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Estimation of the intake of anthocyanidins and their food sources in the European Prospective Investigation into Cancer and Nutrition (EPIC) study

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

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Abstract

Anthocyanidins are bioactive flavonoids with potential health-promoting effects. These may vary among single anthocyanidins considering differences in their bioavailability and some of the mechanisms involved. The aim of the present study was to estimate the dietary intake of anthocyanidins, their food sources and the lifestyle factors (sex, age, BMI, smoking status, educational level and physisical activity) involved among twenty-seven centres in ten European countries participating in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Anthocyanidin intake and their food sources for 36 037 subjects, aged between 35 and 74 years, in twenty-seven redefined centres were obtained using standardised 24 h dietary recall software (EPIC-SOFT). An *ad hoc* food composition database on anthocyanidins (cyanidin, delphinidin, malvidin, pelargonidin, peonidin, petunidin) was compiled using data from the US Department of Agriculture and Phenol-Explorer databases and was expanded by adding recipes, estimated values and cooking factors. For men, the total anthocyanidin mean intake ranged from 19·83 (SE 1·53) mg/d (Bilthoven, The Netherlands) to 64·88 (SE 1·86) mg/d (Turin, Italy), whereas for women the range was 18·73 (SE 2·80) mg/d (Granada, Spain) to 44·08 (SE 2·45) mg/d (Turin, Italy). A clear south to north gradient intake was observed. Cyanidins and malvidins were the main anthocynidin contributors depending on the region and sex. Anthocyanidin intake was higher in non-obese older females, non-smokers, and increased with educational level and physical activity. The major food sources were fruits, wine, non-alcoholic beverages and some vegetables. The present study shows differences in both total and individual anthocyanidin intakes and various lifestyle factors throughout Europe, with some geographical variability in their food sources.

Key words: **Anthocyanidins: Intake: Food sources: EPIC-Europe**

Anthocyanidins are water-soluble plant pigments that form one subgroup of flavonoids. They mainly provide the red, blue and purple colours to fruits, vegetables and flowers. Chemically, they are derivative salts of the flavilium cation. Anthocyanins are glycosides of anthocyanidins, and their sugar moiety (glucose, galactose, rhamnose, xylose and fructose) is mostly bounded to the C3 position of the C-ring[1]. Diglycosides have also been reported, but in smaller amounts[1].

In nature, more than 500 anthocyanins derived from thirty-one anthocyanidins have been identified[2]. However, only six anthocyanidins (cyanidin, delphinidin, malvidin, pelargonidin, peonidin and petunidin) occur ubiquitously and have dietary importance. They are found in fruits, such as berries, red grapes, cherries, and plums; in vegetables, such as red cabbage, red onions, radish and aubergines; and also in fruit and vegetable products, such as juices and wines[3,4]. The anthocyanidin content is enhanced during the ripening process. Moreover, these flavonoids are found mainly in the skin of fruit, except in berries where they are in the skin and flesh[5].

Some epidemiological studies suggest that the consumption of anthocyanidins decreases the risk of total mortality[6] and CVD[7,8] due, in part, to their antioxidant and anti-inflammatory activities[9]. There is also much *in vitro* and *in vivo* evidence in animal models about their anti-carcinogenic properties[9,10], but findings in human subjects are still controversial. Anthocyanidin intake has been associated with a decreased risk of some cancers, especially digestive system cancers[11–15], but, in other epidemiological studies, these significant associations were not observed[6,16–25].

All anthocyanidins are poorly absorbed (usually less than 0·1 %, but up to 5 % has been reported), highly metabolised (more than 65 % is detected in glucuronidated and methylated forms in serum) and rapidly excreted in urine (about 4 h elimination half-life)[9]. Differences in the chemical structure of some anthocyanidins also determine their bioavailability; for example, pelargonidin-3-glucoside has an 8-fold higher apparent absorption rate than cyanidin-3-glucoside[26]. In the same way, several activities of anthocyanidins depend on their chemical structure[9]. For example, delphynidins and cyanidins are able to inhibit lipopolysaccharide-induced cyclo-oxygenase-2 expression, but pelargonidins, peonidins and malvidins are not[27]. For these reasons, further studies are needed, comparing individual anthocyanidin bioavailability and metabolic actions.

To date, there are few population-based descriptive studies of anthocyanidin intake[28,29], especially in European countries[30,31]. The previous studies mainly reported associations between anthocyanidins and markers of disease risk. In general, these studies evaluated anthocyanidins as a group rather than exploring individual anthocyanidins; furthermore, main food sources were not reported. The aims of the present study were to estimate the consumption of the six most important anthocyanidins and their main food sources across the ten European countries participating in the European Prospective Investigation into Cancer and Nutrition (EPIC) study and across population subgroups.

