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Higher habitual dietary flavonoid intake associates with lower central blood pressure and arterial stiffness in healthy older adults

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Abstract

Flavonoids have shown anti-hypertensive and anti-atherosclerotic properties: the impact of habitual flavonoid intake on vascular function, central haemodynamics and arterial stiffness may be important. We investigated the relationship between habitual flavonoid consumption and measures of central blood pressure and arterial stiffness. We performed cross-sectional analysis of 381 non-smoking healthy older adults (mean age 66·0 (SD 4·1) years; BMI, 26·4 (SD 4·41) kg/m^2; 41 % male) recruited as part of the Australian Research Council Longevity Intervention study. Flavonoid intake (i.e. flavonols, flavones, flavanones, anthocyanins, isoflavones, flavan-3-ol monomers, proanthocyanidins, theaflavins/thearubigins and total consumption) was estimated from FFQ using the US Department of Agriculture food composition databases. Measures of central haemodynamics and arterial stiffness included systolic blood pressure (cSBP), diastolic blood pressure (cDBP), mean arterial pressure (cMAP) and augmentation index (cAIx). After adjusting for demographic and lifestyle confounders, each SD/d higher intake of anthocyanins ((SD 44·3) mg/d) was associated with significantly lower cDBP (−1·56 mmHg, 95 % CI −2·65, −0·48) and cMAP (−1·62 mmHg, 95 % CI −2·82, −0·41). Similarly, each SD/d higher intake of flavanones ((SD 19·5) mg/d) was associated with ~1 % lower cAIx (−0·93 %, 95 % CI −1·77, −0·09). These associations remained significant after additional adjustment for (1) a dietary quality score and (2) other major nutrients that may affect blood pressure or arterial stiffness (i.e. Na, K, Ca, Mg, *n*-3, total protein and fibre). This study suggests a possible benefit of dietary anthocyanin and flavanone intake on central haemodynamics and arterial stiffness; these findings require corroboration in further research.

Key words: **Nutrition: Flavonoids: Blood pressure: Arterial stiffness: Epidemiology: Diet and nutrition**

The clinical combination of high blood pressure and large-artery stiffening is implicated in the development of atherosclerotic CVD (ASCVD), the most common non-communicable disease worldwide[1,2]. In a vicious cycle, high blood pressure, diabetes and atherosclerosis appear to amplify vascular changes that accelerate vascular stiffening, while increasing arterial stiffness seems to increase blood pressure, leading to the progression of atherosclerotic alterations[2]. Accumulating evidence indicates that higher intakes of dietary flavonoids, a class of bioactive (poly)phenolic compounds found in plant foods (and comprised of the subclasses: flavonols, flavan-3-ols, anthocyanins, flavones, isoflavones and flavanones), may be associated with a lower risk of ASCVD[3,4]. The benefits of flavonoids on ASCVD are likely due, at least in part, to their favourable effects on vascular function, blood pressure and arterial stiffness[3,5–7].

Flavonoids have shown anti-hypertensive and anti-atherosclerotic properties. Meta-analyses of randomised controlled trials (RCT) investigating specific flavonoid-rich products, such as flavan-3-ol-rich cocoa and black tea, isoflavone-rich soya protein, anthocyanin-rich berries and isolated (purified) flavonol

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; cAIx, central augmentation index; cDBP, central diastolic blood pressure; cMAP, central mean arterial pressure; cSBP, central systolic blood pressure; HEIFA, Healthy Eating Index for Australian Adults; RCT, randomised controlled trial.

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capsules, have found that flavonoid interventions can significantly reduce blood pressure[8–11]. Studies have also shown that intervention with cocoa or isoflavone-rich foodstuffs significantly lowers arterial stiffness, relative to control[12,13]. However, research examining habitual dietary intake of flavonoids in relation to blood pressure and arterial stiffness is unclear. Among observational reports, results more often indicate that higher habitual dietary consumption of anthocyanins may be associated with lower blood pressure and a lower risk of incident hypertension[14–20]. However, support for the other subclasses as well as total flavonoid intake is less consistent[14–20]. Epidemiological evidence also suggests higher habitual dietary anthocyanin or flavone consumption may be associated with lower arterial stiffness[15].

Flavonoids have been shown to directly affect blood pressure and arterial stiffness in clinical trials[8–13]. However, these interventions are often given at concentrations much higher than would be naturally achievable in the diet. Observational studies of habitual flavonoid intakes in a population of healthy adults are thus useful, to explore if the levels of flavonoids habitually consumed are associated with blood pressure and arterial stiffness. Furthermore, observational studies are useful to identify which subclasses show an association and which foods these flavonoids come from. Consequently, the aim of this study was to investigate the relation of habitual dietary flavonoid consumption with central haemodynamics and arterial stiffness.

