Consumption of fresh fruit rich in vitamin C and wheezing symptoms in children

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Abstract

***Background*—A beneficial effect of fresh fruit consumption on lung function has been observed in several studies. The epidemiological evidence of the effect on respiratory symptoms and asthma is limited. The consumption of fruit rich in vitamin C was examined in relation to wheezing and other respiratory symptoms in cross sectional and follow up studies of Italian children.**

***Methods*—Standardised respiratory questionnaires were filled in by parents of 18 737 children aged 6–7 years living in eight areas of Northern and Central Italy. The winter intake of citrus fruit and kiwi fruit by the children was categorised as less than once per week, 1–2 per week, 3–4 per week, and 5–7 per week. A subset of 4104 children from two areas was reinvestigated after one year using a second parental questionnaire to record the occurrence of wheezing symptoms over the intervening period.**

***Results*—In the cross sectional analysis, after controlling for several confounders (sex, study area, paternal education, household density, maternal smoking, paternal smoking, dampness or mould in the child's bedroom, parental asthma), intake of citrus fruit or kiwi fruit was a highly significant protective factor for wheeze in the last 12 months (odds ratio (OR) = 0.66, 95% confidence intervals (CI) 0.55 to 0.78, for those eating fruit 5–7 times per week compared with less than once per week), shortness of breath with wheeze (OR = 0.68, 95% CI 0.56 to 0.84), severe wheeze (OR = 0.59, 95% CI 0.40 to 0.85), nocturnal cough (OR = 0.73, 95% CI 0.65 to 0.83), chronic cough (OR = 0.75, 95% CI 0.65 to 0.88), and non-coryzal rhinitis (OR = 0.72, 95% CI 0.63 to 0.83). In the follow up study fruit intake recorded at baseline was a strong and independent predictor of all symptoms investigated except non-coryzal rhinitis. In most cases the protective effect was evident even among children whose intake of fruit was only 1–2 times per week and no clear dose-response relationship was found. The effect was stronger (although not significantly so (p = 0.13)) in subjects with a history of asthma; those eating fresh fruit at least once a week experienced a lower one year occurrence of wheeze (29.3%) than those eating fruit less than once per week (47.1%) (OR = 0.46, 95% CI 0.27 to 0.81).**

***Conclusions*—Although the effect of other dietary components cannot be excluded, it is concluded that the consumption of fruit rich in vitamin C, even at a low level of intake, may reduce wheezing symptoms in childhood, especially among already susceptible individuals.**

(*Thorax* 2000;**55**:283–288)

Keywords: fruit; vitamin C; lung function; wheezing; children

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Received 3 September 1999
Returned to authors 15 October 1999
Revised manuscript received 5 January 2000
Accepted for publication 12 January 2000

There is an increasing body of data which suggests that low consumption of fresh fruit containing vitamin C is associated with decreased lung function both in children and adults.[1–4] A recent cross sectional study among children in 10 English and Welsh areas found an association between fresh fruit consumption and level of forced expiratory volume in one second (FEV_1); the association was stronger among wheezers than among non-wheezers.[4] A longitudinal study on British adults has suggested that the cross sectional effects of fresh fruit consumption on ventilatory function might be reversible.[5] On the other hand, the epidemiological evidence on the role of dietary vitamins in asthma is controversial and limited to adults.[6–9] It has been postulated that dietary antioxidants, particularly vitamin C, may protect from inflammation resulting from both endogenous and exogenous oxidation.[10] There are hints that asthmatic subjects have low plasma and leucocyte concentrations of vitamin C.[11–12]

To test the hypothesis that intake of fruit rich in vitamin C prevents the occurrence of asthmatic symptoms in children, we examined data collected in a large cross sectional study of Italian children as well as in a follow up study performed in a subgroup of the same study.

Methods

A large multicentre survey was conducted in Italy (SIDRIA, Italian Studies on Respiratory Disorders in Children and the Environment) between October 1994 and March 1995 within the International Study on Asthma and Allergies in Childhood (ISAAC) initiative,[13] to estimate the prevalence of respiratory problems in children and to investigate the role of several potential risk factors on wheeze and asthma. The study was conducted in children aged 6–7 years attending first or second grade in eight

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centres of Northern and Central Italy, encompassing a wide range of geographical areas, urbanisation levels, and socioeconomic conditions; a detailed description of the methods of the study has been reported elsewhere.[14–16] Each randomly chosen school was contacted and followed by one or more trained healthcare workers. The parents' questionnaire was given to the child who took it home for their parents to complete.

