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Estimated dietary intakes of flavonols, flavanones and flavones in the European Prospective Investigation into Cancer and Nutrition (EPIC) 24 hour dietary recall cohort

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Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition; FCDB, food composition database; FLAV, flavonols, flavanones and flavones; 24-HDR, 24 h dietary recall.

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Abstract

Flavonols, flavanones and flavones (FLAV) are sub-classes of flavonoids that exert cardioprotective and anti-carcinogenic properties *in vitro* and *in vivo*. We aimed to estimate the FLAV dietary intake, their food sources and associated lifestyle factors in ten European countries participating in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. FLAV intake and their food sources for 36 037 subjects, aged between 35 and 74 years, in twenty-seven study centres were obtained using standardised 24 h dietary recall software (EPIC-SOFT). An *ad hoc* food composition database on FLAV was compiled using data from US Department of Agriculture and Phenol-Explorer databases and was expanded using recipes, estimations and flavonoid retention factors in order to increase its correspondence with the 24 h dietary recall. Our results showed that the highest FLAV-consuming centre was the UK health-conscious group, with 130·9 and 97·0 mg/d for men and women, respectively. The lowest FLAV intakes were 36·8 mg/d in men from Umeå and 37·2 mg/d in women from Malmö (Sweden). The flavanone sub-class was the main contributor to the total FLAV intake ranging from 46·6 to 52·9 % depending on the region. Flavonols ranged from 38·5 to 47·3 % and flavones from 5·8 to 8·6 %. FLAV intake was higher in women, non-smokers, increased with level of education and physical activity. The major food sources were citrus fruits and citrus-based juices (especially for flavanones), tea, wine, other fruits and some vegetables. We concluded that the present study shows heterogeneity in intake of these three sub-classes of flavonoids across European regions and highlights differences by sex and other sociodemographic and lifestyle factors.

Key words: Flavonols: Flavones: Flavanones: EPIC-Europe

Epidemiological evidence supports claims that a high consumption of fruits and vegetables is associated with lower risk of major chronic diseases[1–3]. In addition to vitamins, minerals and fibre, polyphenolic compounds, particularly flavonoids, have gained substantial interest in recent years as possible contributors to these protective benefits[4,5].

The group of flavonoids comprises of more than 9000 different compounds that occur ubiquitously in the plant kingdom[6,7]. Flavonoids are classified according to their diverse chemical structure, into seven sub-classes: flavonols, flavones, flavanones, flavan-3-ols, proanthocyanidins, anthocyanidins and isoflavones. In some papers, the subgroups of flavonols, flavones and flavanones (FLAV) are also called *Citrus* flavonoids, because these are the most abundant flavonoids, especially flavanones, in the *Citrus* genus (family Rustacea)[8]. Flavanones are found almost exclusively in citrus fruit and their derived products, such as juices and jams[9]. However, flavonols are more widely distributed than flavones. Flavonols occur in tea, onions, kale, apples, some berries, cocoa and red wine, whereas flavones are abundant in herbs and spices (such as parsley, fennel, oregano), artichokes, peppers and oranges[9].

In foods, FLAV are generally found in glycosylated forms, and their bioavailability depends on the kind of their sugar moiety. Between 1 to 20 % of FLAV are absorbed by both the small intestine and the colon as aglycones after being hydrolysed by either enzymes or the microbiota with a high intra- and inter-individuality[10,11]. In the intestinal epithelial cells, they are metabolised to glucuronides, sulfates and/or methylates by phase II enzymes and are then released into the bloodstream. It has been shown by animal studies that FLAV are found in the organs of experimental animals after ingestion, but it is still unclear whether they accumulate in the human body. Neither the aglycones nor their glycosylated forms have been detected in plasma or urine. Therefore, the biological activity of FLAV may be due to their conjugated forms, but preliminary *in vitro* assays have not substantiated this enough. The other possibility is that aglycones may be set free from their conjugates in specific tissues and exert those effects suggested by *in vitro* studies[12]. Finally, they are mostly excreted in urine as conjugated forms; their biological half-life ranges from 11 to 28 h[10].

Despite their low to moderate bioavailability, results from *in vitro* studies have shown that FLAV possess remarkable antioxidant, anti-inflammatory, anti-carcinogenic and anti-allergic properties[8,12–14]. Moreover, some clinical and epidemiological studies indicate that a high intake of FLAV-rich foods may protect against CVD and some kinds of cancers[15,16], but more clinical trials with isolated FLAV are needed. The molecular mechanisms of FLAV may underlie their ability to be linked to their ability

to modulate enzyme activity (kinases, phospholipases, ATPases, lipo-oxygenases, cyclo-oxygenases)[17,18].

These findings are a good starting point when assessing the potential role of FLAV in the prevention of chronic diseases. For this reason, an accurate estimation of exposure of these compounds is essential in the evaluation of their potential effects and, subsequently, in establishing any related dietary recommendations. To date, there are few descriptive studies assessing FLAV intakes[19–24], especially in large European populations. The purpose of the present study was to estimate the consumption of FLAV in ten Western European countries participating in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Furthermore, we aimed to assess the most important food sources of FLAV as well as the sociodemographic, lifestyle and anthropometric determinants.