Materials and methods

Study population

EPIC is an ongoing prospective cohort study designed to investigate the associations between diet, lifestyle and cancer throughout ten western European countries: Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, The Netherlands and the UK[32,33]. The cohort includes approximately 366 000 women and 153 000 men, most aged 35–70 years, who were enrolled between 1992 and 2000. Participants were mostly recruited from the general population residing within defined geographical areas, with some exception: women members of a health insurance scheme for state school employees (France); women attending breast cancer screening (Utrecht in The Netherlands and Florence in Italy); mainly blood donors (centres in Italy and Spain); and a cohort consisting predominantly of vegetarians (the 'health-conscious' cohort in Oxford, UK)[33]. The initial twenty-three EPIC administrative centres were redefined into twenty-seven geographical regions relevant to the analysis of dietary consumption patterns[34]. Of the twenty-seven EPIC centres redefined for dietary analysis, nineteen had both male and female participants, and eight recruited only women (France, Norway, Utrecht in The Netherlands and Naples in Italy).

For calibration purposes, a standardised 24 h dietary recall (24-HDR) interview was administered to a stratified random sample (36 994) by age, sex and centre, and weighted for expected cancer cases in each stratum. A total of 36 037 subjects with 24-HDR data were included in this analysis, after exclusion of 941 subjects aged less than 35 years of age or over 74 years because of low participation in these age categories, and sixteen subjects were excluded due to missing FFQ data. Approval for the EPIC study was obtained from all ethical review boards of participating institutions. All participants provided written informed consent.

Dietary and lifestyle information

The 24-HDR was administered in a face-to-face interview, except in Norway, where it was obtained by telephone interview[35]. A computerised interview program (EPIC-SOFT) was developed specifically for the calibration study[36,37]. A complete description of the rationale, methodology and population characteristics of the 24-HDR calibration study has been described elsewhere[34]. The original diet and health survey from which information used in the present study was obtained had ethical approval from all ethical review boards of participating institutions.

Data on other lifestyle factors, including educational level, anthropometry, physical activity and smoking history, were collected at baseline through standardised questionnaires and clinical examinations, and have been described elsewhere[33,34,38]. Data on age, as well as on body weight and height, were self-reported by the participants during the 24-HDR interview. The mean time interval between completion of the baseline questionnaire measures and the 24-HDR interview varied by country, and ranged from 1 d to 3 years later[34].

Food composition database

In order to estimate the anthocyanidin (cyanidin, delphynidin, malvidin, pelargonidin, peonidin and petunidin) intake from the 24-HDR, a food composition database (FCDB) was developed, which contained 1877 food items (annex table 1; see supplementary material available online at http://www.journals.cambridge.org/bjn). Anthocyanidins are expressed as anthocyanidin aglycones per 100 mg fresh weight and are calculated as the sum of the available forms (glycosides and aglycones) in the literature.

Our database is based on the US Department of Agriculture (USDA) database[3] and expanded with values from Phenol-Explorer[39]. Approximately, 5 and 1 % of our database come from USDA and Phenol-Explorer databases, respectively. To date, these two databases are the most complete and updated databases on flavonoids and polyphenols and they evaluate and compile the most worldwide food composition data published. There are no large differences on the anthocyanidin data between the two databases.

One cannot assume that foods that are not in either of the databases do not contain anthocyanidins. Therefore, for our FCDB we calculated estimated values (89 %) including logical zeros (26 %), estimations based on similar food items (15 %), application of retention factors (29 %) and recipes (19 %). First, logical zeros were applied when no anthocyanidins are expected in a food (for example, animal foods or plant foods without colour, because anthocyanidins are plant pigments). Second, estimations based on similar food items were applied when it was possible to extrapolate the composition from one food to another similar one (for example, different varieties of blueberries). Third, when there was no analytical data for cooked food, retention factors were applied. These were 70, 35 and 25 % after frying, cooking in a microwave oven, and boiling, respectively[40]. Crozier *et al.*[40] calculated these retention factors for flavonols, but these are quite similar to the average of anthocyanidin retention factors available in the literature by each cooking method[41–45], although further investigation is needed in this regard. Recipes were applied when it was feasible to deconstruct the food item into a list of available ingredients in our FCDB. Finally, only 4 % of our FCDB had missing values, which are calculated as a zero by default.

Statistical analyses

Dietary intake data are presented as means (least square means) and standard errors stratified by sex and study centre and ordered according to a geographical south to north gradient. The mean intake data were adjusted for age. The contribution of each food group to the total intake of anthocyanidins was calculated as a percentage. Differences in anthocyanidin intake stratified by sex were also compared according to the categories of age, educational level, smoking status, level of physical activity, BMI and European region (south: all centres in Greece, Spain, Italy and the south of France centre; central: all of France other than the south centre, all centres in Germany, The Netherlands and the UK; north: all centres in Denmark, Sweden and Norway). These models were adjusted for age, region, BMI and energy intake. All models were weighted by season and day of the week of the 24-HDR using generalised linear models to

Table 1. Adjusted* daily intakes (mg/d) of total and single anthocyanidins by sex and centre ordered from south to north
(Mean values with their standard errors)