The project used the ISAAC questionnaire[13] and included additional questions on respiratory symptoms (shortness of breath with wheezing, chronic cough apart from common colds)[17] and on a number of known or suspected risk factors for childhood asthma and other respiratory and allergic diseases. Data on paternal education, household crowding, maternal and paternal smoking, presence of dampness and/or mould in the child's bedroom, and maternal and paternal asthma were collected. Two specific dietary habits of the child were also investigated because of previous suggestions that they might be associated with respiratory symptoms: table salt use[18] and citrus fruit consumption.[6] The parents were asked whether the child had the habit of adding salt to foods before or after tasting. The winter intake of fruits rich in vitamin C was assessed from answers to the question "In winter how often does your child eat citrus fruit (oranges, tangerines, grapefruit) or kiwi or drink fresh squeezed citrus fruit juice?" using a four level scale: less than once a week, 1–2 times per week, 3–4 times per week, 5–7 times per week. In the Italian diet citrus fruit (consumed largely in winter) is the most important source of vitamin C.[19] Kiwi fruit was included in the item because of its high vitamin C content and its widespread consumption in recent years. The questionnaires were completed at home by parents of 18 737 children (response rate 96.3%).

A follow up study was conducted one year after the first investigation in two of the participating centres (the metropolitan area of Rome and the mixed urban/rural area of Viterbo about 80 km from Rome). A new questionnaire was sent to the parents of 5257 previously enrolled children (4027 from Rome and 1230 from Viterbo) to record information on respiratory symptoms over the previous 12 months. In addition to the same questions on respiratory symptoms, occurrence of toothache in the past 12 months (a symptom not expected to be related to dietary vitamins) was added as a reference question in order to assess potential reporting bias. The response rate at follow up was 78.1% for a total of 4104 children. The response rate was higher in the Viterbo area (85.9%) than in Rome (75.7%) but it did not vary by sex, rate of parental asthma, father's education, or citrus/kiwi fruit consumption.

It was decided a priori that the occurrence of any wheeze in the past 12 months[13] or the occurrence of attacks of shortness of breath with wheezing in the past 12 months[17] were the outcome variables to be evaluated in relation to citrus fruit consumption. After positive findings emerged for those items, the following additional respiratory symptoms were also investigated: exercise related wheeze, severe wheeze (more than 12 attacks per week, kept awake one or more night per week, or speech limiting wheeze), nocturnal cough, rhinitis ("sneezing or a runny or blocked nose") apart from colds (non-coryzal rhinitis),[13] and chronic cough apart from colds.[17] Symptomatic children were always compared with all others in the sample.

Logistic regression was performed to analyse the association between citrus fruit/kiwi consumption (in four levels using less than once per week as the reference) and the outcome variables after adjusting for the following potential confounders: sex, study area, paternal education, household crowding, maternal smoking, paternal smoking, dampness or mould in the child's bedroom, parental asthma. Odds ratios (OR) and 95% confidence intervals (95% CI) were computed to estimate the degree of association in both the cross sectional and the follow up studies. In a further analysis citrus fruit/kiwi consumption was included as an ordinal (0, 1, 2, 3) variable to test for trend (Wald test). To assess a departure from linear trend we performed a likelihood ratio test evaluating the change in the model fit when the categorised variable (a four level factor) was replaced by the ordinal (linear trend) variable. Possible effect modification by sex, area of residence, father's education, parental smoking, parental asthma, and a lifetime history of asthma at baseline ("Has your child ever had asthma?") of the relationship between citrus fruit/kiwi intake and wheeze in the past 12 months was evaluated by introducing interaction terms into the regression models, with fruit intake dichotomised as less than once a week versus once a week or more. In the regression analysis no adjustment to standard errors for cluster sampling was needed since (1) autocorrelation within schools appeared to be negligible and (2) adjusted (using generalised estimating equations[20]) and non-adjusted standard errors were practically identical. All analyses were performed using STATA software.[21]

Results

The descriptive characteristics of the children studied in the cross sectional survey and in the follow up study by citrus/kiwi fruit consumption are presented in table 1. In the cross sectional study low citrus/kiwi fruit consumption (less than once a week) was associated with male sex (15.7% in males, 13.1% in females), rural area (16.5% in rural/urban areas, 13.0% in metropolitan areas), low paternal educational level (17.5% for elementary school, 10.1% for university degree), and maternal smoking (15.8% for current smokers, 13.5% for never smokers). The associations were similar in subjects participating in the follow up study.

