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Fruit and Vegetable Intakes and Asthma in the E3N study.

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Short title: Fruit and vegetable intakes and asthma

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ABSTRACT

Objectives: We investigated whether dietary intake predicted the prevalence of adult asthma among French women participating in the E3N study.
Methods: Among the 68,535 women who completed a food frequency questionnaire in 1993, which included 238 food items, 2,145 women (3.1%) reported to have asthma. The distribution of food intake was divided into quartiles (Q_1 to Q_4) and the prevalence of asthma was compared between the different quartiles (lowest as reference) using logistic regression models on cross-sectional data.
Main results: After adjusting for age, body mass index, menopausal status, smoking status, total caloric intake, physical activity, and use of dietary supplements, women who had a greater intake of tomatoes (OR_{Q1-Q4} = 0.85 95% CI 0.75-0.96, test for trend p=0.02), carrots (OR_{Q1-Q4} =0.81 95% CI 0.72-0.92, test for trend p=0.0003)) and leafy vegetables (OR_{Q1-Q4}= 0.82 95% CI 0.73-0.93, test for trend p=0.0009), had a lower prevalence of asthma. Apple intake was marginally related to asthma prevalence. No other fruits or vegetables were significantly associated with asthma prevalence.
Conclusions: These results suggest that the intake of some vegetables may decrease the prevalence of adult asthma.

Keywords: asthma, fruit and vegetable intake, women
Abstract: 183 words

INTRODUCTION

Environmental factors appear to be critical in the increase of asthma prevalence observed in most developed countries recently. Changes in diet such as decreased consumption of fresh fruit and vegetables might play a major role.[1] [2] [3] However, the epidemiological evidence for the role of food intake in asthma prevalence among adults is still scarce. Previous studies have reported that a greater intake of fresh fruit was related to lesser prevalence of respiratory symptoms[4] and to a lower incidence of non-specific lung diseases,[5] but no specific foods were identified. Although vitamin C is believed to be the principal candidate for the apparent benefit of plant foods,[6] a prospective study[7] found no beneficial effect of dietary vitamin C intake and intervention trials provided conflicting results.[8] Antioxidants other than the vitamin C contained in fruit and vegetables might play an important role in asthma. In a recent case-control study, Shaheen et al. reported that the consumption of apples and red wine were negatively related to asthma[9] suggesting the beneficial effect of flavonoids.[9]

There is a number of reasons to explore the effects of fruits and vegetables rather than individual nutrient. Food contains several substances and an analysis focusing on nutrients might miss important components and interaction between nutrients; people eat food and not nutrient therefore foods are easier to convert into dietary recommendation. For these reasons, public health programs have focused on the promotion of consumption of fruits and vegetables.[10] Although this recommendation was mostly based on results from cancer research, it appears that the consumption of fruits and vegetables might also be beneficial for lung health. It is therefore important to determine which fruits and vegetables are most beneficial for asthma prevention. We used data from the E3N (Etude Epidémiologique auprès des femmes de la MGEN) study, the French branch of the European Prospective Investigation into Cancer and Nutrition (EPIC), to evaluate the association of fruit and vegetable intake with asthma prevalence in a large population of adult women.

METHODS

Study population

The E3N study is a prospective investigation of major chronic diseases among a cohort of members from the Mutuelle Générale de l'Education Nationale (MGEN), a national health insurance plan covering mostly teachers. The general characteristics of this population have been reported elsewhere.[11] This study began in 1990 when a baseline questionnaire (Q_1) was sent to 103 089 women aged 40 to 65 years old. A follow up questionnaire was sent in January 1992 (Q_2) and approximately every two years thereafter. In June 1993, in addition to the follow-up questionnaire, a dietary assessment was conducted using a dietary history questionnaire (Q_3) to which 75,518 women responded.

Our study population was composed of 68,535 women who answered Q_1, Q_2 and Q_3 and met the inclusion criteria for our analysis (see figure 1). Reasons for exclusion were: no answer to the previous questionnaire (Q_2) (n=4,424); unrealistic figures reported to the food questionnaire (Q_3) based on the ratio of energy intake/energy requirement (based on the EPIC methodology[11]) (n=1,294); asthma diagnosis during childhood or no specified date for asthma diagnosis (n=1,265). In order to study a homogeneous group of asthmatics, analyses were restricted to those who

reported adult onset asthma. One important reason for this choice is that longitudinal studies performed in cohorts from childhood to adulthood and during adulthood have shown a low tracking of dietary habits from childhood to adulthood[12] while tracking of diet in adulthood is acceptable.[13]

The final participation rate was 69.2% (68,5335/98,997). Data were analyzed cross-sectionally to evaluate the association between fruit and vegetable intake and asthma prevalence.

Definition of a prevalent case of asthma

Our definition of asthma was based on the presence of an affirmative answer to the question “did you have an asthma attack?” and “age at time of the first attack” on the second follow-up questionnaire (Q_3). Among the 68,535 volunteers, we identified 2,145 women with asthma who had reported the first attack occurring in adulthood and provided the age when they had been diagnosed. These were included in the analysis.

