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Dietary intake of flavonoids and asthma in adults

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ABSTRACT: Epidemiological studies have suggested that a high consumption of apples may protect against asthma and chronic obstructive pulmonary disease. This effect has been attributed to their high flavonoid content, but few studies have investigated the relationship between flavonoid intake and obstructive lung disease directly.

In a population-based, case-control study of 1,471 adults aged 16–50 yrs in London (UK), the present study examined whether dietary intake of catechins, flavonols and flavones was negatively associated with asthma, asthma severity and chronic sputum production. Asthma was defined by positive responses to a standard screening questionnaire in 1996 and information about usual diet was obtained by a food frequency questionnaire in 1997.

After controlling for potential confounders, dietary intake of these three flavonoid subclasses was not significantly associated with asthma, (odds ratio per quintile (95% confidence interval)=0.94 (0.86–1.02); 1.00 (0.92–1.09); 0.98 (0.88 –1.08) for flavones, flavonols and total catechins, respectively) nor was it associated with asthma severity, or chronic sputum production.

In conclusion, no evidence was found for a protective effect of three major subclasses of dietary flavonoids on asthma. It is possible that other flavonoids or polyphenols present in apples may explain the protective effect of apples on obstructive lung disease.

KEYWORDS: Antioxidants, apples, asthma, diet, flavonoids

Oxidative stress is thought to play a key role in the pathogenesis of asthma and chronic obstructive pulmonary disease (COPD) [1], and there is considerable interest in the possible protective effects of dietary antioxidants. However, the majority of epidemiological studies have only focused on the possible role of antioxidants and vitamins [2, 3].

Flavonoids, a family of polyphenols, are antioxidants, which are found especially in fruits, vegetables, red wine and tea [4, 5]. In addition to their well-known antioxidant properties, they also have anti-allergic and anti-inflammatory effects [6–9], which might explain reports suggesting that certain flavonoids have beneficial effects in asthma [9, 10].

Indirect epidemiological evidence that flavonoids might protect against obstructive lung disease come from studies that have reported negative associations of apple intake with prevalence [11] and incidence [12] of asthma, and a positive association with lung function [13]. These findings are in keeping with other observations that hard fruit consumption was negatively associated with incidence of chronic nonspecific lung disease [14], prevalence of COPD symptoms [15] and asthma [16], and positively associated with lung function [15].

Few studies have examined associations between intake of specific flavonoid groups and asthma or COPD directly, because flavonoid databases have not been available. However, two recent reports have suggested possible protective effects of quercetin, hesperetin and naringenin on incident asthma in Finland [12] and of catechins on lung function and COPD symptoms in The Netherlands [15].

Therefore, the present study investigated, in a population-based case-control study, whether intakes of three of the six major flavonoid subclasses previously studied in relation to COPD [15] were negatively associated with adult asthma and, if so, whether flavonoid intake explained the current authors' previous observation of a protective effect of apple consumption on asthma [11].

MATERIALS AND METHODS

Study subjects and outcome measures

Details of the present case-control study of dietary antioxidants and adult asthma have been described previously [11]. In brief, the study sample comprised adults aged 16–50 yrs living in Greenwich (London, UK), who took part in an asthma survey in 1996 and a dietary survey in 1997. In total, 1,438 cases of asthma were

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identified by positive responses to questions about attacks of asthma or waking with shortness of breath in the last 12 months, or current use of asthma medication. A random sample of 2,000 controls were identified by negative responses to these questions. Asthma cases were subclassified according to the presence or absence of rhinitis in an attempt to identify those who were more atopic or less atopic, respectively. Asthma severity amongst cases was measured according to the frequency of waking at night with asthma symptoms ($\geqslant$3 times per week *versus* <3 times per week), and by an asthma quality-of-life (QoL) score [17]. Individuals who reported that they usually produced phlegm in the winter (first thing in the morning and/or during the day or night) on most days for $\geqslant$3 months each year were defined as having chronic sputum production.

Dietary assessment and estimation of flavonoid intake

Cases and controls were mailed a food frequency questionnaire (FFQ), which asked about dietary intake in the past 12 months, and included >200 items of food and drink. Replies were received from 720 cases and 980 controls. Prior to the main study this instrument was calibrated against a 7-day weighed record, and repeat FFQ data was subsequently obtained on a subsample of individuals in order to estimate the repeatability of estimates of flavonoid-rich food intakes [11]. Weekly intake (g) of food and food groups was estimated by multiplying frequency of consumption by the weight of standard portion sizes. Daily intake of nonflavonoid nutrients and total energy was estimated in the same way, using British food composition tables [18].