In the cross sectional survey the occurrence of any wheeze and of shortness of breath with wheeze in the past 12 months was 7.6%, and 5.1%, respectively. Prevalence of any wheeze was 9.9%, 7.4%, 7.5%, and 6.6% for less than

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Table 1 Descriptive characteristics (%) of the children participating in the cross sectional study and in the follow up study by citrus/kiwi fruit consumption (Italy, 1995–1996)

	Cross sectional study					*Follow up study*				
Variable	*<1/week (2706)*	*1–2/week (4537)*	*3–4/week (6485)*	*5–7/week (4707)*	*Total (n=18 737)*	*<1/week (530)*	*1–2/week (982)*	*3–4/week (1469)*	*5–7/week (1040)*	*Total (n=4104)*
Male sex	56.1	51.0	49.7	52.1	51.6	52.3	49.7	50.8	52.7	51.2
Area of residence										
Metropolitan	43.6	47.5	48.5	52.0	48.4	72.8	71.4	72.9	79.4	74.2
Urban	19.1	19.1	19.5	18.3	19.1	—	—	—	—	—
Rural/urban	37.2	33.4	32.0	29.7	32.5	27.2	28.6	27.1	20.6	25.8
Father's education										
Primary school	14.9	13.3	11.5	10.3	12.2	13.0	10.3	9.5	8.9	10.0
Middle school	41.2	40.1	38.7	34.1	38.2	37.7	39.0	38.1	31.5	36.7
High school	31.0	31.4	32.9	33.5	32.2	36.8	35.4	36.0	36.4	35.8
University	10.0	12.5	13.8	19.5	14.3	9.8	12.9	14.0	20.5	14.7
Maternal smoking										
Never	42.2	44.5	45.4	46.4	44.9	37.7	44.6	41.7	43.6	42.4
Ex-smoker	18.3	18.4	19.1	19.4	18.8	16.0	17.1	18.5	18.7	17.8
Current smoker	36.9	34.4	33.1	31.9	33.6	43.8	35.1	36.7	34.9	36.7
Paternal smoking										
Never	28.0	28.1	28.6	30.1	28.7	25.1	28.7	27.2	27.9	27.5
Ex-smoker	22.4	23.0	23.8	24.1	23.3	21.3	24.1	22.3	22.8	22.7
Current smoker	45.5	45.2	43.7	42.4	44.0	50.8	44.1	46.1	45.8	46.0
Dampness or mould in the bedroom	8.1	7.8	6.3	6.3	6.9	5.1	4.3	4.4	4.3	4.5
Parental asthma	15.4	13.5	14.9	15.2	14.7	18.03	15.04	17.02	17.00	16.08
Child ever had asthma	10.6	8.2	8.3	8.4	8.6	12.8	9.3	9.7	10.5	10.2
Child uses extra table salt	5.3	4.3	3.9	4.5	4.3	2.6	2.1	1.8	2.8	2.3

The totals in the individual columns do not add up to the final totals because of missing values.

once a week, 1–2 times per week, 3–4 times per week, and 5–7 times per week, respectively (taking less than once a week as the reference, the crude odds ratios were 0.72, 0.73, and 0.64). For the same categories the prevalence of shortness of breath with wheeze was 6.8%, 4.8%, 5.1%, and 4.6%, respectively (crude odds ratios 0.69, 0.71, and 0.66). After controlling for potential confounders, regular citrus/kiwi fruit consumption was a highly significant protective factor for both outcomes (table 2). There were only minimal differences between adjusted and unadjusted odds ratios. Although the test for trend was significant for all comparisons, the protective effect of fresh fruit consumption was already evident among those in the 1–2 times per week category and no clear dose-response relationship was found. In fact, the likelihood test to assess departure from linearity was significant ($p<0.01$). All the other symptoms investigated, except for exercise related wheeze, were significantly associated with citrus/kiwi fruit consumption (table 2), with a stronger effect for severe wheeze. The results were practically unchanged when adjustment was made for table salt use (table salt use had a borderline association only with shortness of breath with wheeze, OR = 1.29, 95% CI 0.96 to 1.73).