Our classification of asthma was further validated using information gathered in the follow-up questionnaire sent in 2003 (Q_7). Asthma was defined by questions based on the ATS questionnaire:[14] "Have you ever had asthma attacks" and if yes “Was this diagnosis confirmed by a doctor ?" Among the 68,535 women included in the present analysis, 62,849 provided information on asthma in 2003 (Q_7). 725 women reporting incident asthma between Q_3 and Q_7 and 374 reporting asthma in childhood in Q_7 were excluded. Based on the 61,750 women with both information at Q_3 and Q_7, the agreement between the asthma definition used in the present analysis (Q_3) and asthma assessed in Q_7 was very strong. Overall, 1,661 (2.7%) women were defined as asthmatics in Q_3 and 1,909 (3.1%) in Q_7. The great majority of women who reported asthma in Q_3 were classified as asthmatics in Q_7. The agreement between the asthma definition used in the present analysis (Q_3) and asthma assessed in Q_7 (ATS definition) was strong (Kappa statistic 0.77) and the definition of asthma at Q_3 had a high sensitivity (72.3%) and specificity (99.4%) using asthma assessed in Q_7 as gold standard.

Food frequency questionnaire

The dietary questionnaire sent to participants in 1993 was composed of 2 parts with a booklet of photos to facilitate the estimation of portion sizes. The first part included questions on the consumption (frequency and quantity) of 66 food groups. The second part included qualitative questions. Overall, the questionnaire provided an estimate for daily consumption of 208 food items. Both the questionnaire and the illustrated booklet were validated previously.[15][16] We considered the food classification proposed by EPIC.[17] Total calorie intake was estimated through the food frequency questionnaire (FFQ) and expressed in kilocalorie per day (kcal/day).

Body mass index

Body mass index was calculated based on the height and weight reported in the questionnaire administered at baseline. Body mass index was used as a continuous and categorical variable.

Other information

We used information provided on the 1993 questionnaire (Q_3). Tobacco consumption was categorized as never, past, and current smoker. Current exercise and energy expenditure were calculated by multiplying the duration of daily activities and leisure physical activities. Estimated metabolic energy spent was based on the values proposed by James and Schofield[18] and categorized in quartiles of physical activity. Women were classified as premenopausal, postmenopausal or perimenopausal. Because our population was composed mostly of teachers from the MGEN, we used years of education as proxy of socio-economic status. The presence of allergy was classified as either present or absent.

STATISTICAL ANALYSIS

The general characteristics of asthmatic and control women were compared by using chi^2 test statistics for categorical data.[19] Fruit and vegetable intake of asthmatic and control women were compared after log transformation of the data to normalize the distribution using t-test statistics.[19] We studied the association between asthma in adulthood and fruit and vegetable intake using logistic regression models,[20] adjusting for potential confounding factors including age, total calorie intake, body mass index (BMI), physical activity, smoking status, menopausal status,[21] [22] [23] and the use of dietary supplements. Because our population came from a fairly homogenous socio-economic status, adjusting for this variable (years of education) did not modify our estimates. Fruit and vegetable intake was categorized into quartiles based on the distribution among control women. The odds ratios (OR) were determined by comparison with the lowest quartiles. Correction for multiple comparisons was performed by the Bonferroni method.[24] We tested the significance of the interaction between smoking status and fruit and vegetable intake. Although the interaction terms were not significant, we further stratified our analysis by smoking status (never smoker, ex-smoker or current smoker) to determine if there was some indication of a modifying effect by this variable. We tested for linear trends in ORs with increasing exposure using the likelihood ratio test.[25] All analyses were conducted using SAS V8.

RESULTS

Among the 68,535 women included in the analysis, we identified 2,145 (3.1%) who reported having had an asthma attack in adulthood prior to the application of the food frequency questionnaire in 1993. The characteristics of the women included and excluded from the analysis were similar regarding age, smoking status, menopausal status, physical activity, SES and use of dietary supplements but women excluded were more likely to have a lower BMI (mean ± SD: 22.9 ± 3.3 vs. 23.3 ± 3.8, $p< 0.0001$), to have a higher total calorie intake (mean ± SD: 2345.1 ± 1537.3 vs. 2141.4 ± 566.0, $p<0.0001$) and to report allergy (45.5% vs. 23%, $p<0.0001$).

Characteristics of the study population are presented in table 1 according to asthma status. Women who suffered from asthma had a larger BMI, smoked less, reported more frequent use of dietary supplements and allergy than women who did not have asthma.

Table 1 Characteristics of the population according to asthma status.