	Men															Women														
		Anthocyanidins (mg/d)		Cyanidin (mg/d)		Delphinidin (mg/d)		Malvidin (mg/d)		Pelargonidin (mg/d)		Peonidin (mg/d)		Petunidin (mg/d)			Anthocyanidins (mg/d)		Cyanidin (mg/d)		Delphinidin (mg/d)		Malvidin (mg/d)		Pelargonidin (mg/d)		Peonidin (mg/d)		Petunidin (mg/d)	
Country and centre	*n*	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	*n*	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Greece	1314	37·87	1·34	14·54	0·79	2·21	0·32	17·30	0·63	0·59	0·31	2·06	0·13	1·15	0·08	1373	25·77	1·31	12·42	0·77	1·28	0·31	9·53	0·61	0·65	0·30	1·31	0·12	0·57	0·08
Spain																														
Granada	214	38·50	3·31	13·92	1·95	2·38	0·79	17·21	1·55	1·08	0·76	2·20	0·31	1·71	0·20	300	18·73	2·80	11·66	1·65	0·85	0·67	3·87	1·31	1·28	0·64	0·76	0·26	0·31	0·17
Murcia	243	36·46	3·11	16·73	1·83	2·09	0·74	13·60	1·46	0·91	0·71	1·64	0·29	1·48	0·18	304	21·40	2·79	11·17	1·64	1·20	0·66	5·59	1·30	2·33	0·64	0·69	0·26	0·43	0·17
Navarra	444	39·45	2·30	10·39	13·52	2·94	0·55	20·20	1·08	1·00	0·53	2·50	0·21	2·42	0·14	271	22·76	2·94	9·73	1·73	0·83	0·70	8·78	1·38	1·75	0·67	1·06	0·27	0·60	0·17
San Sebastian	490	47·49	2·19	16·00	1·29	3·25	0·52	20·93	1·03	2·26	0·50	2·47	0·20	2·58	0·13	244	26·29	3·11	13·20	1·83	0·93	0·74	7·18	1·46	3·54	0·70	0·80	0·29	0·65	0·18
Asturias	386	39·55	2·47	14·76	1·45	2·27	0·59	15·90	1·16	2·59	0·56	2·08	0·23	1·96	0·15	324	25·16	2·69	15·41	1·58	0·77	0·64	5·03	1·26	2·52	0·62	0·94	0·25	0·49	0·16
Italy																														
Ragusa	168	44·39	3·74	19·53	2·20	3·05	0·89	16·85	1·75	0·97	0·85	2·38	0·35	1·60	0·22	138	33·93	4·13	21·68	2·43	1·98	0·98	7·56	1·94	0·84	0·94	1·27	0·38	0·59	0·25
Naples																403	27·55	2·41	15·62	1·42	1·55	0·58	6·04	1·13	2·38	0·55	1·40	0·22	0·57	0·14
Florence	271	44·46	2·94	19·54	1·73	2·71	0·70	16·05	1·38	2·40	0·67	2·04	0·27	1·72	0·17	784	30·29	1·73	14·03	1·02	1·47	0·41	9·56	0·81	3·03	0·40	1·41	0·16	0·80	0·10
Turin	676	64·88	1·86	25·44	1·10	4·05	0·44	26·42	0·87	2·70	0·43	3·61	0·17	2·67	0·11	392	44·08	2·45	23·06	1·44	2·29	0·58	11·44	1·15	4·08	0·56	2·11	0·23	1·11	0·15
Varese	327	55·48	2·68	23·12	1·58	4·16	0·64	21·91	1·26	1·07	0·61	2·79	0·25	2·43	0·16	794	40·04	1·72	21·16	1·01	2·09	0·41	12·33	0·81	1·97	0·39	1·60	0·16	0·89	0·10
France																														
South coast																620	38·42	1·95	15·86	1·15	2·29	0·46	12·55	0·91	4·59	0·45	1·98	0·18	1·15	0·12
South																1425	40·78	1·28	18·56	0·76	1·99	0·31	11·40	0·60	5·80	0·29	1·98	0·12	1·04	0·08
North-east																2059	38·11	1·07	17·60	0·63	2·36	0·26	9·77	0·50	5·58	0·24	1·80	0·10	1·01	0·06
North-west																631	32·37	1·93	15·39	1·14	1·57	0·46	7·28	0·90	5·91	0·44	1·39	0·18	0·82	0·11
Germany																														
Heidelberg	1034	29·79	1·51	12·31	0·89	2·31	0·36	9·78	0·71	2·82	0·34	1·33	0·14	1·24	0·09	1087	36·02	1·48	16·29	0·87	3·31	0·35	8·66	0·70	5·33	0·34	1·29	0·14	1·14	0·09
Potsdam	1233	33·74	1·38	16·86	0·81	2·54	0·33	7·38	0·65	4·85	0·32	1·25	0·13	0·87	0·08	1061	40·80	1·49	20·61	0·88	3·41	0·36	9·02	0·70	5·06	0·34	1·61	0·14	1·08	0·09
The Netherlands																														
Bilthoven	1024	19·83	1·53	9·24	0·90	2·53	0·36	4·37	0·72	2·25	0·35	0·74	0·14	0·69	0·09	1086	23·27	1·49	12·37	0·88	3·32	0·36	3·86	0·70	2·35	0·34	0·69	0·14	0·68	0·09
Utrecht																1870	24·59	1·13	12·03	0·66	2·63	0·27	4·70	0·53	3·54	0·26	0·94	0·10	0·74	0·07
UK																														
General population	403	21·79	2·42	7·83	1·42	1·81	0·58	6·33	1·13	2·15	0·55	2·83	0·22	0·85	0·14	571	24·07	2·03	8·31	1·19	1·39	0·48	7·67	0·95	2·76	0·46	3·18	0·19	0·75	0·12
Health-conscious	113	27·82	4·56	14·60	2·68	2·41	1·09	5·01	2·14	4·20	1·04	0·83	0·42	0·76	0·27	196	30·78	3·46	13·68	2·04	2·26	0·82	8·42	1·62	2·70	0·79	2·82	0·32	0·89	0·21
Denmark																														
Copenhagen	1356	31·60	1·32	10·16	0·77	3·35	0·31	13·28	0·62	1·29	0·30	1·68	0·12	1·82	0·08	1484	26·97	1·26	10·20	0·74	2·56	0·30	10·00	0·59	1·58	0·29	1·30	0·12	1·33	0·08
Aarhus	567	28·02	2·04	11·67	1·20	2·18	0·48	9·83	0·95	1·62	0·46	1·33	0·19	1·40	0·12	510	26·23	2·15	12·38	1·26	1·80	0·51	8·52	1·01	1·30	0·49	1·10	0·20	1·12	0·13
Sweden																														
Malmö	1421	20·22	1·32	6·39	0·77	4·00	0·31	5·92	0·62	1·60	0·30	0·94	0·12	1·37	0·08	1711	20·13	1·19	6·51	0·70	3·52	0·28	6·23	0·56	1·73	0·27	0·93	0·11	1·22	0·07
Umeå	1344	21·24	1·32	7·27	0·78	5·41	0·32	4·72	0·62	1·34	0·30	0·92	0·12	1·58	0·08	1574	22·26	1·22	8·55	0·72	5·77	0·29	4·40	0·57	1·37	0·28	0·82	0·11	1·36	0·07
Norway																														
South and east																1004	27·81	1·55	9·46	0·91	4·16	0·37	9·20	0·72	2·22	0·35	1·25	0·14	1·53	0·09
North and west																793	25·31	1·74	9·32	1·02	3·98	0·41	7·78	0·81	2·00	0·40	0·98	0·16	1·25	0·10