Materials and methods

Study population

The population involved in the present analysis comes from a calibration substudy nested within the EPIC study, which was designed to evaluate the associations between diet, lifestyle and cancer in ten Western European countries: Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, The Netherlands and the UK[25,26].

For the calibration study, a random sample stratified by age, sex and centre, and weighted for expected cancer cases in each stratum (36 994 subjects, approximately 8 % of the entire EPIC cohort) completed a standardised 24 h dietary recall (24-HDR) between 1995 and 2000[27]. Participants were mainly recruited from the general population residing within defined geographical areas, with some exceptions: health insurance (France), women attending breast cancer screening (Utrecht, The Netherlands; Florence, Italy), mainly blood donors (centres in Italy and Spain) and a cohort consisting predominantly of vegetarians (the 'health-conscious' cohort in Oxford, UK)[26]. The initial twenty-three EPIC administrative centres were later redefined into twenty-seven centres for the analysis of dietary patterns. Of the twenty-seven redefined centres, nineteen have both male and female participants, and eight recruited only women (France; Norway; Utrecht, The Netherlands; Naples, Italy).

After exclusion of 941 subjects who were aged younger than 35 years or older than 74 years because of low participation in these age categories, and sixteen subjects due to missing FFQ data, a total of 36 037 subjects were finally included in this analysis. Approval for the study was obtained from the ethics review boards of the International Agency for Research on Cancer (IARC) and all local EPIC participating institutions. All participants provided written informed consent.

Dietary and lifestyle information

The 24-HDR was administered through a face-to-face interview, except in Norway, where a telephone interview was conducted[28]. A computerised interview program (EPIC-SOFT) was developed specifically for the calibration study, which allowed for interview procedures to be standardised across the study centres[29,30]. Previous publications have outlined in detail the rationale, methodology and population characteristics of the 24-HDR calibration study[27,31].

Data on other lifestyle factors, including level of education, anthropometry measures, total physical activity (combining both occupational and leisure time activities) and smoking history, were collected at baseline through standardised questionnaires and clinical examinations, and have been described elsewhere[26,27,32]. Also, body weight and height were mainly self-reported by the participants during the 24-HDR interview. The mean time interval between completion of the baseline assessment and the 24-HDR interview varied by country, from 1 day to 3 years later[27].

Flavonoid food composition database

In order to estimate FLAV intakes from 24-HDR, a flavonoid food composition database (FCDB) was developed. The flavonol group included isorhamnetin, kaempferol, myricetin and quercetin. The flavone group included apigenin and luteolin. The flavanone group included naringenin, hesperetin and eriodictyol. FLAV are expressed as FLAV aglycones per 100 mg fresh weight and are calculated as the sum of the available forms (glycosides and aglycones) in the literature. The FCDB is based on the most recent United States Department of Agriculture (USDA) database on flavonoids updated in 2007[9] and expanded with values from a French database on polyphenols, Phenol-Explorer, released in 2009[33]. Both databases gathered the most exhaustive and updated food composition data published worldwide on flavonoids. There are no large differences on the FLAV data between both databases. Any unavailable data were estimated, as far as possible, using flavonoid retention factors, recipes, estimations based on similar food groups or items and logical zeros. The retention factors applied, based on data for quercetin, were 70, 35 and 25 % after frying, cooking in a microwave oven and boiling, respectively[34]. The final FCDB created contained 1877 food items and only 10 % of unknown values.

Statistical analyses

Intake results are presented as calculated least squared means and standard errors stratified by sex and study centre and ordered in a geographical south/north gradient. Dietary mean intakes were calculated using general linear models and were adjusted for age (as a continuous variable) and weighted by season and day of the week of the 24-HDR to control for different distributions of participants across seasons and days of the dietary recall. The contribution of each individual FLAV compound and each FLAV subgroup to the total intake of both subgroup and total FLAV was calculated as a percentage. The contribution of each food group to the total and subgroup intake of FLAV was also calculated as a percentage.

Differences in FLAV intake were compared according to categories of sex, age groups, level of education, smoking

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Table 1. Adjusted* mean daily intakes of flavonols, flavanones and flavones by sex and centre ordered from south to north
(Mean values with their standard errors)