In the follow up study the occurrence of any wheeze and of shortness of breath with wheeze in the 12 months preceding the second survey were 5.7% and 3.7%, respectively. Low fruit intake recorded at baseline was a strong and independent predictor of these two variables: the crude odds ratios were 0.45, 0.58, and 0.50 for any wheeze and 0.31, 0.41, and 0.36 for shortness of breath with wheeze. The adjusted odds ratios were practically similar and did not indicate a clear dose-response relationship among the three higher levels of intake, thus confirming the findings of the first survey (table 3). All the other symptoms investigated occurred less frequently among those eating citrus or kiwi fruit at least once a week, and statistical significance was achieved for exercise related wheeze, nocturnal cough, and severe wheeze. By contrast, no association was found between fruit intake and the reference question relative to the occurrence of toothache (re-

Table 2 Association (odds ratio (OR) and 95% confidence intervals (95% CI)) between frequency of winter consumption of citrus/kiwi fruit (per week) and 12 month prevalence (%) of respiratory symptoms in the cross sectional study

	<1/week		*1–2/week*		*3–4/week*		*5–7/week*		
	%	*OR*	*%*	*OR (95% CI)*	*%*	*OR (95% CI)*	*%*	*OR (95% CI)*	*p for trend*
Wheeze	9.9	1.0	7.4	0.75 (0.63 to 0.89)	7.5	0.76 (0.65 to 0.89)	6.6	0.66 (0.55 to 0.78)	<0.001
Shortness of breath with wheeze	6.8	1.0	4.8	0.73 (0.60 to 0.90)	5.1	0.75 (0.62 to 0.91)	4.6	0.68 (0.56 to 0.84)	0.002
Exercise related wheeze	2.3	1.0	1.5	0.69 (0.49 to 0.98)	1.5	0.69 (0.50 to 0.95)	1.7	0.74 (0.53 to 1.04)	0.160
Severe wheeze	2.2	1.0	1.6	0.76 (0.53 to 1.08)	1.3	0.64 (0.46 to 0.90)	1.2	0.59 (0.40 to 0.85)	0.003
Nocturnal cough	21.3	1.0	18.4	0.85 (0.75 to 0.96)	17.9	0.83 (0.74 to 0.93)	16.1	0.73 (0.65 to 0.83)	<0.001
Chronic cough	12.1	1.0	10.0	0.83 (0.71 to 0.96)	11.4	0.95 (0.82 to 1.09)	9.3	0.75 (0.65 to 0.88)	0.008
Rhinitis	16.3	1.0	14.0	0.85 (0.74 to 0.96)	13.2	0.79 (0.70 to 0.90)	12.3	0.72 (0.63 to 0.83)	<0.001

Odds ratios adjusted for sex, study area, father's education, household density, maternal smoking, paternal smoking, dampness or mould, and parental asthma.

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Table 3 Association (odds ratio (OR) and 95% confidence intervals (95% CI)) between frequency of winter consumption of citrus/kiwi fruit (per week) and 12 month occurrence (%) of respiratory symptoms in the follow up study

	<1/week		1–2/week		3–4/week		5–7/week		
	%	OR	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	p for trend
Wheeze	9.4	1.0	4.5	0.48 (0.31 to 0.73)	5.7	0.61 (0.42 to 0.89)	5.0	0.54 (0.36 to 0.82)	0.040
Shortness of breath with wheeze	8.1	1.0	2.7	0.33 (0.20 to 0.55)	3.5	0.43 (0.28 to 0.66)	2.9	0.37 (0.22 to 0.60)	0.001
Exercise related wheeze	3.6	1.0	1.2	0.35 (0.17 to 0.73)	1.6	0.43 (0.22 to 0.80)	1.1	0.29 (0.13 to 0.62)	0.005
Severe wheeze	2.5	1.0	0.7	0.31 (0.12 to 0.78)	0.8	0.36 (0.16 to 0.81)	0.8	0.33 (0.13 to 0.82)	0.339
Nocturnal cough	20.2	1.0	12.9	0.60 (0.45 to 0.81)	15.5	0.74 (0.57 to 0.97)	11.4	0.54 (0.40 to 0.71)	0.002
Chronic cough	13.9	1.0	9.7	0.7 (0.50 to 0.96)	10.4	0.75 (0.55 to 1.01)	9.9	0.72 (0.52 to 1.0)	0.159
Rhinitis	13.8	1.0	12.7	0.95 (0.70 to 1.3)	12.4	0.91 (0.68 to 1.22)	11.6	0.85 (0.62 to 1.16)	0.28
Toothache	9.1	1.0	12.0	1.32 (0.92 to 1.90)	11.0	1.33 (0.94 to 1.87)	9.0	1.1 (0.76 to 1.60)	0.897