Daily intake of the major flavonols (quercetin, kaempferol, myricetin) and flavones (apigenin, luteolin) was calculated using food composition data published in 1992 and 1993 on the contents of foods and beverages of vegetable origin, including typical British tea infusions [19, 20]. Intake of six major catechins ((+)-catechin, (+)-gallocatechin, (-)-epicatechin, (-)-epigallocatechin, (-)-epicatechin gallate, and (-)-epigallocatechin gallate) was calculated using Dutch food composition data published in 2000 [21, 22], which were based on analyses of a comprehensive set of commonly consumed plant foods by high performance liquid chromatography with ultraviolet and/or fluorescence detection [23, 24], taking into account several sources of variation.

Only two individuals in the study reported taking supplements containing bioflavonoids.

Statistical analysis

The main exposures of interest were intakes of three flavonoid subclasses, namely, flavones, flavonols (both grouped into quintiles) and total catechins (four categories of intake), which were calculated by adding intakes of each of the major individual flavonoids in each subclass listed above. Also of interest were three individual flavonoids found particularly in apples, namely, quercetin, catechin and epicatechin. However, as intake of quercetin was very highly correlated with total flavonol intake, and epicatechin intake was highly correlated with catechin and total catechin intakes, only intake of catechin was analysed separately. Logistic regression was used to analyse associations of flavonoid intake with asthma, frequent waking with symptoms and chronic sputum production (with inverse probability weighting and robust standard errors for the latter outcome), and linear regression to examine associations with the asthma QoL score (square root transformed). In the regression models, the current authors controlled for potential confounders which included sex, age, body mass index (self-reported weight·height^{-2}) social class, housing tenure (owned/mortgaged or rented), employment status, whether a single parent, smoking (never/ex/current), passive smoke exposure at home, and total energy intake.

Current social class was classified in males and females according to the Registrar General's classification of occupations [25] and was based on the subject's own occupation (or partner's occupation if the latter was classified higher). Students were classified according to their father's occupation. Individuals with insufficient information on their own occupation were assigned social class based on their father's occupation at birth.

RESULTS

The main analyses of asthma were restricted to 1,471 individuals (607 cases and 864 controls) with complete information on diet and confounders. The median (interquartile range) intakes overall (mg·day^{-1}) of flavones, flavonols and total catechins in these individuals were 0.25 (0.10–0.62), 33.2 (21.1– 45.2), and 81.2 (32.5–135.7), respectively.

Table 1 shows the association between asthma and dietary intake of the three flavonoid subclasses. Univariately, intake of flavones was negatively associated with asthma (odds ratio (OR) per quintile=0.89 (95% confidence interval (CI): 0.83–0.96); p=0.002), but there was little evidence for an association after controlling for potential confounders (OR per quintile=0.94 (95% CI: 0.86–1.02); p=0.13). There was no evidence for an association between flavonols or total catechins and asthma (adjusted OR=1.00 (95% CI: 0.92–1.09; p=0.94) and 0.98 (95% CI: 0.88–1.08; p=0.65), respectively).

After controlling for confounders, no evidence of associations was found between flavonoid intake and asthma severity amongst cases, whether measured by frequent waking at night or by QoL score (n=586; data not shown).

Table 2 shows the association between chronic sputum production and flavonoid intake in 1,422 individuals with complete information. Evidence for a negative association was seen univariately for flavone intake, but disappeared after controlling for confounders.

No evidence was found that intake of the individual flavonoid catechin was associated with asthma or any other outcome.

DISCUSSION

In this population-based study, little evidence was found that dietary intake of three major subclasses of flavonoids was associated with asthma in adults. Nor was there evidence that flavonoid intake was associated with chronic sputum production. Given that the present authors previously found significant associations between apple and selenium intake and asthma when similar analyses in the same case-control study were carried out [11], it seems unlikely that strong associations with flavonoid intake have been missed. However, the present authors acknowledge that their study

TABLE 1 Association between asthma and dietary intake of flavonoids

Flavonoids	Quintile/group	Intake within quintile/group	Crude OR (95% CI)	p-value trend	Adjusted OR# (95% CI)	p-value trend
Flavones mg·day^{-1}	1	0.02 (0.01–0.04)	1.0		1.0	
	2	0.12 (0.10–0.14)	0.95 (0.68–1.32)		1.16 (0.82–1.64)	
	3	0.24 (0.20–0.32)	0.94 (0.68–1.30)		1.14 (0.81–1.62)	
	4	0.49 (0.45–0.60)	0.63 (0.45–0.88)		0.78 (0.54–1.12)	
	5	1.05 (0.87–2.41)	0.69 (0.50–0.96)	0.002	0.89 (0.62–1.28)	0.13
Flavonols mg·day^{-1}	1	11.4 (7.9–14.4)	1.0		1.0	
	2	22.5 (20.6–25.1)	0.81 (0.58–1.13)		0.86 (0.61–1.22)	
	3	32.7 (30.0–34.8)	0.70 (0.50–0.97)		0.79 (0.55–1.13)	
	4	43.1 (40.2–45.2)	0.78 (0.56–1.08)		0.92 (0.65–1.32)	
	5	55.1 (50.7–60.5)	0.82 (0.59–1.15)	0.27	0.97 (0.67–1.41)	0.94
Total catechins mg·day^{-1}	1	12.1 (6.4–19.0)	1.0		1.0	
	2	54.2 (37.6–75.5)	0.80 (0.59–1.08)		0.85 (0.62–1.16)	
	3	94.5 (85.3–127.8)	0.67 (0.50–0.90)		0.76 (0.55–1.04)	
	4	170.6 (143.8–178.1)	0.86 (0.64–1.15)	0.20	0.95 (0.69–1.31)	0.65

