of metabolic syndrome in elderly. *J Nutr Health Aging* 2012; **16**: 738–742.
26. Sulibursk J, Bogdanski P, Szulinska M, Stepien M, Pupek-Musialik D, Jablecka A. Effects of green tea supplementation on elements, total antioxidants, lipids, and glucose values in the serum of obese patients. *Biol Trace Elem Res* 2012; **149**: 315–322.
27. Belcaro G, Ledda A, Hu S, Cesarone MR, Feragalli B, Dugall M. Greenselect Phytosome for borderline metabolic syndrome. *Evid Based Complement Alternat Med* 2013; **2013**: 1–7.
28. Yang T-Y, Chou JI, Ueng K-C *et al.* Weight reduction effect of Puerh tea in male patients with metabolic syndrome. *Phytother Res* 2014; **28**: 1096–1101.
29. Maki KC, Reeves MS, Farmer M *et al.* Green tea catechin consumption enhances exercise-induced abdominal fat loss in overweight and obese adults. *J Nutr* 2009; **139**: 264–270.
30. Yang T-Y, Chou J-I, Ueng K-C *et al.* Weight reduction effect of Puerh tea in male patients with metabolic syndrome. *Phytother Res* 2014; **28**: 1096–1101.
31. Davison K, Coates AM, Buckley JD, Howe PRC. Effect of cocoa flavanols and exercise on cardiometabolic risk factors in overweight and obese subjects. *Int J Obes (Lond)* 2008; **32**: 1289–1296.
32. Berry NM, Davison K, Coates AM, Buckley JD, Howe PRC. Impact of cocoa flavanol consumption on blood pressure responsiveness to exercise. *Br J Nutr* 2010; **103**: 1480–1484.
33. Davison G, Callister R, Williamson G, Cooper KA, Gleeson M. The effect of acute pre-exercise dark chocolate consumption on plasma antioxidant status, oxidative stress and immunoendocrine responses to prolonged exercise. *Eur J Nutr* 2012; **51**: 69–79.
34. D'Anna R, Santamaria A, Cannata ML *et al.* Effects of a new flavonoid and Myo-inositol supplement on some biomarkers of cardiovascular risk in postmenopausal women: a randomized trial. *Int J Endocrinol* 2014; **2014**: 653561.
35. Broncel M, Kozirog M, Duchnowicz P, Koter-Michalak M, Sikora J, Chojnowska-Jezierska J. Aronia melanocarpa extract reduces blood pressure, serum endothelin, lipid, and oxidative stress marker levels in patients with metabolic syndrome. *Med Sci Monit* 2010; **16**: CR28–34.
36. Lehtonen H-M, Suomela J-P, Tahvonen R *et al.* Different berries and berry fractions have various but slightly positive effects on the associated variables of metabolic diseases on overweight and obese women. *Eur J Clin Nutr* 2011; **65**: 394–401.
37. Stull AJ, Cash KC, Johnson WD, Champagne CM, Cefalu WT. Bioactives in blueberries improve insulin sensitivity in obese, insulin-resistant men and women. *J Nutr* 2010; **140**: 1764–1768.
38. Barona J, Blesso CN, Andersen CJ, Park Y, Lee J, Fernandez ML. Grape consumption increases anti-inflammatory markers and upregulates peripheral nitric oxide synthase in the absence of dyslipidemias in men with metabolic syndrome. *Nutrients* 2012; **4**: 1945–1957.
39. Basu A, Rhone M, Lyons TJ. Berries: emerging impact on cardiovascular health. *Nutr Rev* 2010; **68**: 168–177.
40. Brat P, George S, Bellamy A *et al.* Daily polyphenol intake in France from fruit and vegetables. *J Nutr* 2006; **136**: 2368–2373.
41. Egert S, Boesch-Saadatmandi C, Wolffram S, Rimbach G, Müller MJ. Serum lipid and blood pressure responses to quercetin vary in overweight patients by apolipoprotein E genotype. *J Nutr* 2010; **140**: 278–284.