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

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control for different distributions of 24-HDR interviews across seasons and days of the week. All analyses were conducted using SPSS Statistics software (version 17.0; SPSS Inc., Chicago, IL, USA).

Results

The mean intakes and for single and total anthocyanidins stratified by centre and sex, adjusted for age, and weighted by season and day of the week are shown in Table 1. For men, the total anthocyanidin intake ranged from 19·83 mg/d (Bilthoven, The Netherlands) to 64·88 mg/d (Turin, Italy), whereas for women the range was from 18·73 mg/d (Granada, Spain) to 44·08 mg/d (Turin, Italy). The main anthocyanidin contributors (Table 2) were malvidin (42·7 % in men and 29·4 % in women) and cyanidin (38·0 % in men and 49·9 % in women) in the southern region, cyanidin (45·6 % in men and 46·8 % in women) in the central region, and cyanidin (34·0 % in men and 36·8 % in women) and malvidin (33·0 % in men and 30·5 % in women) in the northern European region.

Table 3 shows the assessment of the effect of certain lifestyle factors on anthocyanidin intake adjusted for sex, age, BMI and energy intake (where appropriate) and weighted by season and day of the week. In south European countries, men consumed more anthocyanidins than women of these countries, whereas in north European countries, they consumed similar amounts, and in central European countries women ingested greater quantities than men. The difference in intake between the sexes in south European countries was due to malvidin intake which in men was two-fold that of women. A geographical gradient of increasing total anthocyanidin, cyanidin, malvidin and peonidin intakes from north to south Europe was observed. However, there was an inverse regional gradient for delphynidin intake. Older individuals consumed more anthocyanidins, with a maximum intake in those aged 55–64 years. There were positive trends when assessing total anthocyanidin intakes and educational level, smoking status (comparing current *v.* never or former smokers), BMI (obese *v.* normal or overweight) and physical activity.

Table 2. Percentage contribution* of intakes of individual anthocyanidins in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort by European region and sex

		Region		
Anthocyanidin	Sex	South	Central	North
Cyanidin	Men	38·0	45·6	34·0
	Women	49·9	46·8	36·8
Delphinidin	Men	6·4	8·7	16·2
	Women	4·9	8·2	15·9
Malvidin	Men	42·7	25·6	33·0
	Women	29·4	23·8	30·5
Pelargonidin	Men	3·3	12·0	5·7
	Women	8·9	13·7	7·0
Peonidin	Men	5·4	4·7	4·8
	Women	4·6	4·7	4·3
Petunidin	Men	4·2	3·3	6·3
	Women	2·3	2·8	5·4

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

The main food sources of anthocyanidin intake by European region were also studied (Table 4). The group of fruits, nuts and seeds (mainly non-citrus fruit such as grapes, apples and pears) contributed most of the total anthocyanidin intake. In south, central and north European countries this food group contributed 61·2, 52·9 and 38·1 %, respectively. Other major food sources were wine (contributions ranged from 14·4 to 24·5 %), followed by non-alcoholic beverages, such as carbonated, soft and isotonic drinks in northern European countries (15·8 %) and fruit and vegetable juices in central European countries (13·4 %), and some types of vegetables (ranging from 4·8 to 9·7 %). The major food sources of cyanidins were fruits and non-alcoholic beverages derived from either fruits and vegetables or carbonated, soft and isotonic drinks. For delphynidins, the main contributors in southern countries were wine, bananas, grapes and fruiting vegetables, mainly aubergine. However, in central and northern countries the richest sources were banana, non-alcoholic beverages, berries and wine. Malvidins were almost exclusively derived from grape and wine products. The main contributors to pelargonidins were berries, followed by root vegetables and dairy products with berries as ingredients. We identified fruits, wine and non-alcoholic beverages (only in the north and central European countries) as the most abundant sources of peonidins and petunidins.