Method

Study design

The current investigation reports on baseline data collected prior to randomisation as part of a larger clinical trial: the Australian Research Council Longevity Intervention study, which investigated the effects of pharmacological interventions on cognitive and vascular health[21]. The study was approved by the Swinburne University Institutional Human Research Ethics committee (ethics approval number 20190429-1737) and all participants provided informed consent. Described in detail previously[21], a convenience sample of healthy male and female community-dwelling older adults (aged 60–75 years) were recruited from Melbourne, Australia between 2011 and 2020. Volunteers were excluded if they: were taking cognitive enhancing supplements (e.g. Ginkgo biloba); were current smokers; had a history of drug and/or alcohol misuse; a diagnosis of diabetes, CVD, dementia, neurological or psychiatric disorder; a history of depression (as determined by the Geriatric Depression Scale ≥ 10); or were currently taking prescribed antidepressant, anxiolytic or antipsychotic medication. Participants with mild conditions such as medically managed cardiovascular disorders (i.e. hypertension or hypercholesterolemia) were included in the study; those with total cholesterol $> 7{\cdot}7$ mmol/l or peripheral blood pressure $> 160/90$ mmHg were excluded. Participants were cognitively intact with a score of 24 or greater on the Mini-Mental State Examination[22]. Those scoring between 24 and 26 on the Mini-Mental State Examination were assessed for probable dementia using the Dementia Rating Scale-II (with subsequent eligibility determined by a study safety committee)[23]. At baseline, eligible participants attended study centres for assessment, completing questionnaires on sociodemographic factors and dietary intake, while measures of anthropometry, blood pressure and arterial stiffness were obtained by professional staff in a single visit. Of the 575 participants enrolled into Australian Research Council Longevity Intervention at baseline, 496 completed a FFQ with plausible energy intakes (2092–20920 Kj/d). After excluding participants with missing covariate (n 19) or outcome data (n 96), 381 participants remained for analysis.

Study outcomes: blood pressure and arterial stiffness

After a quiet, 5-min rest period, peripheral blood pressure was measured (average of 3 readings) using an automated cuff sphygmomanometer (Omron, Model 705IT). Measures were obtained with participants sitting upright in a chair, legs planted on the ground; their left arm was extended on a desk or resting on their leg. Central vascular measurements were performed using the validated non-invasive SphygmoCor system (AtCor Medical, Model CVMS-CPV)[24]. With peripheral blood pressure as the calibrating measure, this method applies applanation tonometry of the radial artery to estimate aortic pressure waveforms using a validated transfer function[24]. From the aortic pressure waveforms, the following variables were calculated: central systolic blood pressure (cSBP), central diastolic blood pressure (cDBP), central mean arterial pressure (cMAP) and central augmentation index (cAIx). The indices describe different aspects of central haemodynamics and arterial stiffness as follows: cSBP describes blood pressure in the aorta when the heart contracts, with higher pressures implicated in the pathogenesis of CVD[25,26]; cDBP is the minimum aortic pressure when the heart relaxes with a lower pressure desirable for the prevention of hypertension[26,27]; cMAP (calculated as 1/3 cSBP plus 2/3 cDBP) is the average arterial pressure throughout one cardiac cycle and its elevation is implicated in CVD[26,28]; cAIx expresses augmentation pressure as a percentage of central pulse pressure and provides an indirect estimate of aortic stiffness with higher values associating with poorer cardiovascular outcomes[24,29]. The central measures (i.e. cSBP, cDBP, cMAP and cAIx) appear better related to future cardiovascular events than brachial measures (e.g. peripheral BP or AIx), thus providing additional information of disease progression in their assessment[30].

Assessment of diet and flavonoid intake

Dietary data were collected using a 112-item FFQ[21]. The FFQ, which was developed specifically to investigate habitual diet, consisted of eight categories which queried consumption of (1) dairy, (2) breads and cereals, (3) meats, fish and eggs, (4) vegetables, (5) fruit, (6) baked goods and snacks, (7) sugars, spreads and dressings and (8) non-milk beverages including alcohol. Respondents were asked to indicate their usual frequency of consumption of food items during the past year, using a nine-category frequency scale that ranged from never to four or more times per day. Each participant received oral and written instructions on how to complete the FFQ which was conducted on the day of testing, then checked by researchers for accuracy and corrected as needed. Daily food intake in grams was calculated for

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each study participant based on the frequency reported in the FFQ with portion size estimated using standard household measures and previously published sources[31]. In a subsample of participants (n 109), the FFQ was tested for relative validity against the average of three 24-h diet recalls collected over 1 week, including two weekdays and one weekend day. Using the *AUSNUT* 2011–2013 database[32], which contains information on nutrients and food groups, we estimated the average serves of food groups per day (i.e. grains, meats, fruits, vegetables and dairy) as well as each participants' intake of energy and macronutrients reported in the FFQ and 24-h recalls alike. Non-parametric correlations between the FFQ and 24-h recalls were as follows: serves of fruits (r_s 0·475, $P < 0·0001$), vegetables (r_s 0·268, $P = 0·006$), grains (r_s 0·610, $P < 0·0001$), dairy (r_s 0·321, $P < 0·001$) and meats (r_s 0·341, $P < 0·001$); intake of energy (r_s 0·411, $P < 0·0001$), protein (r_s 0·426, $P < 0·0001$), fats (r_s 0·419, $P < 0·0001$) and carbohydrates (r_s 0·489, $P < 0·0001$).