42. Buchholz T, Melzig M. Polyphenolic Compounds as Pancreatic Lipase Inhibitors. *Planta Med* 2015; **81**: 771–783.
43. Baselga-Escudero L, Pascual-Serrano A, Ribas-Latre A *et al.* Long-term supplementation with a low dose of proanthocyanidins normalized liver miR-33a and miR-122 levels in high-fat diet-induced obese rats. *Nutr Res* 2015; **35**: 337–345.
44. Rottiers V, Näär AM. MicroRNAs in metabolism and metabolic disorders. *Nat Rev Mol Cell Biol* 2012; **13**: 239–250.
45. Hanhineva K, Törrönen R, Bondia-Pons I *et al.* Impact of dietary polyphenols on carbohydrate metabolism. *Int J Mol Sci* 2010; **11**: 1365–1402.
46. Mursu J, Virtanen JK, Tuomainen T-P, Nurmi T, Voutilainen S. Intake of fruit, berries, and vegetables and risk of type 2 diabetes in Finnish men: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Am J Clin Nutr* 2014; **99**: 328–333.
47. Andriantsitohaina R, Auger C, Chataigneau T *et al.* Molecular mechanisms of the cardiovascular protective effects of polyphenols. *Br J Nutr* 2012; **108**: 1532–1549.
48. Sivaprakasapillai B, Edirisinghe I, Randolph J, Steinberg F, Kappagoda T. Effect of grape seed extract on blood pressure in subjects with the metabolic syndrome. *Metab Clin Exp* 2009; **58**: 1743–1746.
49. Chiva-Blanch G, Badimon L, Estruch R. Latest evidence of the effects of the Mediterranean diet in prevention of cardiovascular disease. *Curr Atheroscler Rep* 2014; **16**: 446.

© 2016 The Authors. Obesity Reviews published by John Wiley & Sons Ltd on behalf of World Obesity

50. Walther G, Obert P, Dutheil F *et al.* Metabolic syndrome individuals with and without type 2 diabetes mellitus present generalized vascular dysfunction: cross-sectional study. *Arterioscler Thromb Vasc Biol* 2015; **35**(4): 1022–1029.
51. Barona J, Aristizabal JC, Blesso CN, Volek JS, Fernandez ML. Grape polyphenols reduce blood pressure and increase flow-mediated vasodilation in men with metabolic syndrome. *J Nutr* 2012; **142**: 1626–1632.
52. Mulero J, Bernabé J, Cerdá B *et al.* Variations on cardiovascular risk factors in metabolic syndrome after consume of a citrus-based juice. *Clin Nutr* 2012; **31**: 372–377.
53. Ziegenfuss TN, Hofheins JE, Mendel RW, Landis J, Anderson RA. Effects of a water-soluble cinnamon extract on body composition and features of the metabolic syndrome in pre-diabetic men and women. *J Int Soc Sports Nutr* 2006; **3**: 45–53.
54. Askari F, Rashidkhani B, Hekmatdoost A. Cinnamon may have therapeutic benefits on lipid profile, liver enzymes, insulin resistance, and high-sensitivity C-reactive protein in nonalcoholic fatty liver disease patients. *Nutr Res* 2014; **34**: 143–148.
55. Allison DB, Gadbury G, Schwartz LG *et al.* A novel soy-based meal replacement formula for weight loss among obese individuals: a randomized controlled clinical trial. *Eur J Clin Nutr* 2003; **57**: 514–522.
56. Usui T, Tochiya M, Sasaki Y *et al.* Effects of natural S-equol supplements on overweight or obesity and metabolic syndrome in the Japanese, based on sex and equol status. *Clin Endocrinol (Oxf)* 2013; **78**: 365–372.
57. Romualdi D, Costantini B, Campagna G, Lanzone A, Guido M. Is there a role for soy isoflavones in the therapeutic approach to polycystic ovary syndrome? Results from a pilot study. *Fertil Steril* 2008; **90**: 1826–1833.
58. Egert S, Bosy-Westphal A, Seiberl J *et al.* Quercetin reduces systolic blood pressure and plasma oxidised low-density lipoprotein concentrations in overweight subjects with a high-cardiovascular disease risk phenotype: a double-blinded, placebo-controlled cross-over study. *Br J Nutr* 2009; **102**: 1065–1074.