Discussion

To our knowledge, this is the first study to estimate the intake of anthocyanidins and their main food sources in a large adult European cohort, evaluating differences across ten European countries and the most important determinant factors. The use of a unique FCDB on anthocyanidins and the same methodology in the dietary assessment for the whole cohort provided more comparable results across the countries. The FCDB was compiled at the end of 2009 using the most updated and available worldwide databases[3,39] on flavonoids and polyphenols. Furthermore, our database was expanded with recipes, estimations by food or food group and the application of cooking factors[40]. However, the use of different FCDB and different food surveys limits the comparisons between studies.

In men, there were great differences in anthocyanidin intakes across EPIC centres, ranging from 19·83 mg/d in Bilthoven to 64·88 mg/d in Turin. Indeed, the south European region had the highest consumption of total anthocyanidins, and the two main individual anthocyanidins (cyanidins and malvidins). Moreover, regional trends of increasing anthocyanidin, cyanidin, malvidin and peonidin intakes from northern to southern countries were also observed. Meanwhile, women from central and southern regions were the highest anthocyanidin consumers. Individuals aged 55–64 years, who had a university degree, non-smokers (former or never smokers), those doing moderate or active physical activity and those that were overweight (BMI 25 to $< 30\,kg/m^2$) had the highest anthocyanidin consumption. Part of these differences was due to the differences in the consumption pattern of the major food sources in the European countries. For example, in

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Table 3. Adjusted* daily intakes (mg/d) of total and single anthocyanidins by sex and selected characteristics
(Mean values with their standard errors)

		Anthocyanidins (mg/d)			Cyanidin (mg/d)			Delphinidin (mg/d)			Malvidin (mg/d)			Pelargonidin (mg/d)			Peonidin (mg/d)			Petunidin (mg/d)		
Stratification variable	*n*	Mean	SE	*P*	Mean	SE	*P*	Mean	SE	*P*	Mean	SE	*P*	Mean	SE	*P*	Mean	SE	*P*	Mean	SE	*P*
Sex				< 0·001			< 0·001			0·004			0·274			< 0·001			0·017			0·016
Male	13028	29·44	0·53		12·01	0·31		2·26	0·13		10·27	0·25		2·19	0·12		1·49	0·05		1·23	0·03	
Female	23009	33·52	0·39		15·09	0·23		2·71	0·09		9·94	0·18		3·02	0·09		1·64	0·04		1·13	0·02	
European region				< 0·001			< 0·001			< 0·001			< 0·001			< 0·001			< 0·001			< 0·001
South	11285	37·42	0·46		16·35	0·27		2·11	0·11		13·57	0·22		2·27	0·11		1·87	0·04		1·25	0·03	
Central	12988	29·79	0·44		13·64	0·26		2·48	0·11		7·52	0·21		3·81	0·10		1·41	0·04		0·93	0·03	
North	11764	23·45	0·45		8·21	0·27		3·83	0·11		7·55	0·21		1·40	0·10		1·05	0·04		1·40	0·03	
Age (non-adjusted for age) (years)				< 0·001			< 0·001			< 0·001			< 0·001			< 0·001			0·049			< 0·001
35–44	3335	26·43	0·89		11·75	0·53		1·99	0·21		8·23	0·42		2·08	0·20		1·40	0·08		1·00	0·05	
45–54	12595	29·67	0·48		12·86	0·28		2·14	0·12		9·71	0·22		2·32	0·11		1·52	0·04		1·13	0·03	
55–64	14940	33·44	0·45		14·20	0·27		2·76	0·11		10·74	0·21		2·88	0·11		1·62	0·04		1·33	0·03	
54–74	5167	33·34	0·77		14·41	0·46		2·85	0·18		10·34	0·36		2·85	0·18		1·63	0·07		1·27	0·05	
BMI (kg/m^2)				< 0·001			0·030			0·261			0·002			0·039			0·004			0·009
< 25	16854	31·74	0·46		13·80	0·27		2·55	0·11		9·95	0·22		2·69	0·11		1·53	0·04		1·21	0·03	
25 to < 30	13766	32·04	0·46		13·57	0·27		2·49	0·11		10·52	0·22		2·63	0·11		1·65	0·04		1·18	0·03	
≥ 30	5417	28·82	0·70		12·57	0·41		2·24	0·17		9·29	0·33		2·24	0·16		1·42	0·07		1·07	0·04	
Level of schooling				< 0·001			< 0·001			0·010			< 0·001			0·027			< 0·001			< 0·001
None	1709	23·91	1·37		10·00	0·81		2·09	0·33		6·96	0·65		2·67	0·32		1·15	0·13		1·04	0·08	
Primary completed	10469	27·83	0·54		12·63	0·32		2·21	0·13		8·22	0·26		2·44	0·13		1·33	0·05		1·00	0·03	
Technical/professional	8038	32·24	0·63		13·94	0·37		2·45	0·15		10·54	0·30		2·45	0·15		1·66	0·06		1·20	0·04	
Secondary school	7152	33·99	0·63		14·30	0·38		2·70	0·15		11·42	0·30		2·58	0·15		1·72	0·06		1·26	0·04	
University degree	8155	36·10	0·60		14·89	0·35		2·82	0·14		12·20	0·28		2·95	0·14		1·85	0·06		1·39	0·04	
Smoking status				0·020			< 0·001			0·336			< 0·001			0·181			0·369			< 0·001
Never smoker	17483	31·37	0·44		14·05	0·26		2·39	0·11		9·57	0·21		2·73	0·10		1·53	0·04		1·10	0·03	
Former smoker	10288	32·44	0·52		13·62	0·31		2·61	0·13		10·81	0·24		2·52	0·12		1·60	0·05		1·28	0·03	
Current smoker	7726	30·42	0·59		12·47	0·35		2·50	0·14		10·17	0·28		2·48	0·14		1·60	0·06		1·19	0·04	
Physical activity				< 0·001			0·002			0·450			< 0·001			0·041			0·066			0·039
Inactive	7463	29·88	0·61		13·33	0·37		2·28	0·15		9·05	0·29		2·58	0·14		1·54	0·06		1·09	0·04	
Moderately inactive	11969	32·05	0·50		13·78	0·30		2·37	0·12		10·37	0·23		2·81	0·11		1·57	0·05		1·15	0·03	
Moderately active	8400	33·39	0·59		14·05	0·35		2·33	0·14		11·24	0·27		2·84	0·13		1·72	0·06		1·22	0·03	
Active	6380	33·15	0·67		15·28	0·40		2·59	0·16		10·11	0·32		2·39	0·16		1·60	0·06		1·18	0·04	