Flavonoid intake was estimated using the US Department of Agriculture Database for the Flavonoid Content of Selected Foods (release 3.2)[33], the US Department of Agriculture Database for the Isoflavone Content of Selected Foods (release 2.1)[34] and the US Department of Agriculture Database for the Proanthocyanidin Content of Selected Foods (release 2.0)[35]. Intakes of individual flavonoid compounds were estimated using the flavonoid content reported in the databases for each food and beverage item in the FFQ. We applied yield factors where relevant, to convert uncooked foods reported in the US Department of Agriculture databases to their cooked equivalents and calculated recipes for mixed meals using ingredients previously reported in the AUSNUT 2011–2013 database. Where the FFQ described a food with multiple varieties but did not define type (e.g. cup of tea), we included the variety most applicable to the demographic (e.g. black tea instead of green tea) and most generic (e.g. apple (Malus domestica) instead of Granny Smith, etc.). Subclasses of flavonoid intake were summed based on chemical structure as follows: flavanones (eriodictyol, hesperetin and naringenin), anthocyanins (cyanidin, delphinidin, malvidin, pelargonidin, petunidin and peonidin), flavan-3-ols (monomers, proanthocyanidins and theaflavins + thearubigins), flavonols (quercetin, kaempferol, myricetin and isohamnetin), flavones (luteolin and apigenin) and isoflavones (daidzein, genistein and glycitein). Subdivisions of the flavan-3-ol subclass were calculated as follows: monomers (catechins and epicatechins), proanthocyanidins (dimers, trimers, 4–6 mers, 7–10 mers and polymers) and other derived products (theaflavins and thearubigins). Total flavonoid intake was estimated as the sum of flavonols, flavones, flavanones, anthocyanins, isoflavones and flavan-3-ols.

Covariates

Information on age, sex, ethnicity, education and medication use was collected by questionnaire. Physical activity was assessed by asking participants about the nature and frequency of the physical activity they perform in a typical/usual week. Based on these responses, physical activity was classified into five ordered categories ranging from zero (no exercise or walking less than 2 d/week) to five (walking 5+ d/week in addition to 4+ weekly sessions of high intensity physical activity). Scoring of physical activity was performed independently by two researchers to ensure agreement. As less than 10 participants reported no exercise, for analyses purposes, they were collapsed into a nil to low exercise group. Anthropometric measurements were assessed with participants wearing minimal clothing and no shoes. Standing height (m) was measured with the use of a wall-mounted stadiometer to the nearest 0·01 m. Fasting body weight (kg) was measured with the use of electronic scales to the nearest 0·01 kg. BMI was calculated as weight (kg) divided by height (m) squared. The Healthy Eating Index for Australian Adults (HEIFA) was used to assess overall diet quality, with the criteria scoring system modified to meet the Australian Dietary Guidelines for older adults[36]. The HEIFA score summarises the quantity and quality of food groups and nutrients consumed in the diet (including intake of fruits, vegetables, grains/cereals, dairy, meats (including poultry, red meat, fish, eggs, tofu, nuts, and seeds, and legumes/beans) and discretionary foods in addition to water, alcohol, Na, saturated fat, polyunsaturated fat and monounsaturated fat). In the present analysis, major dietary sources of flavonoids (fruit, vegetables, wine, beer, tofu, nuts, seeds and legumes/beans) were excluded from calculation of the HEIFA score to allow for a clearer interpretation of the statistical model including HEIFA as a covariate.

Statistical analysis

We used multivariable linear regression to examine the association between habitual dietary flavonoid intake (SD/d) and blood pressure/arterial stiffness. Three models of adjustment were computed. The basic model (model 1) was adjusted for: age (years) sex (male/female), BMI (kg/m^2), physical activity (nil to low/moderate/medium/high), alcohol intake (g/d), education (high school or early leaver/tertiary/post-graduate), antihypertensive medication use (yes/no), statin use (yes/no) and energy intake (kJ/d) using the standard multivariable method of energy adjustment. Model 2 was adjusted for all covariates in model 1 plus the diet quality score (HEIFA). When AIx was the outcome of interest, models 1 and 2 additionally included heart rate and cMAP[37]. We then conducted additional sensitivity analyses to investigate possible confounding by other key dietary components that have been shown to affect blood pressure or arterial stiffness[38,39]. These dietary factors, added one at a time to model 1, were: Na, K, Ca, n-3, Mg, total protein and fibre. In a further sensitivity analysis, we added total fruit and total vegetable intake to model 2. In all models, linear regression assumptions were checked by visual inspection of residuals v. fitted plots, Q-Q plots and spread-location plots, with no marked violations found. The absence of multicollinearity was confirmed by checking variance inflation factors in all models (all < 2 in primary analyses and < 5 in sensitivity analyses). As determined by Cook's distance, no potential outliers were influential to the regression results, and thus all data were retained in all analyses. Given the conceptual and statistical inter-relationships between flavonoid subclasses, we examined each exposure individually and did not mutually adjust for other flavonoid subclasses in our models. Analyses were performed using R Statistical Software

(R Core team)[40]. Associations were considered significant at a two-tailed *P*-value of 0·05 or less.

Results

Study population

In this non-smoking cohort, free of diabetes and major CVD, participants were mostly female (60 %) and of Caucasian descent (94 %), with a mean age of 66·0 (SD 4·1) years, and an average BMI of 26·4 kg/m^2 (Table 1). The cohort, on average, had a blood pressure within normal range at a mean peripheral SBP of 129·2 (SD 155·7) mmHg over a DBP of 74·4 (SD 10·3) mmHg; their corresponding mean central blood pressure was 120·0 (SD 155·6) mmHg cSBP over 75·2 (SD 10·4) mmHg cDBP (Table 1). Approximately 36 % of study participants were hypertensive (defined as peripheral SBP > 140 mmHg or peripheral DBP > 90 mmHg or anti-hypertensive medication use). On average, the peripheral MAP was within normal range, at a mean of 92·7 (SD 11·2) mmHg; the central measure for cMAP was 90·1 (SD 11·3) mmHg. Central arterial stiffness, as determined by cAIx, was on average within a healthy range (< 30 %) for a Caucasian population of this age group at a mean of 29·8 (SD 9·79) %[41].