	Asthmatic women (n=2,145)	Control women (n=66,390)	P*
Age (years)			
< 48 year	30.6	31.6	
48 – 53	24.5	24.4	
53 – 58	20.9	20.2	0.8
58 – 63	13.6	13.8	
> 63	10.4	10.0	
Physical activity, %			
1st quartile	26.1	25.7	
2nd quartile	22.7	25.3	
3rd quartile	24.8	24.2	0.04
4th quartile	26.4	24.8	
Caloric intake (Kcal/day), %			
1st quartile (< 1737)	24.2	24.5	
2nd quartile (1737 - 2088)	24.2	25.5	
3rd quartile (2088 - 2490)	25.4	25.5	0.2
4th quartile (> 2490)	26.2	24.5	
Body mass index (kg/m²), %			
< 20	12.8	15.5	
20 – 25	60.9	64.3	0.0001
25 – 30	20.2	16.6	
> 30	6.1	3.6	
Tobacco consumption, %			
Never smokers	61.4	64.7	
Ex smokers	27.8	22.6	0.0001
Current smokers	10.8	12.7	
Menopausal status, %			
Pre menopausal	12.0	12.0	
Post menopausal	79.6	79.8	0.9
Peri menopausal	8.4	8.2	
Education / number of years at school			
<12 years	0.5	0.5	
12 years	11.0	11.4	
14 years	49.1	51.2	0.3
16 years	20.4	19.0	
17 years	19.0	17.9	
Vitamins supplementation use, %	25.0	21.1	0.0001
Allergy, %	76.4	21.3	0.0001

* p-value of chi^2 test statistics

+ Food groups: leafy vegetables (chicory, lettuce and spinach), fruity vegetables (artichoke, avocado, tomatoes, cucumber, green beans, eggplants, bell pepper, and zucchini), root vegetables (carrots, radish, beetroot, celeriac, and salsify), fruit (orange, grapefruit, mandarin, apple, pear, banana, kiwi, pineapple, strawberries or raspberries, cherry, peach, melon, apricot, raisins, plums, other fruits) and nuts and seeds.

Table 2 presents the dietary intake of specific fruits and vegetables among prevalent cases of asthma and control women. Caloric intake was higher among women reporting asthma. No significant difference in food intake was observed.

Table 2 Description of fruits and vegetables consumption (grams/day) according to asthma status, E3N study, France

	Asthmatic women (n=2,145)	Control women (n=66,390)	p*
Total caloric intake, m (sd)	2167.70 (585.27)	2140.50 (565.39)	0.03
VEGETABLES[+]			
Leafy vegetables, m (sd)	67.02 (40.35)	68.05 (39.37)	0.2
Fruity vegetables, m (sd)	69.09 (59.52)	69.81 (56.61)	0.6
Root vegetables, m (sd)	29.42 (26.01)	30.00 (25.29)	0.3
Cabbages, m (sd)	22.75 (23.48)	22.70 (22.86)	0.9
Tomatoes, m (sd)	19.41 (16.49)	19.48 (15.65)	0.8
Carrots, m (sd)	16.21 (15.06)	16.75 (14.85)	0.09
FRUITS[+]			
Fruits, m (sd)	265.05 (175.82)	260.36 (167.30)	0.2
Fruits with citrics, m (sd)	48.21 (52.33)	48.61 (50.03)	0.7
Fruits with beta carotene, m (sd)	47.22 (47.73)	47.65 (46.46)	0.7
Nuts and seeds, m (sd)	5.46 (8.09)	5.49 (8.38)	0.9
Apples, m (sd)	20.11 (23.29)	20.81 (22.65)	0.15

* p-value from test-t conducted on log-transformed data

[+] Food groups: leafy vegetables (chicory, lettuce and spinach), fruity vegetables (artichoke, avocado, tomatoes, cucumber, green beans, eggplants, bell pepper, and zucchini), root vegetables (carrots, radish, beetroot, celeriac, and salsify), fruit (orange, grapefruit, mandarin, apple, pear, banana, kiwi, pineapple, strawberries or raspberries, cherry, peach, melon, apricot, raisins, plums, other fruits) and nuts and seeds.

Table 3 presents the associations between quartiles of fruit and vegetable intake and asthma in adulthood. After adjusting for BMI, physical activity, menopausal status, smoking and use of dietary supplements, a decreasing trend in asthma prevalence was observed with the increasing intake of apple (OR_{Q1-Q4} = 0.90, 95% CI =0.80-1.02, test for trend p=0.03). Fruit intake (fruits, citric fruits, fruits rich in betacarotene) was not related to asthma prevalence.

Table 3 Association of fruits and vegetables intake and asthma prevalence in adulthood.