* Adjusted for sex, age, region, energy intake, and BMI (where appropriate) and weighted by season and day of recall.

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Table 4. Percentage contribution of food groups and some main foods to the intake of total and single anthocyanidins by European region*

	Anthocyanidins (%)			Cyanidins (%)			Delphinidins (%)			Malvidins (%)			Pelargonidins (%)			Peonidins (%)			Petunidins (%)		
Food groups and foods†	South	Central	North	South	Central	North	South	Central	North	South	Central	North	South	Central	North	South	Central	North	South	Central	North
Potatoes and other tubers	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	0·0	0·0	0·0	0·0	0·0
Vegetables	9·7	8·8	4·8	15·2	11·4	5·5	24·5	8·6	1·0	0·0	0·0	0·0	16·7	19·9	39·4	0·0	0·0	0·1	0·0	0·0	0·0
Leafy vegetables	7·1	3·8	0·4	14·3	7·8	1·0	7·0	2·5	0·1	0·0	0·0	0·0	0·0	0·0	0·1	0·0	0·0	0·0	0·0	0·0	0·0
Fruiting vegetables	0·9	0·4	0·1	0·0	0·0	0·0	16·7	4·9	0·5	0·0	0·0	0·0	0·1	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0
Root vegetables	1·2	2·8	2·7	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	16·5	19·8	39·2	0·0	0·0	0·0	0·0	0·0	0·0
Cabbages	0·4	1·6	1·5	0·8	3·5	4·2	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
Other and mixed vegetables	0·1	0·1	0·1	0·1	0·1	0·2	0·7	1·2	0·4	0·0	0·0	0·0	0·1	0·0	0·1	0·0	0·0	0·1	0·0	0·0	0·0
Legumes	0·1	0·1	0·1	0·1	0·0	0·1	0·1	0·0	0·0	0·0	0·0	0·0	0·8	0·3	0·6	0·0	0·0	0·0	0·2	0·1	0·0
Fruits, nuts and seeds	61·2	52·9	38·1	76·6	56·8	55·5	25·9	33·8	20·2	46·5	47·6	32·5	73·9	66·3	38·4	54·9	44·6	27·7	25·8	33·1	17·5
Citrus fruits	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	0·0	0·0	0·0	0·0	0·0
Apples and pears	14·2	10·0	12·7	30·1	21·3	34·9	0·3	0·1	0·0	0·0	0·0	0·0	0·2	0·1	0·1	0·1	0·3	0·4	0·0	0·0	0·0
Grapes	18·9	13·0	10·6	0·9	0·7	0·7	20·8	9·4	3·7	46·3	44·5	28·0	0·1	0·0	0·1	30·3	21·7	18·5	25·1	18·5	7·7
Stone fruits	14·8	10·0	2·8	29·6	20·0	7·6	0·0	0·0	0·0	0·0	0·0	0·0	1·5	0·6	0·1	16·3	14·1	0·8	0·0	0·0	0·0
Berries	6·3	16·5	10·1	2·6	9·6	8·3	2·2	22·5	15·8	0·1	2·9	4·2	68·1	61·5	34·5	0·4	7·1	6·1	0·6	14·4	9·7
Other and mixed fruits	2·5	2·3	1·1	3·5	3·2	1·4	2·6	1·7	0·5	0·0	0·0	0·0	4·0	4·1	3·7	7·8	1·5	1·8	0·1	0·2	0·1
Olives	4·5	0·8	0·9	9·6	1·7	2·5	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
Nuts and seeds	0·2	0·1	0·1	0·3	0·3	0·2	0·0	0·1	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0
Dairy products	0·5	1·5	0·8	0·1	0·2	0·2	0·1	0·3	0·0	0·0	0·0	0·0	6·5	9·3	10·8	0·0	0·0	0·0	0·0	0·1	0·0
Cereal, cakes and confectionery	1·0	6·5	4·5	1·4	7·4	6·4	1·3	19·7	3·8	0·2	2·4	2·0	1·9	2·8	3·4	1·3	5·1	7·7	0·9	9·0	6·4
Meat, fish and eggs	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	0·0	0·0	0·0	0·0	0·0
Non-alcoholic beverages	1·7	13·6	19·7	3·1	21·7	26·5	0·1	16·7	49·0	0·7	3·3	0·3	0·0	0·8	5·5	0·9	21·9	7·4	0·4	7·9	19·7
Fruit and vegetable juices	1·7	13·4	3·9	3·0	21·5	8·6	0·1	16·4	3·3	0·7	3·2	0·2	0·0	0·8	0·8	0·9	21·7	2·0	0·4	7·7	1·4
Carbonated, soft, and isotonic drinks	0·0	0·2	15·8	0·1	0·2	17·9	0·0	0·3	45·8	0·0	0·1	0·1	0·0	0·0	4·7	0·0	0·2	5·4	0·0	0·2	18·3
Coffee, tea and herbal teas	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	0·0	0·0	0·0	0·0	0·0
Alcoholic beverages	25·5	15·9	25·4	3·4	2·3	4·0	47·6	19·5	15·3	52·2	45·2	55·6	0·0	0·1	0·0	42·6	27·3	46·6	72·1	47·2	39·2