Odds ratios adjusted for sex, study area, father's education, household density, maternal and paternal smoking, dampness or mould, parental asthma.

Table 4 Association (odds ratio (OR) and 95% confidence intervals (95% CI)) between frequency of winter consumption of citrus/kiwi fruit (at least once a week versus less than once a week) with wheeze (past 12 months)

	Cross sectional study				Follow up study			
	<1/week		⩾1–2/week		<1/week		⩾1–2/week	
	%	OR	%	OR (95% CI)	%	OR	%	OR (95% CI)
All	10.1	1.0	7.2	0.73 (0.63 to 0.83)	9.4	1.0	5.2	0.55 (0.40 to 0.77)
Sex								
Male	11.4	1.0	8.5	0.74 (0.62 to 0.89)	11.6	1.0	6.2	0.54 (0.36 to 0.84)
Female	8.1	1.0	5.8	0.70 (0.56 to 0.89)	7.1	1.0	4.1	0.53 (0.31 to 0.94)
Parental asthma								
No	8.0	1.0	5.9	0.75 (0.63 to 0.89)	7.4	1.0	3.9	0.53 (0.35 to 0.80)
Yes	19.7	1.0	14.7	0.72 (0.55 to 0.96)	18.6	1.0	10.8	0.53 (0.29 to 0.96)
Personal history of asthma								
No	4.7	1.0	3.9	0.86 (0.69 to 1.06)	3.9	1.0	2.5	0.67 (0.40 to 1.14)
Yes	52.1	1.0	41.9	0.62 (0.48 to 0.82)	47.1	1.0	29.3	0.46 (0.27 to 0.81)

Odds ratios adjusted for sex, study area, father's education, household density, maternal and paternal smoking, dampness or mould, and parental asthma.

ported in 10.3% of the subjects). Table salt use was not associated with wheezing symptoms in the follow up evaluation and the results were practically unchanged when adjustment was made for this factor (not shown).

In both the cross sectional and the follow up study the interaction terms related to sex, area of residence, father's education, parental smoking, parental asthma, and a lifetime history of asthma at baseline of the relationship between fruit intake and wheeze were far from significant (p>0.50), although relatively small p values were found for previous history of asthma (p = 0.13 and p = 0.19, respectively, in the cross sectional and follow up studies). When the cross sectional analysis was performed separately in children with or without a previous history of asthma, the protective effect of citrus fruit consumption on the crude prevalence of wheeze in the past 12 months was stronger in asthmatic than in non-asthmatic children: 52.1% of asthmatic children who ate fruit less than once per week had any wheeze and 41.9% of the others (OR = 0.62, 95% CI 0.48 to 0.82) compared with 4.7% and 3.9% for non-asthmatic children (OR = 0.86, 95% CI 0.69 to 1.06). Similarly, in the follow up study, wheezing occurred in 47% of asthmatic children with low fruit consumption and in 29.2% of those who ate fruit at least once a week (OR = 0.46, 95% CI 0.27 to 0.80). In non-asthmatic children wheeze occurred in 3.9% and 2.5%, respectively (OR = 0.67, 95% CI 0.40 to 1.14; table 4).

There was a limited power to fully exploit the longitudinal component of the study—that is, to evaluate the occurrence of new symptoms in negative subjects at the baseline. Among 3612 children with no wheeze at the baseline, only for 91 subjects (2.5%) did the parents report wheeze during the 12 months of follow up. However, an association was found between eating fruit at least once a week and the incidence of wheeze (3.4% in 436 children eating fruit less than once per week and 2.4% in the others, OR = 0.69, 95% CI 0.39 to 1.21), which is consistent with the overall findings.

