Interaction of vitamin C with the relation between smoking and obstructive airways disease in EPIC Norfolk

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ABSTRACT: Previous studies have reported an association between plasma vitamin C levels and respiratory function, but have not examined the role of vitamin C as an effect modifier of the relation between cigarette smoking and obstructive airways disease (OAD).

This question was investigated in a cross-sectional analysis of a population-based study of 3,714 males and 4,256 females aged 45–74 yrs. Undiagnosed OAD was defined as a forced expiratory volume in one second (FEV₁) of <80% of the predicted value and FEV₁/forced vital capacity of <70% without self-reported OAD.

An increase of 20 µmol·L⁻¹ (or 1 SD) in plasma vitamin C concentration was associated with a 13% reduction in the risk of having OAD (adjusted odds ratio (OR) (95% confidence interval) 0.87 (0.77–0.98)). The OR for current smokers relative to never smokers within the lowest quintile of plasma vitamin C concentration was 5.93 (3.03–11.61). The risk in the upper four quintiles was 2.84 (1.92–4.19). Within the lowest quintile of plasma vitamin C concentration, the risk in former smokers was strongly related to the time since quitting (interaction significant, $p=0.001$).

These findings support a protective role for vitamin C against the risk of obstructive airways disease and support the hypothesis that vitamin C may be an effect modifier for the adverse effects of smoking on the risk of obstructive airways disease.

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Obstructive airways disease (OAD) refers to a group of conditions characterized by limitation of expiratory airflow and for which cigarette smoking is the principal risk factor [1, 2]. Several studies support a beneficial effect for vitamin C on lung function [3–8], particularly when the outcome is defined in terms of objective assessment of respiratory function as opposed to respiratory symptoms or clinical diagnoses of OAD [8–12].

Most studies have examined vitamin C intake, assessed mainly by food frequency questionnaires or 24-h recall [9]. Smokers have a lower dietary intake of vitamin C than nonsmokers, but their requirements are higher [13, 14]. Dietary vitamin C may not reflect true vitamin C status in smokers. Plasma vitamin C may therefore be a more accurate measure of vitamin C in studies of OAD aetiology given the importance of smoking as a risk factor.

Vitamin C exhibits a positive relationship with lung function that is independent of the effect of smoking [3–9]. However, it is likely that the protective effect of vitamin C on lung function may be partly due to amelioration of the oxidative stress induced by cigarette smoking [15, 16]. Adjustment for plasma vitamin C concentration as a confounder of the relationship between lung function and smoking may, therefore, underestimate the importance of vitamin C. Stratification by plasma vitamin C levels may allow detection of effect modification by vitamin C of the adverse effects of cigarette smoking. Few studies have shown adequate power after stratification for the detec-

tion of a statistically significant interaction between cigarette smoking and vitamin C as regards OAD risk [9].

It was examined whether enhanced plasma vitamin C status reduced the risk of undiagnosed OAD based on the criteria of the British Thoracic Society [17], and whether it modified the effect of different smoking exposures on the risk of OAD in a large population-based cross-sectional study.

Methods

Subjects and measurements

Individuals for this analysis were recruited between 1993–1996 as part of the East Anglian (UK) component of the European Prospective Investigation into Cancer and Nutrition (EPIC-Norfolk). The study group forms part of a multicentre international cohort designed to investigate the relationship between diet, cancer and chronic disease. The detailed design and operation of the study have been described previously [18, 19].

At baseline survey between 1993–1998, in the EPIC-Norfolk, males and females aged 45–74 yrs were identified from participating general practice patient lists and invited to participate in the study. Those who volunteered completed a detailed health and lifestyle questionnaire and a semiquantitative food frequency questionnaire (FFQ).

Postal codes were used to classify subjects as urban or rural dwellers. Postcodes correspond closely to city and town limits in the county of Norfolk, UK, where urban centres and rural areas are clearly demarcated. Social class was coded according to the Registrar General's 1991 classification [20]. Self-reported OAD and asthma were identified by positive responses to the bronchitis/emphysema and asthma options of the question "Has the doctor ever told you that you have any of the following?"