The range of total daily flavonoid intake was wide (12·1–1844·9 mg) with participants consuming a mean of 678·4 (SD 375·8) mg/d (Table 2). Subclasses with the largest contribution to total flavonoid intake were proanthocyanidins (36·5 %), theaflavins and thearubigins (33·4 %) and flavan-3-ol monomers (14·3 %), with anthocyanins (7·2 %), flavonols (4·3 %), flavanones (3·3 %), isoflavones (0·8 %) and flavones (0·2 %) contributing less (Table 2). Food sources contributing the most to total flavonoid intake were black tea (47·4 %), berries (11·7 %), dark chocolate (9·5 %) and apples/pears (5·9 %) (Table 2). Among subclasses, intake was driven by black tea (36·6 %) and salad (10·2 %) for flavonols; celery (15·4 %) and pumpkin (14·3 %) for flavones; citrus fruit (63·4 %) and fruit juice (16·3 %) for flavanones; berries (60·4 %) and red wine (13·9 %) for anthocyanins; soyamilk (34·0 %) and bread with soya (31·0 %) for isoflavones; and black tea (54·3 %) and dark chocolate (11·2 %) for total flavan-3-ols (Table 2). Compared with participants consuming low total flavonoids, those consuming higher intakes tended to be female, have a lower BMI, be more physically active and use less medications (Table 1). They also consumed more fruits and vegetables and had an overall better dietary quality (Table 1).

Associations between habitual flavonoid intake and blood pressure

After adjusting for potential demographic and lifestyle confounders, each one SD/d higher anthocyanin intake ((SD 44·3) mg/d) was associated with a 1·72 mmHg lower cSBP (95 % CI −3·42, −0·03), a 1·56 mmHg lower cDBP (95 % CI −2·65, −0·48) and a 1·62 mmHg lower cMAP (95 % CI −2·82, −0·41; model 1; Table 3). Following additional adjustment for diet quality, the relationship between anthocyanins and cSBP was not significant (−1·44 mmHg, 95 % CI −3·16, 0·29) yet an association with cDBP and cMAP was present (model 2; Table 3). Among other subclasses, higher intakes (per one SD/d) of flavones ((SD 0·73) mg/d) and proanthocyanidins ((SD 155·2) mg/d) were significantly associated with lower cDBP (flavones: −1·33 mmHg, 95 % CI −2·44, −0·23; proanthocyanidins: −1·35 mmHg, 95 % CI −2·56, −0·15; Model 1; Table 3). Both the flavone and proanthocyanidin subclasses remained significantly associated with cDBP after additional adjustment for dietary quality (model 2; Table 3). Intakes of flavonols were also inversely associated with cDBP (−1·11 mmHg, 95 % CI −2·20, −0·02; model 1) and following additional adjustment for dietary quality, a marginal association remained (−1·00 mmHg, 95 % CI −2·09, 0·10; model 2; Table 3). Total flavonoid intake was not associated with any measure of blood pressure or arterial stiffness (Table 3).

Associations between habitual flavonoid intake and arterial stiffness

The only subclass clearly associated with lower arterial stiffness was flavanones. In the demographic and lifestyle adjusted model, for each 19·5 mg/d higher flavanone intake, cAIx was 0·93 % lower (95 % CI −1·77, −0·09); this association remained statistically significant following additional adjustment for dietary quality (models 1 and 2; Table 3). Intake of theaflavins and thearubigins was marginally associated with cAIx in models 1 and 2, as was flavan-3-ol monomer intake, with higher consumption being associated with lower arterial stiffness (theaflavins and thearubigins: −0·78 %, 95 % CI −1·58, 0·01; monomers: −0·76 %, 95 % CI −1·57, 0·06; model 2; Table 3). We then examined derived flavan-3-ol compounds excluding thearubigins, as current quantification methods of their analysis are somewhat crude[3]. Total theaflavin intake ((SD 12·2) mg/d) per additional one SD/d was marginally inversely associated with lower cAIx after adjustment for dietary quality (−0·79 %, 95 % CI −1·59, 0·003; model 2).

Investigating potential dietary confounders

Given the potential for confounding by other key nutrients that may be associated with blood pressure or arterial stiffness, we performed additional sensitivity analyses that individually adjusted for intakes of Na, K, Ca, *n*-3, Mg, total protein and fibre (per one SD/d) including covariates in model 1. The significant beneficial associations of anthocyanins with cMAP and cDBP remained as did the relationship between flavanones and cAIx, when either Na, K, Ca, Mg, *n*-3, total protein or fibre were added to the model (data not shown). However, the significant beneficial associations of cDBP with flavones and proanthocyanidins were both attenuated by the addition of K, but not any of the other nutrients/factors, with the risk estimate for each subclass changing by >15 % in both models (flavones: −1·08 mmHg, 95 % CI −2·46, 0·30; proanthocyanidins: −1·16 mmHg, 95 % CI −2·39, 0·07; model 1 + K). When total fruit and total vegetable intake was added to the demographic, lifestyle and diet quality adjusted model, the inverse associations between anthocyanins and cMAP and cDBP, as well as flavanones with cAIx, remained significant (data not shown).