Discussion

Our data show a clear association between a low intake of oranges and other vitamin C containing fruits during winter and an increased risk of wheezing symptoms in children. The finding was confirmed in both the cross sectional and follow up studies. The protective effect does not appear to be dose related. A previous study had suggested a similar relationship,[3] but it did not have the statistical power allowed by the large sample examined here: Cook *et al*[3] reported relative risks by fresh fruit consumption of a similar order to those reported here, although the number of subjects in their reference category was very small. Our data suggest, in particular, that consumption of citrus fruit prevents recurrence of symptoms in

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subjects with a previous history of asthma. These findings confirm previous evidence in adults that low dietary vitamin C is associated with increased symptoms of bronchitis and wheezing,[6] and indications that the association between low consumption of fresh fruit and FEV_1 decrement is stronger in already susceptible patients with asthma or bronchitis.[1 3]

The biological plausibility of a protective role of vitamin C in asthma has been extensively reviewed.[1 10] Reactive oxygen species, released from eosinophils, alveolar macrophages, and neutrophils, seem to play a key role in asthma. They may directly contract airways smooth muscle, stimulate histamine release from mast cells and mucus secretion,[10] and interact with α_1-protease inhibitor.[22 23] Hatch has suggested that vitamin C is the major antioxidant present in the airway surface liquid of the lung, and it may protect against endogenous oxidants as well as against exogenous agents such as cigarette smoke and environmental air pollutants.[10] Asthma is associated with an oxidant-antioxidant imbalance and patients with asthma have low plasma concentrations of vitamin C and increased oxidative stress.[24 25] So far, however, experimental studies conducted in asthmatic subjects have yielded conflicting results regarding the effect of vitamin C supplementation on lung function and bronchial responsiveness.[26 27]

Most of the exacerbations of asthma in children have been associated with upper respiratory viral infections, especially rhinovirus.[28] Although the ability of vitamin C supplementation to reduce the incidence of common colds is controversial, there are suggestions that vitamin C supplementation may affect the susceptibility to common cold in subjects with a low intake of vitamin C.[29] Moreover, vitamin C reduces the duration of episodes and the severity of symptoms of the common cold.[30] In a longitudinal study of adults, biological markers of infection (C reactive protein and α_1-antichymotrypsin concentrations) have been found to be inversely related to serum ascorbate concentration, an indicator of low dietary intake.[31] It may be postulated that, in asthmatic subjects, vitamin C modulates the biological response to viral infections. However, given the observed link between a low intake of foods containing vitamin C and a low ventilatory function,[3] and that children with lower pulmonary function levels are more likely to wheeze than children with higher levels, we cannot exclude the hypothesis that the association that we have found reflects the occurrence of symptoms in children with lower lung function on average.

We found that the protective effect of citrus fruit consumption did not follow a dose-response relationship. Instead, a positive effect was already evident among children eating fruit at least once a week. It might therefore be possible that wheezing symptoms are more likely to appear only below a threshold of vitamin C intake. There are few studies on the association between vitamin C and asthma symptoms, and there are suggestions that the relationship may be non-linear. Schwartz and Weiss first reported in 1990 an inverse association between bronchitis and wheezing and both dietary and plasma vitamin C levels in a representative sample of the adult population in the USA.[6] They found that the relation was more or less linear on a logistic scale—that is, exponential on a linear scale. Troisi *et al*[7] found no association between dietary vitamin C intake and the incidence of asthma over a 10 year period in the longitudinal Nurses' Health Study. However, they noted that the adult female population under study had a greater than average mean vitamin C consumption, few having a low intake. In a case-control study of adults in Scotland Soutar *et al*[8] reported a fivefold increased risk of bronchial hyperreactivity for the lowest tertile of vitamin C intake compared with the highest tertile, but no association was found for the intermediate level of vitamin C intake. Finally, Cook and colleagues[3] found an extremely high prevalence of wheeze in children who never ate fresh fruit in a cross sectional sample of 2650 children in the UK, but they failed to find a dose-response relationship between wheezing and fresh fruit consumption. Fresh fruit consumption had a beneficial effect on lung function, especially among wheezers.