	Men									Women								
Country and centre	Subjects (*n*)	Sum of flavonols, flavones and flavonones (mg/d)		Flavonols (mg/d)		Flavanones (mg/d)		Flavones (mg/d)		Subjects (*n*)	Sum of flavonols, flavones and flavonones (mg/d)		Flavonols (mg/d)		Flavanones (mg/d)		Flavones (mg/d)	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE		Mean	SE	Mean	SE	Mean	SE	Mean	SE
Greece	1314	57·96	2·24	21·80	1·19	28·39	1·80	7·77	0·21	1373	47·22	2·19	15·22	1·16	27·05	1·75	4·95	0·20
Spain																		
Granada	214	94·21	5·54	38·39	2·94	50·28	4·44	5·55	0·52	300	70·92	4·68	20·06	2·49	45·94	3·75	4·93	0·44
Murcia	243	113·87	5·20	37·33	2·76	69·54	4·16	7·00	0·49	304	88·11	4·65	32·29	2·47	50·95	3·73	4·87	0·44
Navarra	444	85·87	3·85	35·34	2·04	45·08	3·08	5·46	0·36	271	69·71	4·92	27·04	2·62	39·60	3·94	3·07	0·46
San Sebastian	490	93·10	3·67	40·79	1·95	46·18	2·94	6·12	0·34	244	67·85	5·19	29·26	2·76	34·80	4·16	3·79	0·49
Asturias	386	64·09	4·12	26·35	2·19	33·05	3·30	4·70	0·39	324	46·69	4·50	14·53	2·39	29·55	3·61	2·61	0·42
Italy																		
Ragusa	168	65·73	6·25	22·79	3·32	36·13	5·01	6·80	0·59	138	47·61	6·90	15·26	3·67	25·95	5·53	6·39	0·65
Naples										403	46·18	4·04	15·19	2·15	27·34	3·23	3·65	0·38
Florence	271	58·60	4·92	24·80	2·62	28·20	3·94	5·60	0·46	784	48·31	2·89	19·54	1·54	25·07	2·32	3·70	0·27
Turin	676	70·83	3·12	30·24	1·66	32·47	2·50	8·12	0·29	392	56·90	4·09	22·79	2·18	28·60	3·28	5·51	0·38
Varese	327	73·66	4·48	27·49	2·38	37·14	3·59	9·04	0·42	794	53·78	2·88	20·00	1·53	27·75	2·30	6·03	0·27
France																		
South coast	–	–	–	–	–	–	–	–	–	620	65·18	3·26	27·14	1·73	33·10	2·61	4·94	0·30
South	–	–	–	–	–	–	–	–	–	1425	67·54	2·15	28·49	1·14	34·71	1·72	4·33	0·20
North-East	–	–	–	–	–	–	–	–	–	2059	72·91	1·79	28·11	0·95	40·47	1·43	4·34	0·17
North-West	–	–	–	–	–	–	–	–	–	631	75·48	3·23	27·57	1·72	43·66	2·59	4·25	0·30
Germany																		
Heidelberg	1034	85·47	2·52	40·48	1·34	37·81	2·02	7·19	0·24	1087	77·66	2·48	33·28	1·32	35·54	1·99	8·84	0·23
Potsdam	1233	92·92	2·31	45·05	1·23	41·52	1·85	6·36	0·22	1061	86·91	2·50	32·46	1·33	46·50	2·00	7·95	0·23
The Netherlands																		
Bilthoven	1024	64·33	2·55	29·13	1·36	32·77	2·05	2·44	0·24	1086	78·54	2·49	30·85	1·32	43·89	2·00	3·80	0·23
Utrecht										1870	91·58	1·88	39·72	1·00	48·62	1·51	3·24	0·18
UK																		
General population	403	97·61	4·04	51·01	2·15	42·85	3·24	3·76	0·38	571	88·83	3·39	42·40	1·80	43·13	2·72	3·31	0·32
Health-conscious	113	130·87	7·62	54·88	4·05	69·03	6·11	6·96	0·71	196	96·99	5·79	50·05	3·08	40·41	4·64	6·54	0·54
Denmark																		
Copenhagen	1356	75·44	2·20	33·81	1·17	36·68	1·76	4·95	0·21	1484	73·33	2·10	31·56	1·12	36·75	1·69	5·02	0·20
Aarhus	567	76·82	3·40	34·22	1·81	38·18	2·73	4·43	0·32	510	73·02	3·59	31·12	1·91	35·94	2·87	5·97	0·34
Sweden																		
Malmö	1421	37·34	2·20	18·90	1·17	16·91	1·76	1·53	0·21	1711	37·24	1·99	17·20	1·06	18·42	1·59	1·63	0·19
Umeå	1344	36·75	2·21	20·11	1·18	15·41	1·77	1·23	0·21	1574	40·32	2·04	19·81	1·09	19·02	1·64	1·50	0·19
Norway																		
South and East	–	–	–	–	–	–	–	–	–	1004	47·49	2·58	24·17	1·37	20·03	2·07	3·29	0·24
North and West	–	–	–	–	–	–	–	–	–	793	40·56	2·90	20·32	1·54	16·66	2·33	3·57	0·27

* Adjusted for age and weighted by season and day of recall.

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status, level of physical activity, BMI and four European regions (South: all centres in Greece, Spain, Italy and the south of France; Central: all centres in the north-east and north-west of France, Germany, the Netherlands and the general population of the UK; North: all centres in Denmark, Sweden and Norway; UK health-conscious population) using general lineal models. All these models were adjusted for sex, age (continuous), centre, BMI (continuous) and energy intake (continuous) as well as weighted by day of the week and season of the 24-HDR collection. All analyses were performed using SPSS Statistics software (version 17.0; SPSS Inc., Chicago, IL, USA).