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Table 1. Characteristics of the non-smoking study participants (*n* 381)[1]
(Numbers and percentages; mean values and standard deviations)

	Total population		Total flavonoid intake			
			Low (Q1) *n* 96		High (Q4) *n* 95	
Demographics						
Sex [male; *n* (%)]	155	40·7	37	38·5	32	33·7
Age (years)	66·0	4·1	65·7	4·1	66·1	4·2
BMI (kg/m^2)	26·4	4·41	27·3	4·9	25·6	4·2
Education [*n* (%)]						
High school or early leaver	93	24·4	26	27·1	25	26·3
Tertiary	167	43·8	43	44·8	43	45·3
Post-graduate	121	31·8	27	28·1	27	28·4
Physical activity [*n* (%)]						
Nil to low	84	22·0	30	31·2	18	18·9
Moderate	144	37·8	35	36·5	35	36·8
Medium	121	31·8	21	21·9	32	33·7
High	32	8·4	10	10·4	10	10·5
Hypertensive medication use [yes; *n* (%)]	78	31·8	24	25·0	19	20·0
Statin use [yes; *n* (%)]	62	16·3	16	16·7	10	10·5
Dietary intake						
Energy (kJ)	8150	2700	6560	2370	9270	2490
Food groups (serves/d)						
Fruit	2·3	1·5	1·5	1·0	3·0	2·00
Vegetables	3·6	1·7	3·0	1·3	4·4	2·1
Dairy	1·6	1·0	1·2	0·9	1·8	0·9
Meat	3·1	1·5	2·6	1·2	3·6	1·6
Grains	4·8	2·2	4·1	2·1	5·1	2·3
Diet quality (modified HEIFA score)	53·8	6·7	53·6	6·3	54·9	5·8
Other factors						
Total protein (g/d)	91·3	34·4	76·3	27·5	103	31·5
Na (m/d)	1790	670	1500	625	1970	681
K (mg/d)	3520	1200	2830	982	4090	1290
Mg (mg/d)	609	234	529	245	653	247
Ca (mg/d)	835	351	666	314	962	325
Fibre (g/d)	26·1	9·8	20·0	7·39	31·8	11·4
n-3 (mg/d)	737	809	602	550	779	595
Alcohol (g/d)	8·1	9·9	6·0	8·40	9·3	13·3
Clinical parameters						
Central systolic blood pressure (mmHg)	120·0	15·6	121·5	15·8	120·1	15·7
Central diastolic blood pressure (mmHg)	75·2	10·4	76·8	10·6	74·1	10·5
Central mean arterial pressure (mmHg)	90·1	11·3	91·7	11·5	89·4	11·5
Central augmentation index (%)	29·8	9·79	30·9	10·1	29·3	9·17

[1]Results presented as means (SD) unless stated. HEIFA, Healthy Eating Index for Australian Adults.

Discussion

In this cohort of healthy, older, non-smoking, male and female adults, we found higher habitual consumption of several flavonoid subclasses appear associated with lower central haemodynamics and arterial stiffness. In demographic and lifestyle adjusted models, a higher habitual anthocyanin intake was significantly associated with lower cDBP and cMAP. Independent of demographic and lifestyle factors, a higher flavanone consumption was significantly associated with lower arterial stiffness. To lessen the chance of residual confounding by other nutrients or dietary factors, we show that these results remain statistically significant after the additional adjustment of a dietary quality score (excluding fruits and vegetables), the dietary quality score plus total fruit and total vegetable intake as well as individually controlling for Na, K, Ca, Mg, *n*-3, total protein and fibre. Overall, these results support the hypothesis that higher habitual intake of selected flavonoids may protect against ASCVD through anti-hypertensive and arterial stiffness lowering properties[3,42].

Our study found evidence which supports a benefit of anthocyanin intake on blood pressure. This is in agreement with most prior observational studies which have observed significant inverse associations between anthocyanin consumption and blood pressure outcomes including hypertension[16–18,20,43]. Indeed, a recent meta-analysis of observational studies found higher anthocyanin intake, but not other flavonoid subclasses, associated with lower incident hypertension[5]. This concurs with findings of another recent meta-analysis which pooled results from > 30 RCT examining intakes of anthocyanin-rich berries or their products and showed that intervention significantly improves blood pressure in comparison with control[11]. Interestingly, berry intake drove ~60 % of anthocyanin consumption in the present study. It is unclear however, why there was a clear association with diastolic, but not systolic pressure in our study, although differential blood pressure findings have been previously observed[44]. For example, in a crossover RCT, mixed (poly)phenol intervention reduced only DBP[44]. In the trial, the change in DBP was accompanied by a significant increase in

Table 2. Flavonoid intake of the study participants (*n* 381)
(Mean values and standard deviations)