Smoking history was derived from yes/no responses to the questions "Have you ever smoked as much as one cigarette a day for as long as a year?" and "Do you smoke cigarettes now?". Subjects were asked to record the age at which they had started to smoke and, for those who had stopped smoking, the age at which they gave up. The number of cigarettes smoked at ages 20, 30, 40 and 50 yrs and at the time of the study were also recorded. Cumulative cigarette consumption (in pack-yrs) was calculated from these data, assuming that the smoking patterns indicated at each age applied to that decade of life. One pack-year was defined as 20 cigarettes·day⁻¹ for 1 yr.

Dietary intake of vitamin C and vitamin E were derived from FFQ data. Subjects were asked to record their average diet over the past year by means of a list of food items and frequency categories. Nutrient intakes were calculated by multiplying the frequency of food consumption by standard portion weights to obtain the amount of food consumed per day; these were then converted into nutrient intakes using food tables [21].

Following completion of the questionnaire, subjects were invited to attend their general practice surgery, where research nurses performed a health check. Height and weight were measured with subjects in light clothing and with shoes removed. Height was measured to the nearest 0.1 cm using a stadiometer. Weight was measured to the nearest 100 g using Salter scales (Salter Industrial Measurement Ltd., West Bromwich, UK).

Forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were measured with an electronic turbine spirometer (Micro Medical Instruments, Rochester, UK). Two measurements were made with the subjects standing and looking forwards. The nurses made a subjective judgement of the subjects' spirometry technique and recorded it as good or poor. The higher of the two values for FEV₁ and FVC were used for analysis.

Volunteers had blood taken after the health check. The nonfasting plasma vitamin C level was measured from blood drawn into citrate bottles (Sodium Citrate was the anticoagulant). The blood was stored in a dark box in a refrigerator overnight at 4–7°C, and then centrifuged for 15 min at 2,100 × g at 4°C. Plasma was stabilized in a standardized volume of metaphosphoric acid and then stored at -70°C. The plasma vitamin C level was determined using a fluorometric assay within 1 week of sampling [22]. The coefficient of variation was 5.6% at the lower end of the range (mean 33.2 µmol·L⁻¹) and 4.6% at the upper end (mean 102.3 µmol·L⁻¹).

Statistical analysis

Predicted FEV₁ were calculated using European Coal and Steel Community formulae for males and females [23]. Subjects were considered to have undiagnosed OAD if they had measured FEV₁ of <80% of the predicted, had

a FEV₁/FVC ratio of <70% [17] and did not have self-reported OAD (bronchitis/emphysema or asthma).

Statistical analysis was performed using Stata Version 6.0 (StataCorp, College Station, TX, USA). Significance testing was carried out using analysis of variance (ANOVA) with post-ANOVA t-test comparison for means and the Chi-squared test for proportions. The risk of prevalent undiagnosed OAD was analysed using logistic regression modelling. Interaction between plasma vitamin C (grouped as a binary variable: lowest quintile, 1; upper 4 quintiles, 0) and smoking exposures (categorical variables) was tested using interaction terms in logistic regression models.

Results

Data on health and lifestyle factors, social class, dietary intake and plasma vitamin C measurement were available for 95% (8,926) of participants who were recruited between February 1993 and May 1996 and had data entry by October 1998. Nine hundred and fifty-six excluded 956 (10.7%) individuals were excluded from the analysis because of poor technique or missing data (300) or because their FEV₁ exceeded 98% of their FVC (656). Excluded subjects were older (60.3 yrs compared to 59.5 yrs, $p=0.006$) but did not differ with respect to body mass index (BMI), plasma vitamin C level or proportions of current, former and never smokers from those who formed the study group. A lower proportion (9.2 *versus* 15.5%, $p<0.001$) of excluded subjects had self-reported OAD. The characteristics of the 3,714 males and 4,256 females included in the study group are shown in table 1.