Results

Centre-specific mean intakes of total and the subgroups of FLAV, stratified by sex, adjusted for age, and weighted by season and day of the week of the 24-HDR, are presented in Table 1. For both men and women, the highest mean daily intake of total FLAV was in the UK health-conscious group (men 130·9 mg/d, women 97·0 mg/d) and the lowest in Sweden (in Umeå men 36·7 mg/d, in Malmö women 37·2 mg/d). In both men and women, the highest flavonol intake was in the two UK centres. The highest intakes of flavanones were observed in men from Murcia (Spain) and the UK health-conscious group and in women in Murcia (Spain) and Utrecht (The Netherlands). Among males, the highest consumption of flavones was recorded in Varese (Italy), with the highest among females in Heidelberg (Germany). In general, participants in Sweden had the lowest intakes of all FLAV subgroups, except in women for flavonol (Asturias (Spain) and Greece) and for flavanone intakes (North and West Norway). The same analyses but for single FLAV compounds are tabulated in Supplemental Table Annex 1 (available online at http://www.journals.cambridge.org/bjn).

There was an increasing south–north gradient corresponding to the percentage contribution of flavonol compounds to total FLAV (ranging from 38·5 to 47·4 %). For flavanones and flavones, a decreasing south–north gradient of percentage contribution was shown (52·9–46·6 % and 8·6–5·8 %, respectively) (Table 2). The most abundant individual FLAV were hesperetin and quercetin, which each contributed to approximately a third of the total FLAV, followed by naringenin (ranging from 13·3 to 20·8 %). The rest of the FLAV compounds contributed less than 10 % in all regions.

To assess the association of some sociodemographic, lifestyle and anthropometric characteristics on FLAV intakes, we carried out stratified analyses adjusted for age, sex, centre, energy intake and BMI (where appropriate) and weighted by season and day of 24-HDR (Table 3). Women had statistically significant higher total FLAV, flavanone and flavone intakes, but men consumed more flavonols. No differences among age groups were observed in total FLAV intake. The UK health-conscious group had the highest intake of total and subgroups of FLAV, followed by Central, South and North European regions. FLAV intake increased with physical activity ($P<0·001$) and with level of education ($P<0·001$). Intake of total and all subgroups of FLAV was lower in

Table 2. Percentage contribution of individual and subgroups of flavonol, flavanone and flavone intake in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort by European region

		South		Central		North		UK health-conscious	
Subgroup	Compound	% of subgroup	% of total	% of subgroup	% of total	% of subgroup	% of total	% of subgroup	% of total
Flavonols			38·5		42·8		47·4		47·3
	Isorhamnetin	3·3	1·3	2·2	0·9	1·9	0·9	2·2	1·0
	Kaempferol	15·0	5·8	18·2	7·8	20·5	9·7	18·4	8·7
	Myricetin	6·5	2·5	8·6	3·7	11·7	5·5	9·5	4·5
	Quercetin	75·2	28·9	71·1	30·4	65·9	31·2	69·9	33·1
Flavanones			52·9		51·0		46·8		46·6
	Eriodictyol	1·7	0·9	1·5	0·8	1·8	0·8	1·4	0·7
	Hesperetin	58·9	31·2	67·9	34·6	63·1	29·5	70·1	32·7
	Naringenin	39·3	20·8	30·6	15·6	35·1	16·4	28·5	13·3
Flavones			8·6		6·2		5·8		6·1
	Apigenin	45·8	3·9	35·2	2·2	50·2	2·9	32·1	2·0
	Luteolin	54·2	4·7	64·8	4·0	49·8	2·9	67·9	4·2

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Table 3. Adjusted* mean daily intakes of flavonols, flavanones and flavones by sex and selected characteristics
(Mean values with their standard errors)