Flavonoids				
Class	Intake (mg/d)			
	Mean	SD	Respective makeup	Top dietary contributors
Total flavonoids*	678·4	375·8	Proanthocyanidins (36·5 %), theaflavins/thearubigins (33·4 %), monomers (14·3 %), anthocyanin (7·2 %), flavonols (4·3 %), flavanones (3·3 %), isoflavones (0·8 %), flavones (0·2 %)	Black tea (47·4 %), berries (11·7 %), dark chocolate (9·5 %), apple/pear (5·9 %), fruit salad (4·2 %), red wine (3·3 %), kidney beans (2·8 %), stone fruit (2·6 %), citrus fruit (2·1 %), mixed nuts (2·1 %), milk chocolate (1·3 %), other fruit (1·2 %)
Subclasses				
Flavonols	29·2	14·0	Quercetin (65·2 %), kaempferol (23·1 %), myricetin (7·2 %), isorhamnetin (4·4 %)	Black tea (36·6 %), mixed salad (10·2 %), spinach/rocket (7·0 %), berries (6·6 %), onion/leeks (5·5 %), apple/pear (5·1 %)
Flavones	1·28	0·73	Luteolin (83·8 %), apigenin (16·8 %)	Celery (15·4 %), pumpkin (14·3 %), other fruits (10·1 %), fruit salad (9·3 %), mixed salad (7·4 %)
Flavanones	22·3	19·5	Hesperetin (58·8 %), naringenin (41·2 %), eriodictyol (0·3 %)	Citrus fruit (63·4 %), fruit juice (16·3 %), fruit salad (13·8 %), red wine (3·8 %), white wine (0·9 %)
Anthocyanins	48·9	44·3	Malvidin (44·7 %), delphinidin (14·3 %), petunidin (12·5 %), cyanidin (10·0 %), pelargonidin (9·3 %), peonidin (9·2 %)	Berries (60·4 %), red wine (13·9 %), fruit salad (10·4 %), other fruits (7·3 %), stone fruits (3·8 %)
Isoflavones	5·2	10·1	Genistein (55·2 %), daidzein (37·9 %), glycitein (6·5 %)	Soyamilk (34·0 %), bread with soya/linseed (31·0 %), soyabean (28·7 %), coffee (2·1 %), wholemeal bread (1·6 %)
Flavan-3-ols	571·5	340·4	Proanthocyanidins (43·3 %), theaflavins/thearubigins (39·7 %), monomers (17·0 %)	Black tea (54·3 %), dark chocolate (11·2 %), berries (8·4 %), apple/pear (6·6 %), fruit salad (3·5 %)
Subdivisions of flavan-3-ols				
Monomers	97·3	72·5	Epigallocatechin 3-gallate (25·5 %), epigallocatechin (22·8 %), epicatechin (16·9 %), epicatechin 3-gallate (15·9 %), catechin (15·5 %), gallocatechin (3·5 %)	Black tea (76·1 %), dark chocolate (4·9 %), red wine (4·0 %), apple/pear (3·6 %), banana (3·0 %)
Proanthocyanidins†	247·5	155·2	Polymers (44·3 %), 4–6 mers (21·2 %), 7–10 mers (14·2 %), dimers (13·5 %), trimers (6·8 %)	Dark chocolate (24·0 %), berries (18·7 %), kidney bean (7·7 %), fruit salad (7·4 %), stone fruit (5·7 %)
Theaflavins and thearubigins	226·7	217·8	Thearubigins (94 %), theaflavin-3,3′-digallate (2·0 %), theaflavin (1·8 %), Theaflavin-3'-gallate (1·8 %)	Black tea (100 %)

* Total flavonoid intake is the sum of subclasses: flavonols, flavones, flavanones, anthocyanins, isoflavones and flavan-3-ols.
† Excludes monomers.

Table 3. Differences in blood pressure and arterial stiffness associated with higher daily flavonoid intake (one SD/d) in 381 non-smokers over 60 years of age* (β-coefficients and 95 % confidence intervals)