59. Rizza S, Muniyappa R, Iantorno M *et al.* Citrus polyphenol hesperidin stimulates production of nitric oxide in endothelial cells while improving endothelial function and reducing inflammatory markers in patients with metabolic syndrome. *J Clin Endocrinol Metab* 2011; **96**: E782–792.
60. Brown AL, Lane J, Coverly J *et al.* Effects of dietary supplementation with the green tea polyphenol epigallocatechin-3-gallate on insulin resistance and associated metabolic risk factors: randomized controlled trial. *Br J Nutr* 2009; **101**: 886–894.
61. Fujitaka K, Otani H, Jo F *et al.* Modified resveratrol Longevinex improves endothelial function in adults with metabolic syndrome receiving standard treatment. *Nutr Res* 2011; **31**: 842–847.
62. Dash S, Xiao C, Morgantini C, Szeto L, Lewis GF. High-dose resveratrol treatment for 2 weeks inhibits intestinal and hepatic lipoprotein production in overweight/obese men. *Arterioscler Thromb Vasc Biol* 2013; **33**: 2895–2901.
63. Méndez-del Villar M, González-Ortiz M, Martínez-Abundis E, Pérez-Rubio KG, Lizárraga-Valdez R. Effect of resveratrol administration on metabolic syndrome, insulin sensitivity, and insulin secretion. *Metab Syndr Relat Disord* 2014; **12**: 497–501.
64. Van der Made SM, Plat J, Mensink RP. Resveratrol does not influence metabolic risk markers related to cardiovascular health in overweight and slightly obese subjects: a randomized, placebo-controlled crossover trial. *PLoS One* 2015; **10**: e0118393.
65. Most J, Goossens GH, Jocken JWE, Blaak EE. Short-term supplementation with a specific combination of dietary polyphenols increases energy expenditure and alters substrate metabolism in overweight subjects. *Int J Obes (Lond)* 2014; **38**: 698–706.
66. Phenol-explorer. Database on polyphenol content in foods (http://phenol-explorer.eu)
67. Larsson SC. Coffee, Tea, and Cocoa and Risk of Stroke. *Stroke* 2014; **45**: 309–314.
68. Brown AL, Lane J, Coverly J *et al.* Effects of dietary supplementation with the green tea polyphenol epigallocatechin-3-gallate on insulin resistance and associated metabolic risk factors: randomized controlled trial. *Br J Nutr* 2009; **101**: 886–894.
69. Legeay S, Rodier M, Fillon L, Faure S, Clere N. Epigallocatechin gallate: a review of its beneficial properties to prevent metabolic syndrome. *Nutrients* 2015; **7**: 5443–5468.
70. Dulloo AG, Duret C, Rohrer D *et al.* Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans. *Am J Clin Nutr* 1999; **70**(6): 1040–5.
71. Dulloo AG, Seydoux J, Girardier L, Chantre P, Vandermander J. Green tea and thermogenesis: interactions between catechin-polyphenols, caffeine and sympathetic activity. *Int J Obes Relat Metab Disord* 2000; **24**(2): 252–8.
72. Lin J-K, Lin-Shiau S-Y. Mechanisms of hypolipidemic and anti-obesity effects of tea and tea polyphenols. *Mol Nutr Food Res* 2006; **50**: 211–217.
73. Yang CS, Zhang J, Zhang L, Huang J, Wang Y. Mechanisms of body weight reduction and metabolic syndrome alleviation by tea. *Mol Nutr Food Res* 2016; **60**: 160–174.
74. Basu A, Fu DX, Wilkinson M *et al.* Strawberries decrease atherosclerotic markers in subjects with metabolic syndrome. *Nutr Res* 2010; **30**: 462–469.
75. Basu A, Betts NM, Ortiz J, Simmons B, Wu M, Lyons TJ. Low-energy cranberry juice decreases lipid oxidation and increases plasma antioxidant capacity in women with metabolic syndrome. *Nutr Res* 2011; **31**: 190–196.
76. Li Z, Hong K, Saltsman P *et al.* Long-term efficacy of soy-based meal replacements vs an individualized diet plan in obese type II DM patients: relative effects on weight loss, metabolic parameters, and C-reactive protein. *Eur J Clin Nutr* 2005; **59**: 411–418.