Stratification variable	Subjects (*n*)	Sum of flavonols, flavonones and flavones (mg/d)			Flavonols (mg/d)			Flavanones (mg/d)			Flavones (mg/d)		
		Mean	SE	*P*†	Mean	SE	*P*†	Mean	SE	*P*†	Mean	SE	*P*†
Sex				0·001			0·013			<0·001			0·002
Men	13 028	66·76	0·89		29·84	0·48		32·35	0·72		4·58	0·08	
Women	23 009	70·32	0·65		28·40	0·35		37·03	0·52		4·89	0·06	
Age				0·292			<0·001			0·237			0·004
35–44 years	3335	66·94	1·49		26·67	0·79		35·95	1·20		4·31	0·14	
45–54 years	12 595	68·43	0·80		28·41	0·43		35·29	0·64		4·73	0·08	
55–64 years	14 940	69·33	0·77		30·10	0·41		34·38	0·62		4·85	0·07	
65–74 years	5167	67·33	1·29		29·39	0·69		33·26	1·04		4·68	0·12	
European region				<0·001			<0·001			<0·001			<0·001
South	11 285	63·72	0·78		24·95	0·42		33·20	0·63		5·56	0·07	
Central	12 679	80·73	0·75		35·22	0·40		40·45	0·60		5·07	0·07	
North	11 764	50·61	0·76		24·07	0·41		23·56	0·61		2·98	0·07	
UK health-conscious	309	110·10	4·64		52·17	2·46		51·21	3·71		6·73	0·44	
BMI				0·205			<0·001			0·533			<0·001
< 25 kg/m^2	16 854	69·21	0·77		30·07	0·41		34·22	0·62		4·92	0·07	
25 to < 30 kg/m^2	13 766	68·32	0·77		28·65	0·41		35·02	0·62		4·65	0·07	
≥ 30 kg/m^2	5417	66·85	1·18		27·34	0·63		35·14	0·95		4·38	0·11	
Level of schooling				<0·001			<0·001			<0·001			<0·001
None	1709	67·79	2·30		27·90	1·23		35·46	1·85		4·43	0·22	
Primary completed	10 469	60·61	0·91		25·86	0·48		30·47	0·73		4·28	0·09	
Technical/professional	8038	68·97	1·05		28·35	0·56		35·77	0·85		4·84	0·10	
Secondary school	7152	70·60	1·06		29·70	0·57		36·06	0·86		4·83	0·10	
University degree	8155	77·52	1·00		33·80	0·53		38·44	0·81		5·29	0·09	
Smoking status				<0·001			<0·001			<0·001			<0·001
Never smoker	17 483	70·88	0·74		28·92	0·40		37·16	0·60		4·80	0·07	
Former smoker	10 288	70·70	0·87		31·61	0·47		34·13	0·70		4·97	0·08	
Current smoker	7726	60·70	0·99		26·20	0·53		30·47	0·80		4·30	0·09	
Physical activity				<0·001			0·002			0·043			<0·001
Inactive	7463	64·58	1·50		26·75	0·80		33·28	1·20		4·54	0·12	
Moderately inactive	11 969	67·60	1·37		27·74	0·73		35·11	1·10		4·76	0·09	
Moderately active	8400	67·39	1·46		28·09	0·78		34·49	1·18		4·82	0·08	
Active	6380	71·70	1·56		29·46	0·83		36·88	1·26		5·36	0·16	

* Adjusted for sex, age, energy intake and BMI and weighted by season and day of recall.
† *P* value is for differences in means.

smokers than non-smokers ($P<0·001$). Consumption of flavonols and flavones decreased with BMI ($P<0·001$), but for total FLAV the trend was not significant.

Table 4 shows the food groups contributing to the intake of total and subgroups of FLAV stratified by European region, adjusted for age and sex and weighted by season and day of 24-HDR. In all regions, fruits, vegetables, non-alcoholic (mainly juices and tea) and alcoholic beverages (mainly wines) accounted for approximately 90 % of FLAV intake. Although the dietary sources of FLAV were similar, the profiles were different; for example, in the South European region fruits, especially citrus fruits, were the main contributors. However, in the other regions the most abundant sources were non-alcoholic beverages, particularly juices and tea. The major contributors to flavonol intake (in varying proportions) among regions were vegetables (leafy vegetables, and onions and garlic), non-alcoholic beverages (tea), fruit (apples and pears), alcoholic beverages (wine) and soups. Combined citrus fruit and citrus fruit juice intake was by far the main source of flavanones in all regions. Herbal tea was the most important dietary source of flavones in the Central, North regions and the UK health-conscious group; however, in the South European region, wine, fruits and vegetables were the main sources.

Discussion

To our knowledge, this is the first study that estimates the intake of FLAV in a large European population assessing differences among countries, sexes, age groups and other characteristics. For the first time in 1976, Kühnau[35] estimated the mean daily intake of the sum of all flavonoids to be approximately 1 g, about 170 mg of which were FLAV (expressed as glycosides). This corresponds to about 115 mg/d as flavonoid aglycones (without sugar moiety). This estimation was based on food balance sheets and flavonoid composition data that were obtained using an outdated analytical methodology; hence, the flavonoid content in foods was imprecise and probably overestimated[19]. Therefore, this first estimation was twofold that of the present study, which ranged from 66·8 mg and 70·3 mg for men and women, respectively. Nevertheless, FLAV intakes in some centres of the present study were similar to those reported by Kühnau[35], such as men in both UK centres, and Murcia (Spain), and women in

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Table 4. Percentage contributions of food groups and some main foods to the intake of flavonols, flavanones and flavones by European region*