	Central systolic blood pressure (mmHg)			Central diastolic blood pressure (mmHg)			Central mean arterial pressure (mmHg)			Central augmentation index (%)†		
	β	95 % CI	*P*	β	95 % CI	*P*	β	95 % CI	*P*	β	95 % CI	*P*
Flavonols ((SD 14·0) mg/d)												
Model 1	−1·26	−2·95, 0·43	0·146	−1·11	−2·20, −0·02	0·046	−1·16	−2·36, 0·05	0·060	−0·45	−1·32, 0·43	0·319
Model 2	−1·01	−2·71, 0·70	0·248	−1·00	−2·09, 0·10	0·076	−1·00	−2·21, 0·22	0·108	−0·49	−1·38, 0·39	0·278
Flavones ((SD 0·73) mg/d)												
Model 1	−0·98	−2·70, 0·75	0·269	−1·33	−2·44, −0·23	0·019	−1·21	−2·44, 0·01	0·053	0·39	−0·51, 1·28	0·396
Model 2	−0·58	−2·35, 1·19	0·521	−1·18	−2·32, −0·05	0·042	−0·98	−2·24, 0·28	0·128	0·35	−0·57, 1·27	0·456
Flavanones ((SD 19·5) mg/d)												
Model 1	0·76	−0·88, 2·39	0·366	0·56	−0·49, 1·61	0·299	0·62	−0·54, 1·79	0·295	−0·93	−1·77, −0·09	0·030
Model 2	0·87	−0·76, 2·51	0·295	0·62	−0·43, 1·67	0·250	0·70	−0·46, 1·87	0·237	−0·96	−1·80, −0·11	0·027
Anthocyanins ((SD 44·3) mg/d)												
Model 1	−1·72	−3·42, −0·03	0·047	−1·56	−2·65, −0·48	0·005	−1·62	−2·82, −0·41	0·009	0·38	−0·51, 1·27	0·404
Model 2	−1·44	−3·16, 0·29	0·103	−1·44	−2·55, −0·34	0·011	−1·44	−2·67, −0·22	0·022	0·35	−0·56, 1·25	0·453
Isoflavones ((SD 10·1) mg/d)												
Model 1	0·72	−0·91, 2·34	0·388	0·54	−0·50, 1·59	0·309	0·60	−0·56, 1·76	0·310	0·41	−0·43, 1·25	0·339
Model 2	0·80	−0·83, 2·42	0·337	0·58	−0·46, 1·63	0·275	0·65	−0·50, 1·81	0·269	0·40	−0·44, 1·24	0·353
Flavan-3-ols ((SD 340·4) mg/d)												
Model 1	−0·62	−2·29, 1·04	0·463	−0·59	−1·66, 0·49	0·285	−0·60	−1·79, 0·59	0·324	−0·60	−1·46, 0·25	0·169
Model 2	−0·51	−2·17, 1·15	0·550	−0·53	−1·60, 0·54	0·335	−0·52	−1·71, 0·67	0·390	−0·62	−1·48, 0·24	0·158
Monomers ((SD 72·5) mg/d)												
Model 1	−0·44	−2·02, 1·15	0·591	−0·18	−1·20, 0·84	0·728	−0·27	−1·40, 0·87	0·645	−0·76	−1·57, 0·06	0·069
Model 2	−0·35	−1·93, 1·23	0·663	−0·14	−1·16, 0·88	0·789	−0·21	−1·34, 0·92	0·716	−0·77	−1·59, 0·05	0·065
Proanthocyanidins ((SD 155·2) mg/d)												
Model 1	−0·59	−2·48, 1·30	0·540	−1·35	−2·56, −0·15	0·029	−1·10	−2·44, 0·24	0·110	0·44	−0·54, 1·43	0·377
Model 2	−0·46	−2·34, 1·43	0·636	−1·29	−2·50, −0·08	0·037	−1·01	−2·36, 0·33	0·141	0·43	−0·56, 1·41	0·395
Theaflavins and thearubigins ((SD 217·8) mg/d)												
Model 1	−0·42	−1·98, 1·13	0·592	−0·09	−1·09, 0·92	0·867	−0·20	−1·31, 0·91	0·726	−0·78	−1·58, 0·01	0·054
Model 2	−0·36	−1·91, 1·19	0·651	−0·05	−1·05, 0·95	0·920	−0·15	−1·26, 0·95	0·786	−0·79	−1·59, 0·00	0·052
Total flavonoids ((SD 375·9) mg/d)												
Model 1	−0·78	−2·47, 0·92	0·371	−0·73	−1·82, 0·36	0·190	−0·75	−1·96, 0·46	0·228	−0·58	−1·46, 0·29	0·193
Model 2	−0·61	−2·31, 1·09	0·482	−0·65	−1·75, 0·44	0·245	−0·64	−1·85, 0·58	0·304	−0·61	−1·49, 0·27	0·176

* Mean (95 % CI) difference in blood pressure and arterial stiffness associated with higher daily flavonoid intake (one SD/d) obtained from multivariable linear regression. *P* is for the corresponding coefficient, testing the null hypothesis that the coefficient is equal to zero. Model 1 adjusted for age, sex, BMI, education, physical activity, anti-hypertensive medication use, statin use, alcohol and energy intake; model 2 adjusted for covariates in model 1 plus a diet quality score (Healthy Eating Index for Australian Adults).

† All models for augmentation index are additionally adjusted for heart rate and mean arterial pressure.

urinary excretion of nitrate and nitrite suggesting the mechanism responsible could be related to an increase in nitric oxide bioavailability, a major vasodilator[44]. This is interesting as mechanistic data suggest anthocyanins may increase endothelial-derived nitric oxide, through modulation of endothelial nitric oxide synthase expression[45]. While this is so, the hypotensive actions of nitric oxide *in vivo* appear systemic[46], and as such, we cannot rule out an association of anthocyanin intake with SBP. The magnitude of our reported associations is similar to those seen in other studies. In the present study, a higher habitual anthocyanin intake by ~45 mg/d was significantly associated with ~1·5 mmHg lower cDBP and cMAP, an intake roughly equivalent to a single serve (150 g) of strawberries (anthocyanins = ~40 mg), or easily achieved by a serve of blueberries (anthocyanins = ~150 mg). By comparison, a 6-month RCT showed that increasing fruit serves by ~1·4 portions/d significantly reduced SDP and DSP by ~4 and ~1·5 mmHg, respectively, compared with the control arm[47]. While these treatment effects may appear small in comparison with medication intervention, they are realistic for lifestyle modifications, do not come with other side effects and confer a range of other health benefits[3]. In fact, a 2 mmHg lower DBP has been associated with a ~15 % and ~6 % lower risk of stroke and ischaemic heart disease, respectively, signifying that even small reductions in average blood pressure, on a population scale, may prevent large numbers of premature deaths[48].

Our second major finding is that higher flavanone intakes are associated with lower arterial stiffness after adjustment for demographics, lifestyle and diet quality. While this finding conflicts with one other cross-sectional study, our results are supported by findings of two RCTs[15,49,50]. In the RCTs, participants were provided flavanone-rich or flavanone-depleted fruit juices, and it was found that carotid-femoral pulse wave velocity and pulse pressure, two indices of arterial stiffness, were significantly improved by higher flavanone intervention[49,50]. As citrus flavanones have been reported to reduce inflammation, oxidative stress and vasoconstriction, this may explain their beneficial effects on arterial stiffness[7]. In our cohort, a 20 mg/d higher flavanone intake was associated with ~1 % lower arterial stiffness as measured by cAIx; an intake met by a single serve (150 g) of mandarin (flavanones = ~20 mg) or orange (flavanones = ~60 mg). Comparably, Jennings *et al.* report a 1-year study designed to increase participants overall diet quality towards a Mediterranean-style eating pattern, significantly reduced arterial stiffness, as measured by cAIx, by –12·4 % (95 % CI –24·4, –0·5) when compared with the control group who ate their habitual diet[51]. Thus, while the magnitude of the association in our study is modest, it is not inconsequential considering there is generally a lack of interventions that reduce arterial stiffness. Moreover, arterial stiffness has implications beyond ASCVD, contributing to cognitive decline and possibly dementia, as cerebral vasculature is exposed to damaging forces of augmented arterial pulse pressures[52]. Collectively, our findings suggest that even small differences to dietary intake may benefit arterial stiffness.