Food groups and foods[+]	Quartile of intake (g/day)				P Test for trend
	Q1	Q2	Q3	Q4	
	≤ 145.3	>145.3-235.4	>235.4-333.6	>333.6	
Fruits					
Cases (n)	543	522	515	565	
Controls (n)	16339	16700	16789	16562	
Age-adjusted OR (95%CI)		0.94 (0.83-1.06)	0.92 (0.81-1.04)	1.02 (0.90-1.15)	0.8
Multivariate OR (95%CI)[a]	1.00	0.93 (0.82-1.05)	0.91 (0.81-1.03)	0.98 (0.87-1.11)	0.7
Citric fruits	≤1.2	>1.2-38.4	>38.4-73.3	>73.3	
Cases (n)	556	538	511	540	
Controls (n)	16375	16606	16745	16664	
Age-adjusted OR (95%CI)	1.00	0.96 (0.85-1.08)	0.90 (0.80-1.02)	0.95 (0.84-1.07)	0.3
Multivariate OR(95%CI) [a]	1.00	0.97 (0.86-1.10)	0.90 (0.80-1.02)	0.94 (0.83-1.06)	0.2
Fruits rich in betacarotene	≤2.6	>2.6-40.1	>40.1-72.1	>72.1	
Cases (n)	556	534	523	532	
Controls (n)	16373	16617	16848	16552	
Age-adjusted OR (95%CI)	1.00	0.95 (0.84-1.07)	0.91 (0.81-1.03)	0.94 (0.84-1.07)	0.3
Multivariate OR (95%CI)[a]	1.00	0.96 (0.85-1.08)	0.92 (0.81-1.04)	0.94 (0.83-1.06)	0.2
Apple	0	>0-16.2	>16.2-31.2	>31.2	
Cases (n)	572	560	498	515	
Controls (n)	16969	16305	16452	16664	
Age-adjusted OR (95%CI)	1.00	1.02 (0.91-1.15)	0.90 (0.80-1.02)	0.91 (0.81-1.03)	0.04

Multivariate OR (95%CI)[a]	1.00	1.04 (0.92-1.17)	0.90 (0.80-1.02)	0.90 (0.80-1.02)	0.03
Nuts and seeds	0	>0-2.9	>2.9-31.2	>31.2	
Cases (n)	631	507	461	546	
Controls (n)	18776	15891	15080	16643	
Age-adjusted OR (95%CI)	1.00	0.95 (0.85-1.07)	0.91 (0.81-1.03)	0.98 (0.87-1.11)	0.6
Multivariate OR (95%CI)[a]	1.00	0.95 (0.85-1.07)	0.90 (0.79-1.01)	0.93 (0.82-1.05)	0.16
Leafy vegetables	≤39.3	>39.3-62.9	>62.9-90.0	>90.0	
Cases (n)	572	542	516	515	
Controls (n)	16335	16694	16797	16564	
Age-adjusted OR (95%CI)	1.00	0.93 (0.82-1.05)	0.88 (0.78-0.99)	0.89 (0.79-1.00)	0.03
Multivariate OR (95%CI)[a]	1.00	0.91 (0.81-1.02)	0.85 (0.75-0.95)	0.82 (0.73-0.93)	0.0009
Fruity vegetables	≤24.9	>24.9-64.8	>64.8-101.6	>101.6	
Cases (n)	578	529	501	537	
Controls (n)	16316	16711	16747	16616	
Age-adjusted OR (95%CI)	1.00	0.89 (0.79-1.01)	0.85 (0.75-0.95)	0.91 (0.81-1.03)	0.08
Multivariate OR (95%CI)[a]	1.00	0.92 (0.81-1.04)	0.84 (0.74-0.95)	0.87 (0.77-0.99)	0.01
Tomatoes	≤6.4	>6.4-17.9	>17.9-28.2	>28.2	
Cases (n)	570	516	546	513	
Controls (n)	16357	16689	16719	16625	
Age-adjusted OR (95%CI)	1.00	0.90 (0.79-1.00)	0.94 (0.83-1.06)	0.89 (0.79-1.00)	0.11
Multivariate OR (95%CI)[a]	1.00	0.91 (0.80-1.02)	0.93 (0.83-1.05)	0.85 (0.75-0.96)	0.02
Root vegetables	≤8.6	>8.6-27.5	>27.5-44.6	>44.6	
Cases (n)	571	552	498	524	
Controls (n)	16331	16673	16757	16629	
Age-adjusted OR (95%CI)	1.00	0.95 (0.84-1.07)	0.85 (0.75-0.96)	0.90 (0.80-1.02)	0.03

Multivariate OR (95%CI)[a]	1.00	0.97 (0.86-1.09)	0.85 (0.75-0.96)	0.86 (0.77-0.98)	0.004
Carrots	≤3.8	>3.8-14.9	>14.9-24.9	>24.9	
Cases (n)	576	557	517	495	
Controls (n)	16313	16710	16698	16669	
Age-adjusted OR (95%CI)	1.00	0.95 (0.84-1.06)	0.88 (0.78-0.99)	0.84 (0.74-0.95)	0.002
Multivariate OR (95%CI)[a]	1.00	0.97 (0.86-1.09)	0.86 (0.78-0.99)	0.81 (0.72-0.92)	0.0003
Cabbage	≤1.3	>1.3-18.1	>18.1-34.8	>34.8	
Cases (n)	568	520	505	552	
Controls (n)	16358	16653	16705	16674	
Age-adjusted OR (95%CI)	1.00	0.90 (0.80-1.02)	0.87 (0.77-0.98)	0.95 (0.85-1.07)	0.3
Multivariate OR (95%CI)[a]	1.00	0.93 (0.82-1.05)	0.87 (0.77-0.98)	0.91 (0.81-1.03)	0.07