	Sum of flavonols, flavonones and flavones (%)				Flavonols (%)				Flavanones (%)				Flavones (%)			
Food groups and foods	South	Central	North	UK health-conscious	South	Central	North	UK health-conscious	South	Central	North	UK health-conscious	South	Central	North	UK health-conscious
Potatoes and other tubers	0·5	0·7	1·3	0·5	1·4	1·7	2·9	1·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0
Vegetables	17·2	8·5	9·0	7·4	38·0	17·2	17·8	14·7	1·9	0·7	0·7	0·5	21·7	12·5	8·3	7·3
Leafy vegetables	6·1	3·3	1·6	1·1	13·2	6·6	3·3	2·1	0·0	0·0	0·0	0·0	13·4	7·1	1·8	1·9
Fruiting vegetables	3·5	1·4	1·6	0·9	5·0	2·1	2·4	1·3	1·9	0·7	0·7	0·4	6·8	3·0	3·0	1·9
Root vegetables	0·1	0·2	0·3	0·1	0·3	0·3	0·3	0·2	0·0	0·0	0·0	0·0	0·2	0·8	2·1	0·4
Cabbages	0·2	0·4	1·1	0·7	0·5	0·8	2·4	1·3	0·0	0·0	0·0	0·0	0·2	0·3	0·4	0·6
Grain vegetables	0·4	0·1	0·2	0·2	1·0	0·3	0·5	0·5	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0
Onion, garlic	5·1	2·1	3·4	2·7	13·5	4·9	7·4	6·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0
Sprout vegetables	0·6	0·5	0·3	0·2	1·4	1·1	0·6	0·4	0·0	0·0	0·0	0·0	0·5	0·6	0·3	1·0
Other vegetables	1·2	0·5	0·4	1·5	3·0	1·0	0·7	3·0	0·0	0·0	0·0	0·0	0·6	0·6	0·6	1·5
Legumes	0·2	0·1	0·0	0·1	0·6	0·1	0·1	0·3	0·0	0·0	0·0	0·0	0·3	0·1	0·0	0·1
Fruits, nuts and seeds	47·8	21·5	33·0	21·7	20·2	9·6	13·1	9·1	71·0	33·0	53·7	35·4	24·3	9·1	16·1	10·2
Citrus fruits	39·1	17·0	26·8	17·1	1·3	0·5	0·8	0·5	70·3	32·4	53·2	34·5	10·3	5·2	10·4	5·9
Apples and pears	3·6	2·6	4·5	2·8	9·6	5·9	9·7	6·0	0·0	0·0	0·0	0·0	0·2	0·4	1·4	0·9
Grapes	0·7	0·3	0·3	0·3	1·6	0·7	0·6	0·6	0·0	0·0	0·0	0·0	1·4	0·9	1·0	0·8
Stone fruits	1·1	0·5	0·3	0·3	3·0	1·2	0·7	0·6	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0
Berries	0·2	0·3	0·3	0·2	0·4	0·7	0·6	0·5	0·0	0·1	0·0	0·0	0·0	0·0	0·0	0·0
Bananas	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0
Kiwis	0·1	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·8	0·4	0·4	0·0
Other fruits	0·3	0·1	0·0	0·1	0·2	0·0	0·0	0·2	0·7	0·6	0·5	0·9	2·0	0·5	0·4	0·5
Nuts and seeds	0·3	0·4	0·3	0·5	0·2	0·2	0·1	0·2	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0
Olives	2·3	0·3	0·4	0·3	3·8	0·4	0·5	0·5	0·0	0·0	0·0	0·0	9·6	1·6	2·4	2·0
Dairy products	0·2	0·4	0·1	0·3	0·3	0·7	0·1	0·3	0·2	0·2	0·1	0·2	0·0	0·1	0·0	0·1
Cereal and cereal products	0·1	0·2	0·2	0·4	0·2	0·4	0·3	0·9	0·0	0·0	0·0	0·0	0·1	0·0	0·2	0·1
Meat and meat products	0·0	0·2	0·0	0·0	0·1	0·1	0·0	0·0	0·0	0·0	0·0	0·0	0·0	1·9	0·4	0·0
Fish and shellfish	0·0	0·0	0·0	0·0	0·0	0·0	0·1	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·1	0·0
Egg and egg products	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0
Fat	0·2	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	1·9	0·1	0·1	0·1
Sugar and confectionery	1·1	1·8	2·5	1·1	2·4	3·5	4·6	1·9	0·3	0·5	0·9	0·4	0·3	0·3	0·6	0·3
Cakes and biscuits	0·3	0·5	0·8	0·7	0·8	0·9	1·7	1·2	0·1	0·3	0·1	0·2	0·0	0·1	0·0	0·1
Non-alcoholic beverages	16·1	51·1	38·9	56·6	11·1	37·3	40·4	50·7	19·8	61·6	37·6	61·3	15·3	59·7	38·3	64·6
Juices	10·6	32·2	18·3	30·0	0·6	2·1	1·5	1·3	19·0	60·1	35·5	59·9	1·8	12·7	6·8	12·4
Carbonated drinks	0·4	0·6	1·5	0·4	0·1	0·2	1·4	0·1	0·6	0·9	1·8	0·6	0·0	0·0	0·0	0·0
Coffee	0·2	0·6	1·3	0·5	0·6	1·4	2·8	1·1	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0
Tea	3·4	13·5	15·6	20·9	8·8	31·2	33·5	45·5	0·0	0·0	0·0	0·0	0·7	0·7	4·0	0·0
Herbal tea	1·6	4·3	2·3	4·9	1·1	2·5	1·2	2·7	0·2	0·7	0·4	0·8	12·8	46·3	27·5	52·1
Alcoholic beverages	10·2	5·8	10·4	2·7	13·3	7·7	13·1	3·3	6·4	3·5	6·0	1·8	20·6	12·2	25·9	5·3
Wine	9·7	4·1	8·0	1·8	11·9	4·3	8·0	1·7	6·4	3·2	5·9	1·6	20·5	11·4	25·4	4·8
Beer and ciders	0·5	1·4	2·3	0·7	1·3	3·1	4·9	1·4	0·0	0·1	0·0	0·1	0·0	0·0	0·0	0·1
Spirits	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0
Cocktails, punches	0·0	0·3	0·2	0·1	0·0	0·3	0·2	0·1	0·0	0·2	0·1	0·1	0·1	0·8	0·4	0·3
Condiments and sauces	2·2	0·8	2·3	1·5	2·2	1·1	2·8	1·4	0·2	0·2	0·9	0·2	15·1	3·9	10·0	11·7
Soups, bouillons	3·6	8·5	1·4	6·9	9·4	19·7	3·0	15·0	0·0	0·0	0·0	0·0	0·3	0·1	0·2	0·2
Soya products	0·1	0·0	0·0	0·1	0·2	0·1	0·0	0·3	0·0	0·0	0·0	0·0	0·1	0·0	0·0	0·1