77. Anderson JW, Fuller J, Patterson K, Blair R, Tabor A. Soy compared to casein meal replacement shakes with energy-restricted diets for obese women: randomized controlled trial. *Metab Clin Exp* 2007; **56**: 280–288.
78. Naaz A, Yellayi S, Zakroczymski MA *et al.* The soy isoflavone genistein decreases adipose deposition in mice. *Endocrinology* 2003; **144**: 3315–3320.
79. Setchell KDR, Cole SJ. Method of defining equol-producer status and its frequency among vegetarians. *J Nutr* 2006; **136**: 2188–2193.
80. Konings E, Timmers S, Boekschoten MV *et al.* The effects of 30 days resveratrol supplementation on adipose tissue morphology and gene expression patterns in obese men. *Int J Obes (Lond)* 2014; **38**: 470–473.
81. Moreno-Luna R, Muñoz-Hernandez R, Miranda ML *et al.* Olive oil polyphenols decrease blood pressure and improve endothelial function in young women with mild hypertension. *Am J Hypertens* 2012; **25**: 1299–1304.
82. Petrone AB, Gaziano JM, Djoussé L. Effects of dark chocolate and cocoa products on endothelial function: a meta-analysis. *Current Nutrition Reports* 2013; **2**: 267–273.
83. Cook NR, Cohen J, Hebert PR, Taylor JO, Hennekens CH. Implications of small reductions in diastolic blood pressure for primary prevention. *Arch Intern Med* 1995; **155**: 701–709.
84. Van der Made SM, Plat J, Mensink RP. Resveratrol does not influence metabolic risk markers related to cardiovascular health in overweight and slightly obese subjects: a randomized, placebo-controlled crossover trial. *PLoS One* 2015; **10**: e0118393.

© 2016 The Authors. Obesity Reviews published by John Wiley & Sons Ltd on behalf of World Obesity

85. Fisher NDL, Hughes M, Gerhard-Herman M, Hollenberg NK. Flavanol-rich cocoa induces nitric-oxide-dependent vasodilation in healthy humans. *J Hypertens* 2003; **21**: 2281–2286.
86. Medina-Remón A, Tresserra-Rimbau A, Pons A *et al*. Effects of total dietary polyphenols on plasma nitric oxide and blood pressure in a high cardiovascular risk cohort. The PREDIMED randomized trial. *Nutr Metab Cardiovasc Dis* 2015; **25**: 60–67.
87. Di Renzo L, Rizzo M, Sarlo F *et al*. Effects of dark chocolate in a population of normal weight obese women: a pilot study. *Eur Rev Med Pharmacol Sci* 2013; **17**: 2257–2266.
88. Edmands WM, Ferrari P, Rothwell JA *et al*. Polyphenol metabolome in human urine and its association with intake of polyphenol-rich foods across European countries. *Am J Clin Nutr* 2015; **102**(4): 905–13.
89. Clemente JC, Ursell LK, Parfrey LW, Knight R. The impact of the gut microbiota on human health: an integrative view. *Cell* 2012; **148**: 1258–1270.
90. Tuohy KM, Fava F, Viola R. "The way to a man's heart is through his gut microbiota"—dietary pro- and prebiotics for the management of cardiovascular risk. *Proc Nutr Soc* 2014; **73**: 172–185.
91. Etxeberria U, Fernández-Quintela A, Milagro FI, Aguirre L, Martínez JA, Portillo MP. Impact of polyphenols and polyphenol-rich dietary sources on gut microbiota composition. *J Agric Food Chem* 2013; **61**: 9517–9533.
92. Cardona F, Andrés-Lacueva C, Tulipani S, Tinahones FJ, Queipo-Ortuño MI. Benefits of polyphenols on gut microbiota and implications in human health. *J Nutr Biochem* 2013; **24**: 1415–1422.
93. Laparra JM, Sanz Y. Interactions of gut microbiota with functional food components and nutraceuticals. *Pharmacol Res* 2010; **61**: 219–225.
94. Espley RV, Butts CA, Laing WA *et al*. Dietary flavonoids from modified apple reduce inflammation markers and modulate gut microbiota in mice. *J Nutr* 2014; **144**: 146–154.

© 2016 The Authors. Obesity Reviews published by John Wiley & Sons Ltd on behalf of World Obesity