Wine	24·5	14·4	24·5	2·0	1·2	2·6	45·9	17·9	15·0	51·8	42·3	55·7	0·0	0·0	0·0	42·0	25·5	45·7	70·5	44·1	38·5
Beer, cider	0·6	0·3	0·4	1·2	0·7	1·2	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·1	0·0	0·0	0·0	0·0
Liqueurs and spirits	0·4	1·2	0·5	0·2	0·4	0·2	1·7	1·6	0·3	0·5	2·9	1·0	0·0	0·1	0·0	0·6	1·8	0·8	1·6	3·1	0·7
Soups, bouillons	0·0	0·3	5·9	0·0	0·1	1·7	0·0	0·9	10·3	0·0	0·4	7·3	0·0	0·0	0·0	0·0	0·4	9·5	0·0	1·3	16·4
Miscellaneous	0·3	0·5	0·7	0·2	0·1	0·2	0·4	0·5	0·4	0·4	1·0	1·2	0·2	0·6	1·8	0·3	0·6	1·1	0·5	1·1	0·8

* Values are percentages derived from models adjusted for age and sex and weighted by season and day of recall. There were differences between European regions for all food sources ($P < 0·001$), except for food sources where anthocyanidin contributions are less than 0·2 % for all regions (NS differences).

† Leafy vegetables include red leaf lettuce, red chicory, radicchio and trevise (red Treviso lettuce); fruiting vegetables include aubergines; root vegetables include beetroot, red radish and black radish; cabbages include red cabbage and Chinese cabbage; stone fruits include plums, peaches, nectarines, apricots, mangoes and paraguayos; other and mixed fruits include cherries, red fruit not specified, sour cherries, persimmon, sharon fruit and pomegranate; cereal, cakes and confectionery include fruit cakes, biscuits with jam and plum cake; fruit and vegetable juices include blackcurrant juice, cranberry juice, redcurrant juice, cherry juice, peach juice, apricot juice, plum juice and beetroot juice; carbonated, soft and isotonic drinks include blackcurrant syrups, syrups of fruits and berries, cherry coke, pommac and jaffa; soups and bouillons include bilberry soup, berry soup and elderberry soup.

southern countries, a high intake of wine[46], non-citrus fruits (especially grapes, stone fruits, apples and pears, and olives) and leafy vegetables[47] was observed. However, in central and northern countries the main contributors were non-citrus fruits (mainly berries, apples and pears, and grapes), wine and, finally, non-alcoholic beverages (juices and soft drinks of anthocyanidin-rich fruits). The large differences in anthocyanidin intakes between men (45·47 mg/d) and women (31·73 mg/d) in the southern region (Italy, Spain, Greece) were due to the high consumption of red wine, which is very rich in malvidins, as observed in a previous Spanish cohort[30]. The present results are comparable with previously published data of intakes in the southern European region; median intakes of 9·3 to 28·0 mg/d have been reported[7,12–15,17,18,21,24,25,48–50] although a Greek cohort was found to consume 52·6 mg/d[22]. Two previous studies in northern countries (Finland) also reported great differences in mean intakes; 5·9 mg/d in the Kuopio Ischaemic Heart Disease Risk Factor Study[23] and 47 mg/d in the FINDIET 2002 Study[31]. In non-European countries, lower intakes have been observed than in European countries. For example, in the USA mean intakes were found to range from less than 1 to 10·1 mg/d[6,11,16,19,20,29], while in Australia 2·9 mg/d[28], and in Japan 11·3 mg/d[51] were reported.