*Values are percentages derived from models adjusted for age and sex and weighted by season and day of recall.

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the UK health-conscious group. In 1992, Hertog *et al.* developed an accurate HPLC technique to analyse flavonols and flavones in foods[36]. Since then, most of the worldwide food composition data were generated using this technique and have been compiled to create the actual FCDB on flavonoids[9,33]. Although in the last decade there has been a great increase of composition data, there are still many missing values. Furthermore, discrepancies exist among researchers on such topics as the application of retention factors. Hertog *et al.*[19] found cooking losses lower than 20 %, but Crozier *et al.*[34] showed losses of about 30, 65 and 75 % after frying, cooking in a microwave and boiling, respectively. Each study adopts a FCDB with slight differences in compositional data and particularly in the estimated missing values, thus limiting our ability to compare published results. We used a unique FCDB containing a large number of food items (*n* 1877) and few missing values (<10 %) for the entire cohort. This reduces the underestimation and facilitates the comparison among countries and population subgroups.

In the present study, the highest flavonol intake varied between 3- and 4-fold among study centres in both men (from 18·9 to 54·9 mg/d) and women (from 14·5 to 50·0 mg/d). South and North European regions had intakes of approximately 25 mg/d. This is similar to Spanish (18·7 mg/d)[23], Greek (20·6–30·4 mg/d)[24,37,38] and Italian (21·6 mg/d)[39] studies, but was clearly higher than that reported in other studies such as those performed in Greece (9·6 mg/d)[40] and Finland (5·4 mg/d)[22]. The present results showed that individuals from the Central European region consumed significantly more flavonols (35·2 mg/d) than in the other regions. However, in the literature these values are somewhat lower; for instance, in two Dutch studies, median intakes ranged from 21·4 to 25·9 mg/d[19,41]. In other non-European countries the results were also similar; for example, in Australia (20·7 mg/d) and in the USA, intakes varied twofold among studies (from 12·0 to 20·7 mg/d)[20,21,42]. In the present study, the UK health-conscious group was the highest consumer group (52·2 mg/d) due to the high consumption of fruits and vegetables in vegetarian populations. This result is much higher than other results, but a study from the Netherlands also reported that the vegan group consumed more flavonols than the general population[19]. The main food sources were basically the same in all the studies: tea, onions and apples[19,20,22,41,42]. In the present study, leafy vegetables were also abundant dietary contributors especially in the South European region and the group of soups and bouillons, particularly in Central European countries, mainly because of onion soups. Quercetin is the most important contributor of flavonols in the present study ranging from 66 to 75 %, followed by kaempferol (15–21 %), myricetin (6·5–11·6 %), and finally isorhamnetin (<3·3 %). This is concordant with the literature[19,20,23,41].

As mentioned previously, flavanones are typically found in citrus fruits and their derived products such as juices and jams. In both sexes, southern Spanish centres (Murcia and Granada) had the highest flavanone consumption because of high citrus fruit intakes[43]. The UK health-conscious group and the Central European region also had a high flavanone intake, but their main food source was citrus-based fruit juices. The North European region had significantly lower flavanone intakes, particularly the Scandinavian countries (<20 mg/d)[22]. The present results in the South European region (33·2 mg/d) are in keeping with the previous results from Spain (50·6 mg/d)[23], Italy (38·3 mg/d)[39] and Greece (27–58·1 mg/d)[24,37,40], but these results are clearly lower than that showed in a Greek case–control study (106·1 mg/d)[38]. The intake of flavanones in non-European countries is similar to northern European countries, being 14·4 mg/d[21] and 22·7 mg/d[42] in two US populations and 6·9 mg/d[44] in Australia. The most important flavanone contributor was hesperetin (ranging from 59·0 to 70·1 %), naringenin (28·5–39·3 %), and remotely followed by eriodictyol (1·4–1·8 %), depending on the European region as in the previous studies[23,24,39,40].