[a] adjusted for age, total caloric intake, BMI, physical activity, smoking status, menopausal status, and vitamin supplementation use

[+] Food groups: leafy vegetables (chicory, lettuce and spinach), fruity vegetables (artichoke, avocado, tomatoes, cucumber, green beans, eggplants, bell pepper, and zucchini), root vegetables (carrots, radish, beetroot, celeriac, and salsify), fruit (orange, grapefruit, mandarin, apple, pear, banana, kiwi, pineapple, strawberries or raspberries, cherry, peach, melon, apricot, raisins, plums, other fruits) and nuts and seeds.

Leafy vegetable intake was inversely related to asthma prevalence with a significant decreasing trend when intake was increased. Women in the highest quartile of leafy vegetable intake (>90.0 g/day) had a 22.0% lesser risk of reporting asthma than women in the lowest quartile (≤39.3 g/day) (OR= 0.82, 95% CI= 0.73-0.93, test for trend p=0.0009). Fruity vegetable intake was inversely associated with asthma (test for trend p=0.01); women in the highest quartile of tomato intake (>28.2 g/day) had a 17.6% lower risk of having asthma than women in the lowest quartile (≤6.4g/day) (OR_{Q1-Q4} = 0.85, 95% CI 0.75 -0.96, test for trend p=0.02). Increased intake of root vegetables was also inversely related to asthma prevalence (test for trend p=0.004). Women in the highest quartile of carrot intake (>24.9 g/day) had a 20.0% decrease in the risk of having asthma (OR_{Q1-Q4} = 0.81 95 % CI 0.72-0.92, test for trend p=0.0003) when compared to women with low carrot intake (<=3.8 g/day). No significant association was observed with cabbage intake. In multi-food models including leafy vegetables and tomatoes, or leafy vegetables and carrots and the potential confounding factors previously mentioned, results remained similar, suggesting that leafy vegetable, tomato and carrot intake may independently play a beneficial role on asthma prevalence.

Twenty six foods were studied: leafy vegetables, chicory, lettuce, spinach, fruity vegetables, artichoke, avocado, tomatoes, cucumber, green beans, eggplants, bell pepper, zucchini, root vegetables, carrots, radish, beetroot, celeriac, salsify, fruits, fruits with citrics, fruits with beta carotene, nuts and seeds and apples, blue fish, other fish. Therefore, Bonferroni correction was applied by multiplying by 26 the p value presented in the tables. Two out of the three main associations remained statistically significant. P values of 0.0009 (leafy vegetables), 0.02 (tomatoes) and 0.0003 (carrots) became respectively 0.02, 0.5 and 0.008.

We calculated the association between specific vegetable intake and asthma prevalence for non smokers, ex-smokers and current smokers because smokers are known to have a lower serum antioxidant levels[26] and higher antioxidant requirements[27] (Table 4). We observed that the beneficial effect of leafy vegetable, tomato and carrot intake was slightly stronger in women who reported smoking when compared to non smokers although the small number of asthma cases reporting smoking limited the power of our analysis (Table 4).

Table 4 Association of leafy vegetables, tomato and carrot with asthma prevalence in adulthood according to smoking status

Food groups or foods[+]	Quartile of intake (g/day)				P Test for trend
	Q1	Q2	Q3	Q4	
Leafy vegetables	≤39.3	>39.3-62.9	>62.9-90.0	>90.0	
Non smokers					
Cases (n)	342	324	312	313	
Controls (n)	10369	10693	10781	10249	
Age-adjusted OR (95%CI)	1.00	0.92 (0.79-1.07)	0.88 (0.75-1.03)	0.93 (0.79-1.08)	0.2
Multivariate OR (95%CI)[a]	1.00	0.90 (0.77-1.05)	0.85 (0.72-0.99)	0.86 (0.74-1.01)	0.04
Ex smokers					
Cases (n)	148	155	137	144	
Controls (n)	3409	3636	3715	3948	
Age-adjusted OR (95%CI)	1.00	0.98 (0.78-1.24)	0.85 (0.67-1.07)	0.83 (0.66-1.05)	0.06
Multivariate OR (95%CI)[a]	1.00	0.97 (0.77-1.22)	0.82 (0.65-1.05)	0.78 (0.61-0.99)	0.01
Current smokers					
Cases (n)	73	52	57	47	
Controls (n)	2246	2042	1977	2018	
Age-adjusted OR (95%CI)	1.00	0.78 (0.54-1.12)	0.89 (0.62-1.26)	0.72 (0.49-1.04)	0.13
Multivariate OR (95%CI)[a]	1.00	0.78 (0.54-1.11)	0.88 (0.62-1.25)	0.69 (0.47-1.00)	0.10
Tomatoes	≤6.4	>6.4-17.9	>17.9-28.2	>28.2	
Non smokers					
Cases (n)	327	322	336	306	
Controls (n)	10253	10752	10631	10456	
Age-adjusted OR (95%CI)	1.00	0.94 (0.80-1.10)	0.99 (0.85-1.16)	0.92 (0.78-1.07)	0.4
Multivariate OR (95%CI)[a]	1.00	0.96 (0.82-1.12)	0.98 (0.85-1.16)	0.88 (0.75-1.03)	0.17