Interestingly, we did not observe clear associations with blood pressure or arterial stiffness for several other flavonoid subclasses with promising prior findings. Meta-analyses of RCTs show that intakes of products rich in isoflavones, flavonols or flavan-3-ols lower blood pressure, and that isoflavone or flavan-3-ol treatment may also improve arterial stiffness[8–10,12,13]. In our study, we did not detect an association of isoflavone intake with blood pressure or arterial stiffness; however, this is possibly attributable to the relatively low intake of this flavonoid subclass by our cohort's participants. In contrast, we did find weak evidence that flavonol intake beneficially associates with cDBP in demographic, lifestyle and diet adjusted models. Given our small sample, this finding needs further investigation in larger cohorts. We also observed flavan-3-ol proanthocyanidins were significantly associated with lower cDBP following adjustment for demographic and lifestyle factors, and this remained so after further adjustment for dietary quality as well as many other key nutrients that may affect blood pressure (i.e. Na, Ca, Mg, *n*-3, total protein and fibre). However, controlling for K attenuated the association of proanthocyanidins with cDBP, suggesting that the association may be due, at least in part, to the anti-hypertensive properties of K. Although, the association between proanthocyanidins and cDBP was only marginally attenuated when controlling for K (+demographics and lifestyle) and given our small sample, we cannot rule out a false negative. In contrast, the relationship between flavones and cDBP was also attenuated by K (but none of the other dietary covariates) but as other research has less often implicated a benefit of this subclass on blood pressure this suggests this finding is less likely to be a false negative[10,28–30]. We also observed a marginal beneficial association between arterial stiffness and flavan-3-ol monomer intake as well as theaflavin/thearubigin consumption in models adjusted for demographics, lifestyle and dietary quality. This is interesting as black tea consumption drove both monomer and theaflavin/thearubigin intake in this cohort. To our knowledge, only two RCT have investigated black tea intake and arterial stiffness. While one study reported a significant worsening of arterial stiffness[53], the other reported a significant benefit to arterial stiffness following black tea intervention[54]. Overall, studies on this are currently too sparse for any firm conclusions to be drawn.

Our findings should be interpreted within the context of the studies' strengths and limitations. First, the FFQ was not validated specifically for flavonoid intake which may have biased our results towards the null. However, the relative validity of our FFQ against 24-h recalls was shown for intake of food groups, energy and macronutrients which increases our confidence in its global performance. Although, measurement error will be present in any subjective dietary collection method and as such, the extrapolation of absolute values of flavonoid intake should be interpreted as estimates. Second, our assessment of wave amplitude was based on cuff pressure measurements; more reliable means of assessing central haemodynamic and arterial stiffness are known; however, the techniques used in this study are commonly utilised in research settings. Common limitations of observational research also apply: we are unable to infer causality and although we incorporated a large range of confounders, including dietary quality and major nutrients beneficial for blood pressure, residual confounding is possible. Moreover, we did not correct for multiple comparisons, as correcting may increase

false negatives especially in this cohort, given the small sample size. However, we also acknowledge that not correcting for multiplicity increases the possibility of spurious significant findings. Even still, the detected associations were relatively modest in effect size and it may be so, that this sample is unsuitably powered to detect those associations with even smaller effect sizes. For these reasons, future studies should be conducted in larger samples when available. The data were also modelled in a linear equation, as the assumption of linearity was not violated in these data; in reality, the true relationship between flavonoid intake (as well as other lifestyle factors) and blood pressure would likely not follow a linear relationship indefinitely, rather, the relationship probably plateaus at the tail ends of intake. Finally, the results may only be generalisable to people of similar age, race, health status and socio-economic standing. It is of interest that meta-analyses stratified by clinical characteristics have observed flavonoid-rich interventions appear even more effective in patients with metabolic disorders; given our relatively healthy population, the associations may be even stronger in those with such conditions[55].

In conclusion, we observed that a higher anthocyanin intake appears to be associated with lower cDBP and cMAP and that a higher flavanone intake appears to be associated with lower arterial stiffness, as assessed by cAIx, in a healthy older population. These findings were consistent following adjustment for demographics, lifestyle and dietary quality as well as other major dietary components that have been reported to affect blood pressure (including Na, K, Ca, Mg, *n*-3, total protein and fibre). However, given our small sample size, high number of comparisons and the possibility of type I and II errors alike, these results require corroboration in further samples and should be interpreted with caution. Nonetheless, as hypertension is a major public health problem, if confirmed, our findings have important clinical and public health implications; the intake of flavonoids associated with lower blood pressure and arterial stiffness in our cohort is easily achievable in the habitual diet. Thus, increasing flavonoid intakes could be a valuable public health strategy for maintaining vascular function, blood pressure and arterial health in older adults.

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There are no conflicts of interest.

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