Flavones were the least consumed FLAV group in all regions (ranging from 5·8 to 8·6 %). The UK health-conscious group had the highest intake and the North European region had the lowest, similar to a finding in a Finnish population[22]. The South and Central European regions were intermediate consumers[19,23,24,37–40]. These differences could be attributable to the variation in the main food sources. In the UK and Central European countries the most abundant contributors were herbal teas and fruit and vegetables juices, whereas in the South European region they were vegetables, fruits and wine. Another food source that needs to be taken into account is the group of condiments and sauces, because spices and herbs are the most abundant flavone sources per 100 g fresh matter[9,33]. In comparison with other non-European countries, the present results are higher than shown in US (0·3–1·6 mg/d)[20,21,42] and Australian studies (0·5 mg/d)[44]. Apigenin and luteolin were the main flavones, having similar contributions in the South and North European regions[23,24]. Luteolin is the major contributor in the UK health-conscious group and the Central European region and the differences can be attributed to the previously commented variations of the main food sources among regions.

FLAV intake varied by demographic, anthropometric and lifestyle variables. In the present study, women consumed more flavanones and flavones than men, but fewer flavonols as observed in the EPIC Spanish cohort[23]. However, in the Dutch study women seem to consume more flavonols and flavones[19], while in the US study there were no statistically significant sex differences[21]. The group aged 55–64 years was the highest consuming group of flavonols and flavones in the present study as in other Spanish[23], Dutch (aged >60 years)[19] and US studies (aged 51–70 years)[21]. Flavanones were also highest in the age group of 55–64 years in the Spanish cohort[23], but in the present study differences across age groups were not significant. The highest consumers were subjects of normal weight (BMI <25 kg/m^2) with a university degree, non-smokers, and those who reported being physically active. Therefore, individuals with a healthier lifestyle had a higher FLAV intake as was also found in the Spanish and US study[21,23]. In the Dutch study, non-smokers and light smokers (between 1 and 9 cigarettes/d) consumed more flavonols and flavones than heavy smokers (>10 cigarettes/d)[19]. In this study, Hertog *et al.* also

showed that vegetarians had higher flavonol and flavone intakes than non-vegetarians[19] given that all FLAV food sources are from plants. Also in the present study, the UK health-conscious group had higher FLAV intake than the UK general population.

A myriad of *in vitro* evidence on the potential beneficial role of FLAV in health shows that they exert a wide range of biological activities[8,12–14]. Several epidemiological studies have also suggested beneficial effects against chronic diseases, particularly CVD and some cancers[15,45,46]. A recent meta-analysis showed that flavonoid-rich foods and extracts have effects on some biomarkers of cardiovascular health[15]. Furthermore, a recent prospective study reported that flavanones are associated with lower CVD mortality[45]. With respect to cancer, in a meta-analysis about lung cancer the authors concluded that high or increased intake of flavonoids is associated with reduced cancer risk in some populations (in males, smokers, prospective studies, and studies using dietary history interview) but not in others[46]. There are five possible reasons for this:

(i) The dose used in the *in vitro* studies is normally too high compared with tissue FLAV levels observed after ingesting FLAV.
(ii) *In vitro* studies do not use FLAV metabolites, which are the forms found in blood owing to the fact that FLAV are heavily metabolised inside the body.
(iii) The differences in bioavailability of individual FLAV are not taken into account in epidemiological studies. Moreover, studies have shown a high inter- and intra-variability in the absorption, metabolism and excretion[10]. Therefore, further studies focusing on bioavailability and biological effects using nutritional doses of individual FLAV are needed.
(iv) Limitations in the dietary assessment methods, especially FFQ, should be considered[47,48].
(v) FCDB on FLAV are usually limited, containing a small number of food items and many missing values. Newly developed or updated FCDB[9,33] may assist in the accurate estimation of FLAV intake and in exploring their potential associations with chronic diseases.

This is a large study estimating the FLAV intake in ten Western European countries. The strengths of the present study are the large sample size (*n* 36 037) and the comparability of these results across the countries. The results of the present study originated from standardised single 24-HDR and the flavonoid standardised database across all the participating EPIC countries. However, as not all the EPIC cohorts are population based, these findings cannot be extrapolated to the general population of each region[49]. The other limitation of the present study is an underestimation of real FLAV intake. This underestimation is due to the unknown composition data (about 10 % of missing values in our FCDB) and the omission of herb/plant supplement intake in this analysis (up to 5 % in Denmark, the highest consumer country)[50].

In summary, the data generated in the present study show the intakes of dietary FLAV among twenty-seven centres in ten European countries, according to sex, age and some lifestyle factors. These descriptive data provide a platform to further investigate the role of FLAV in health and disease.

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