Information bias is a possible problem in this study since we used parental questionnaires to assess both the exposure and the outcomes. However, questionnaire data on dietary items recorded by the parents are generally considered to be reliable, especially regarding vitamin C intake.[32] The possibility that parents may have under-reported fruit consumption because their children were symptomatic is unlikely because (1) the news regarding the possible protective effect of vitamin C on lung health had not been reported in the media at the time of the study; (2) the questionnaire covered a number of other environmental exposures in addition to the dietary items; (3) the cross sectional association was confirmed longitudinally in the follow up study; and (4) no association was found for the reference symptom (toothache) used to evaluate reporting bias in this study.

These analyses were designed specifically to focus on vitamin C, and we tend to interpret our findings as being due to this nutrient. Caution is needed, however, when interpreting the results. An infrequent consumption of fresh fruit may be an indicator of a poor diet, which may lack several other factors (including other vitamins such as A and E) that may also have a protective effect on respiratory health. Vitamin E has been associated with a protective effect against the onset of asthma[7] and current wheeze in adults.[9] Intakes of vitamins C and E are usually correlated,[4] and both are likely to play a synergistic role in the antioxidant defence mechanism.[9] Low magnesium intake from a diet based on processed foods has been associated with increased wheezing symptoms, bronchial hyperreactivity, and decreased lung function in adults.[33] It has been suggested that omega-3-fatty acids, contained in fish oil, may protect children from asthma.[34] Olive oil, an important component of the Italian diet which

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is rich in vitamin E and other antioxidants, could also have a protective effect.[34 35] We were able to control only for table salt use, which turned out to be a marginal risk factor. We cannot therefore completely address the issue of confounding from other dietary factors in the present investigation. Although this is a clear limitation, it should be considered that, if confounding is present in this study, it should be from a dietary factor that exerts an even more powerful effect than fruits rich in vitamin C. Finally, a possibility of residual confounding from socioeconomic status should be mentioned since we controlled only for father's education. However, this possibility is unlikely since the protective effect of citrus/kiwi fruit consumption on wheezing symptoms in this study was found even in the lowest category of father's education, even if maternal education was controlled for (data not shown). Moreover, despite the fact that we controlled for several potential confounders, crude and adjusted odds ratios were very similar.

The novel aspects of this study compared with other related published papers should be underlined. The large sample of young children enabled us to find an association which has been previously suggested but never detected. After controlling for several potential confounders, our results suggest that the relation between vitamin C intake and respiratory symptoms may be non-linear and that a history of asthma exerts an effect modification. In the prospective study the explanatory variables were recorded at the start of the period, reducing the possibility of reporting bias and allowing for temporality.

In conclusion, low intake of fruit rich in vitamin C is associated with an increased frequency of wheezing symptoms in children, especially among already susceptible individuals. These findings may have important scientific and public health implications.

The SIDRIA Collaborative Group is grateful to all the schoolchildren and to their parents for participation and to the teachers for helpful collaboration. Special thanks to all the physicians and staff members of the local health units of the National Health Service for their precious work in the collection of data. The authors also thank Dr Susan Levenstein for revision of the text and for helpful comments, and Patrizia Compagucci for editorial help. The study has received funds from the Italian regional health authorities and from the AIRC.

The members of the SIDRIA Collaborative Group (Italian Studies on Respiratory Disorders in Children and the Environment; Studi Italiani sui Disturbi Respiratori nell' Infanzia e l'Ambiente) are the following: G Ciccone, A Camerlengo, M Bugiani, P Dalmasso, F Faggiano, T Fatur Volante, C Magnani, P Natale, P Piccioni (Turin), L Bisanti, V Gianelle, F Rusconi, S Sideri (Milan), S Piffer, F Filippetti, E Nava (Trento), C Galassi, M Biocca, E Canossa, B Cavalchi, D Cervino, S Cattani, E De'Munari, M Deserti, S Ferro, F Fortezza, F Frigo, M Martini, P Mazzali, L Paterlini, R Sogni, M Zanini (Emilia Romagna) E Chellini, L Agati, E Barletta, A Biggeri, G Bini, M Bini, L Chetoni, D Grechi, A Seniori Costantini (Florence), E Renzoni, P Sestini (Siena), G Viegi (Pisa), F Forastiere, N Agabiti, G Corbo, V Dell'Orco, S Mallone, C Micera, P Palermo, G Pallotti, G Piras, R Pistelli (Rome), E Salera (Frosinone), D Argentini, G Chiarucci (Latina)

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