Ex smokers					
Cases (n)	154	132	154	144	
Controls (n)	3540	3558	3798	3812	
Age-adjusted OR (95%CI)	1.00	0.86 (0.68-1.09)	0.94 (0.75-1.18)	0.88 (0.69-1.10)	0.4
Multivariate OR (95%CI)[a]	1.00	0.88 (0.69-1.11)	0.95 (0.75-1.19)	0.85 (0.67-1.07)	0.2
Current smokers					
Cases (n)	79	52	44	54	
Controls (n)	2232	2054	1982	2015	
Age-adjusted OR (95%CI)	1.00	0.72 (0.50-1.02)	0.63 (0.43-0.91)	0.75 (0.53-1.07)	0.07
Multivariate OR (95%CI)[a]	1.00	0.74 (0.52-1.06)	0.63 (0.43-0.92)	0.75 (0.52-1.07)	0.06
Carrots	≤3.8	>3.8-14.9	>14.9-24.9	>24.9	
Non smokers					
Cases (n)	337	334	315	305	
Controls (n)	10002	10467	10812	10811	
Age-adjusted OR (95%CI)	1.00	0.95 (0.81-1.10)	0.87 (0.74-1.01)	0.84 (0.72-0.98)	0.01
Multivariate OR (95%CI)[a]	1.00	0.97 (0.83-1.13)	0.87 (0.74-1.02)	0.81 (0.69-0.95)	0.004
Ex smokers					
Cases (n)	153	148	145	138	
Controls (n)	3606	3627	3717	3758	
Age-adjusted OR (95%CI)	1.00	0.97 (0.77-1.22)	0.92 (0.73-1.16)	0.86 (0.68-1.09)	0.18
Multivariate OR (95%CI)[a]	1.00	0.99 (0.79-1.25)	0.93 (0.73-1.17)	0.83 (0.66-1.06)	0.10
Current smokers					
Cases (n)	76	63	45	45	
Controls (n)	2360	2285	1863	1775	
Age-adjusted OR (95%CI)	1.00	0.85 (0.61-1.20)	0.75 (0.52-1.09)	0.78 (0.54-1.14)	0.13
Multivariate OR (95%CI)[a]	1.00	0.88 (0.63-1.24)	0.76 (0.52-1.11)	0.78 (0.53-1.14)	0.12

[a] adjusted for age, total caloric intake, BMI, physical activity, menopausal status and vitamin supplementation use
[+] Food groups: leafy vegetables (chicory, lettuce and spinach).

DISCUSSION

In this large population of women, we observed that asthma was less frequent in women with higher intake of leafy vegetables, tomatoes and carrots, and significant dose-responses were observed. The effect persisted after adjusting for potential confounding factors. After correction for multiple comparisons, the main result for leafy vegetables and carrots remained statistically significant. This suggests that intake of specific vegetables may play a beneficial role against asthma prevalence in our population.

The strengths of our study include our large number of prevalent cases of asthma, a wide variability in dietary intake,[28] and the use of a validated dietary questionnaire with a very detailed assessment. In addition this questionnaire has proven useful to evaluate the association of dietary intake and cancer.[29] Still, the cross-sectional nature of our analysis limits the interpretation of our results, given that women with asthma might have modified their dietary pattern toward a more "healthy diet" or have avoid some foods because of their symptoms. We do not have information on change of diet over time and therefore cannot assess this. However, it is unlikely that women with asthma symptoms will decrease their intake of tomatoes, carrots or leafy vegetable because of their symptoms given that these foods are not know to produce allergic reactions. In contrast, if women increased their intake of these vegetables, this would tend to underestimate the association; therefore our estimates are likely to be conservative. Correction for multiple comparisons using a conservative approach showed that the main result for leafy vegetables and carrots remained statistically significant.