Cyanidins were the most prevalent anthocyanidins (34–50 %) except in men from the southern European region. Cyanidin intake ranged from 8·2 to 16·4 mg/d; these values are slightly higher than our previous results in Spain (6·2 mg/d)[30] and in Greece (4 mg/d)[50], lower than Finland (25 mg/d)[31] and much higher than in Australia (0·42 mg/d)[28]. In Finland the main contributors were berries and their derived products (88 %)[31], whereas in the present study berries and berry products (juices, soft drinks and soups) represented approximately 6, 31 and 37 % in southern, central and northern countries, respectively. In the present study, leafy vegetables, apples and pears, and stone fruits were also major food sources of cyanidins. Malvidin was the main anthocyanidin in men from the southern European region, which is in line with findings from our previous study in Spain[30] and in Australia[28]. In the entire cohort and in the literature the main contributors were red wine and red grapes. Delphynidin was usually the third most abundant anthocyanidin (5·6 and 16·0 % in southern and northern countries, respectively). Moreover, a geographical trend was observed, with increasing intakes from south (0·8 mg/d women in Navarra, Spain) to north (5·8 mg/d women in Umeå, Sweden), as has previously been observed in Spain (2·5 mg/d)[30] and Finland (14 mg/d)[31]. Pelargonidins (3·3–13·7 %), peonidins (4·3–5·4 %) and petunidins (2·3–6·3 %) were the least abundant anthocyanidins, similar to findings reported in previous papers[28,30,31].

Anthocyanidins have been shown to have protective effects in clinical and epidemiological studies, especially against some chronic diseases. In a US breast cancer case–control study, a reduction of all mortality at 6 years of follow-up after a high intake of anthocyanidins and other flavonoids[6] was reported. Concerning CVD, an Italian case–control study observed a significant inverse trend between acute myocardial infarction and anthocyanidin intake, and an OR of 0·45 (95 % CI 0·26, 0·78) when comparing extreme quintiles[7]. However, in two Greek case–control studies no associations were found between anthocyanidin consumption and peripheral arterial occlusive disease[48] or CHD[49]. Indeed, in a recent meta-analysis, Hooper *et al.* concluded that there were insufficient data from clinical trials to confirm the beneficial effects on CVD[52]. Several epidemiological studies have suggested contradicting results regarding cancer. However, these differences can be explained, in part, by low anthocyanidin bioavailability (less than 5 %)[9] and the wide range of anthocyanidin intakes among studies. Overall, all cancers studied not related to the digestive system (breast, ovarian, prostate, lung, pancreatic, liver, renal cancers, and diffuse and follicular β-cell lymphomas) have not been significantly associated with anthocyanidin intake[6,17–20,22–25,53]. Concerning cancers of the digestive system, when the mean consumption of anthocyanidins is low (< 20 mg/d), non-significant associations have been reported for upper aero-digestive and colorectal cancer, colorectal and oesophageal squamous cell cancer in the Iowa Women's Health Study[19], the Kuopio Ischaemic Heart Disease Risk Factor Study[23] and a US case–control study[11], respectively. However, when their mean intake is high (southern European countries), a protective effect against colorectal, oral cavity, pharyngeal and laryngeal oesophageal cancers comparing extreme quintiles has been observed, although the trend analysis has usually not been significant[12–15]. Gastric cancer has only been studied in a Greek case–control study, in which no statistical association with anthocyanidin intake was shown, even though the mean intake was slightly high (20·4 mg/d)[21]. More recently, anthocyanidins have been shown to reach some brain regions after consumption of blueberries in rats[54]; therefore they are able to cross the haemato–encephalic barrier. This finding suggests the potential role of anthocyanidins as anti-inflammatory and antioxidant agents against the deleterious effects of ageing and its related neurodegenerative diseases[55] and in improving memory function in older adults[56]. Further basic and epidemiological investigation is needed to confirm these potential effects against cancer and cardiovascular and neurodegenerative diseases, but taking into account possible differences among individual anthocyanidins.

To our knowledge, this is a unique study and the largest to date describing anthocyanidin intake across several European countries. However, as not all the EPIC cohorts are representative of the population, the observed level of intake cannot be extrapolated to the general population of each region. Another limitation of the present study is an underestimation of the real anthocyanidin intake, because there are some food items with missing composition data. However, our database was compiled from the most updated flavonoid databases, with only 10 % of missing values. Indeed, the major strength of the present study is the use of a unique and specifically developed FCDB, for that allowed results to be compared across countries. Further underestimation may be due to the omission of dietetic supplements in this analysis. However, there are few consumers of herb or plant

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supplements in the present study (up to 5 % in Denmark, the highest consumer country)[57].

The present study generated data for total and individual anthocyanidin intakes among twenty-seven centres in ten European countries, according to sex, age and some lifestyle factors. Main food sources and differences among European regions were also identified. These descriptive data will be valuable for future aetiological research focused on the relationships between anthocyanidins and chronic diseases.

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