Data are presented as median (interquartile range), unless otherwise stated. OR: odds ratio; CI: confidence interval. #: controlling for: sex, age, body mass index, social class, housing tenure, whether a single parent, employment, smoking, passive exposure to smoke and total energy intake.

TABLE 2 Association between chronic sputum production and dietary intake of flavonoids

Flavonoids	Quintile/Group	Crude OR (95% CI)	p-value trend	Adjusted OR# (95% CI)	p-value trend
Flavones mg·d^{-1}	1	1.0		1.0	
	2	0.87 (0.54–1.40)		0.99 (0.60–1.66)	
	3	0.89 (0.56–1.42)		1.16 (0.71–1.89)	
	4	0.74 (0.46–1.19)		1.01 (0.61–1.68)	
	5	0.47 (0.28–0.78)	0.004	0.79 (0.46–1.35)	0.50
Flavonols mg·d^{-1}	1	1.0		1.0	
	2	0.69 (0.40–1.16)		0.81 (0.46–1.40)	
	3	1.08 (0.67–1.74)		1.36 (0.79–2.34)	
	4	0.97 (0.60–1.59)		1.21 (0.70–2.11)	
	5	0.97 (0.60–1.58)	0.61	1.31 (0.75–2.29)	0.15
Total catechins mg·d^{-1}	1	1.0		1.0	
	2	0.65 (0.42–1.02)		0.83 (0.52–1.32)	
	3	0.59 (0.38–0.93)		0.77 (0.47–1.26)	
	4	0.91 (0.61–1.38)	0.70	1.03 (0.65–1.63)	0.94

OR: Odds ratio; CI: confidence interval. #: controlling for: sex, age, body mass index, social class, housing tenure, whether a single parent, employment, smoking, passive exposure to smoke and total energy intake.

may have had insufficient power to detect more modest effects. Also, given that response rates were not high in the current study, the possibility that the findings may have been influenced by selection bias cannot be ruled out, although response rates were similar in cases and controls.

The authors are only aware of one study which has examined the association between dietary intake of specific flavonoids and asthma. KNEKT *et al*. [12] studied intake of flavonols, flavones and flavonones, but not catechins, in Finland, and reported that intakes of quercetin (the predominant flavonol), and hesperetin and naringenin (flavonones) were negatively associated with incident asthma, although the findings for quercetin and naringenin were of borderline statistical significance. In contrast, a negative association was not found between flavonol intake and prevalent asthma. In keeping with the study by KNEKT *et al*. [12], no convincing evidence of an association between flavone intake and asthma was found. Whilst it was not possible to examine the effect of flavonones, such as hesperetin and naringenin, the current authors previously found that the major dietary source of these flavonoids, citrus fruit, was not related to asthma [11].

In contrast to a Dutch study which reported a negative association between catechin intake and COPD symptoms, including chronic phlegm [15], no association was found between catechin intake and chronic sputum production in the present study. However, that study included older adults and did not control for potential confounding by socioeconomic status in the analyses. Furthermore, mean intake of catechins in the current study was much higher than that reported in The Netherlands [15], probably because tea consumption is higher in the UK. In keeping with that study, no association between flavonol or flavone intake and chronic sputum production was found.

A secondary aim of the present study was to see whether intake of flavonoids might explain the protective effect on asthma of apples reported previously by SHAHEEN *et al*. [11] and by KNEKT *et al*. [12]. Taken together, quercetin and catechins are thought to represent between 54% and 72% of the flavonoids present in apples [26]. However, in the current study intakes of total flavonols (comprising mainly quercetin) and total catechins were not associated with asthma. This is not surprising, as previously no association was found between asthma and intake of onions and tea [11], which are rich sources of quercetin and catechins, respectively. Therefore, it is likely, as previously speculated, that the protective effects of apples on asthma may be attributable to other flavonoids and nonflavonoid polyphenols found in apples that could not be studied, and which contribute to the powerful antioxidant properties of apples [27]. These include anthocyanidins, dihydrochalcones (phloridzin), hydroxycinnamates and phenolic acids, in particular chlorogenic acid [26].

In conclusion, no clear evidence has been found to suggest that dietary intake of three major subclasses of flavonoids protect against asthma or chronic sputum production. However, as more comprehensive flavonoid databases become available, it will be of interest to explore whether intake of other flavonoids, especially those found in apples, is associated with asthma and chronic obstructive pulmonary disease.

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