Women who reported using dietary supplements (n=14,826) were on the average thinner, were more likely to report allergy, and ate significantly more fruits and vegetables than those who did not report using supplements. However, we did not observed a significant interaction between supplement use and the effect of fruit and vegetable intake on asthma. In addition, in a sub analysis including only women who did not report using dietary supplements, the results remained similar. We also evaluated the association of food intake and asthma prevalence stratified by time since the first asthma attack because responses to the dietary questionnaire may be influenced by the most recent food intake.[13] A similar association was observed for each time period suggesting that dietary pattern had been practically constant during adulthood, supporting a potential causal association (for example: for leafy vegetable intake with a 20-year delay since first attack $OR_{Q1\text{-}Q4} = 0.74$ (95% CI 0.61-0.90), test for trend p= 0.003).

Analyses were conducted in detail for vegetables and fruits in relation to hypotheses regarding protection by antioxidant,[1] and for fish in relation to hypotheses regarding anti-inflammatory aspects of omega 3.[1] We adjusted for total caloric intake and conducted two food models including in turn two of the following foods - leafy vegetable, tomato or carrot- but were not able to adjust for other dietary factors that might be relevant for asthma a part from fish for which we did not find significant association.[8] Therefore we cannot completely exclude the issue of confounding by other dietary factors. Although this is a limitation, if confounding is present, it should be from dietary factors that exert an even more powerful effect than vegetables. Additionally, the decreasing prevalence of asthma with increasing intake of leafy vegetables, and carrots provide further evidence for a causal association. We also considered other potential confounding factors, in particular BMI, menopausal status and smoking status. BMI has been related to the frequency of asthma in this [30] and other populations,[31] and a diet poor in fruits and vegetables is usually related to higher BMI. So lack of control for this variable might have biased the

association. Similarly, female reproductive hormone are thought to play a role on asthma,[21] [22] [23] although controversy exists, and should be accounted for. Ex-smokers had a higher frequency of asthma as compared to people who never smoked, which is coherent with other studies showing that as asthma developed, subjects stopped smoking.[32] Although, our models were adjusted for smoking, there is a possibility for residual confounding by this variable, given that smokers are in general more likely to have a diet poor in fruits and vegetables as observed in our study.

Our definition of asthma was based on one question regarding the occurrence of asthma attacks and the given date of the first attack. Because this information was not ascertained by a physician, we further validated responses with a more detailed questionnaire derived from the ATS questionnaire[14] and observed a high concordance. Although self reported asthma in older women may have included COPD, 61.4% of the cases reported never smoking and are therefore unlikely to have COPD. However given that we did not count with pulmonary functions, we cannot excluded the possibility of COPD in older women particularly in ex and current smokers. The attributable risk for asthma of atopy is a matter of debate[33] and asthma may occur without atopy, whereas COPD and allergy can occur together. However the high proportion of women with asthma who reported allergy (76%) represents an argument in favor of the diagnosis. In some cases, women may have had childhood asthma which because it remitted and relapsed in adulthood was being classified as adult asthma. These women are likely to report food intake in the same way as women with asthma starting in adulthood. Thus, reporting error, if any, would be random and lead to an underestimation of the association.

Hypothesized biologic mechanisms associated with the beneficial effect of vegetable intake on asthma include the effect of antioxidant vitamins[1] [8] such as carotenoids among others. Carrots and leafy vegetables are rich in carotenoids (α-carotene, β-carotene, lutein and zeaxanthin) which protect cells from oxidative stress.[34] [35] Tomato juice, carrot juice and spinach powder have been shown to increase plasma levels of cystolic glutathione transferase (GST-π), effect attributed to the up-regulation of GST activity by carotenoids.[36] Carotenoids are known to modulate immune function by enhancing lymphocyte proliferation and citotoxic T-cell activity and could modulate the production of PGE_2 by altering the activation of arachidonic acid cascade from which PGE2 is derived. In addition, folate, for which a major source is leafy vegetables, plays a role in DNA repair and is likely to potentiate the role of antioxidant enzyme.[36] Smokers are exposed to an extra burden of oxidative stress and have a significantly lower serum level of antioxidants.[26] It is expected that the protective effect of leafy vegetables and carrots should be larger among women reporting smoking. This is suggested by our data but the small sample size of women in this category limits the power of our analysis.

Our findings on the protective effect of vegetables with a high content of carotenoids are consistent with data from a prospective study of asthma onset among women.[7] Other studies have reported no association between carotenoid intake and asthma but most of the studies focused only on beta-carotene intake and did not assess the impact of other carotenoids.[1] [8] As reported in other studies, we did no observe a protective effect from citrus fruits;[4] [7] [9] [37] foods rich in vitamin C has been more consistently related to lung function than respiratory symptoms.[1] Caution is needed however when interpreting the results since an infrequent consumption of fruits and vegetables may be an indicator of a poor diet and unhealthy habits; therefore, we cannot totally exclude residual confounding by life style.

Fruits and vegetables contain thousands of biologically active phytochemicals, but food composition tables often lack this information and the content of specific nutrients may also be subject to error. Focusing on food intake might be more readily applicable for dietary recommendations and might also enhance our understanding of the relation between phytochemicals and asthma. Public health messages need to be simple and recommendations for food intake are easier to follow than recommended dietary intakes of specific nutrients. This has lead to the standard recommendation of 5 portions of fruits and vegetables a day.[10] The WHO has recommended a daily intake of at least 400g of fruits and vegetables a day but studies of median fruit and vegetable intake in ten European countries have shown that a considerable number of consumers failed to meet this target.[17] In our population 27% of the women had a fruit and vegetable intake under 400g/day; 65.3% had an intake under 200 g/day of leafy, fruity and roots vegetables and 93.4% had an intake under 200 g/day of leafy vegetables, tomatoes and carrots. For the implementation of public health policies, it is important to know which fruits and vegetables might be more likely to prevent specific diseases. Our results suggest that a higher intake of leafy vegetables, carrots and tomatoes may have a beneficial effect against prevalent adult asthma. Further studies are needed to confirm these results and consider the effect of fruit and vegetable intake on the severity of the disease.

Figure legend

Figure 1 Diagram for the study design

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Figure 1 Diagram for the study design

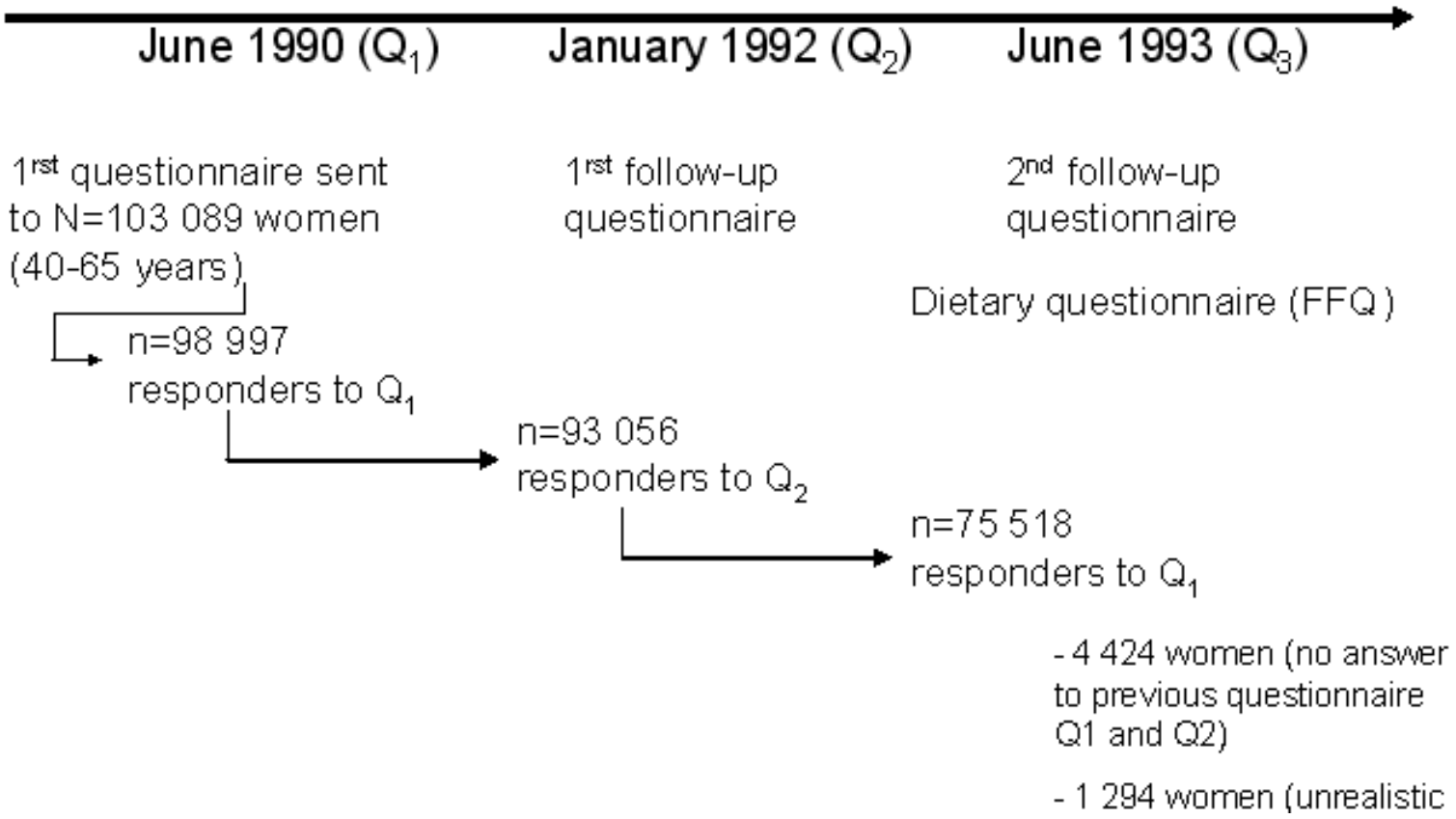

Figure 1