The characteristics by category of OAD status: self-reported OAD, prevalent undiagnosed OAD, and others considered not to have OAD are shown in table 2. Prevalent undiagnosed disease, defined by FEV₁ of <80% pred and an FEV₁/FVC ratio of <70% without self-reported OAD, accounted for 27% of the OAD prevalence in males and 19% in females. Among those classified as having self-reported OAD, 47% reported having bronchitis/emphysema only, 38% asthma only and 15% both conditions.

Subjects classified as having undiagnosed OAD were significantly older than those with self-reported OAD. The mean FVC was similar in both groups for males and females. Mean plasma vitamin C concentrations were also similar, but both groups had significantly lower mean concentrations than did subjects who were classified as not having OAD. Subjects with undiagnosed disease were more likely to be current smokers compared to those with self-reported disease. There were no significant differences in dietary vitamin C or vitamin E among the three categories before or after adjusting for total energy intake. Subjects without OAD were more likely to be never smokers and least likely to be current smokers.

Self-reported OAD and undiagnosed OAD were examined separately as outcome variable in logistic models with sex, age, social class and residential area as explanatory variables. Adding dietary vitamin E adjusted for total energy intake to the models did not change the risk estimates of the other variables and did not improve the fit of the models. Plasma vitamin C concentration modelled best as a continuous variable. Relative to never smokers, the adjusted odds ratio (OR) (95% confidence interval

Table 1. – Characteristics of study group, aged 45–74 yrs, of the EPIC-Norfolk cohort, 1993–1996

Variable	Males	Females
Subjects n	3,714	4,256
Age yrs	59.9±8.6	59.1±8.5
Height cm	174.1±6.7	161.1±6.0
Weight kg	80.4±11.2	67.8±11.4
Body mass index kg·m ⁻²	26.5±3.2	26.1±4.2
Dietary vitamin C mg·day ⁻¹	109.4±49.2	131.4±57.0
Dietary vitamin E mg·day ⁻¹	11.6±6.3	10.6±5.4
Plasma vitamin C µmol·L ⁻¹	46.8±18.2	58.2±19.7
Social class*		
I	7.8 (279)	5.8 (236)
II	39.7 (1412)	36.3 (1473)
III NM	12.4 (441)	20.6 (838)
III M	23.9 (851)	19.8 (804)
IV	13.4 (478)	13.8 (559)
V	2.8 (98)	3.8 (153)
Urban postcode	18.8 (697)	19.2 (816)
Never smokers	34.3 (1269)	58.9 (2490)
Former smokers	54.6 (2017)	29.9 (1264)
Current smokers	11.1 (410)	11.2 (473)
Time stopped smoking		
0–4.9 yrs	10.4 (180)	12.1 (139)
6–14.9 yrs	28.2 (489)	27.4 (316)
15–24.9 yrs	29.2 (507)	30.5 (351)
>25 yrs	32.3 (561)	30.0 (346)
Cumulative smoking among ever smokers pack-yrs ⁺	20 (10–30.8)	13 (5–22.5)
Teetotallers	4.7 (173)	10.8 (461)
No OAD	78.2 (2904)	81.4 (3465)
Undiagnosed OAD	5.8 (216)	3.5 (148)
Self-reported OAD	16.0 (594)	15.1 (643)

Data are presented as mean±SD or percentages with absolute values in parentheses. ⁺: median (interquartile range). *: social class; I: professional occupations; II: managerial and technical occupation; III NM: nonmanual skilled occupations; III M: manual skilled occupations; IV: partly skilled occupations; V: unskilled occupations. OAD: obstructive airway disease.

(CI) for self-reported OAD in current smokers was 1.29 (1.05–1.60) and in former smokers was 1.35 (1.18–1.55). The OR (95% CI) for a 20 µmol·L⁻¹ increase in vitamin C concentration was 0.91 (0.85–0.97). Since the diagnosis of OAD may cause changes in smoking and dietary patterns, the analyses were restricted to individuals with undiagnosed OAD, in whom such changes are unlikely.

Plasma vitamin C had a protective effect against the risk of undiagnosed OAD that just failed to achieve conventional statistical significance after adjustment for smoking category, age, sex, social class and residential area. The OR (95% CI) for a 20 µmol·L⁻¹ increase in vitamin C was 0.89 (0.79–1.00) (p=0.056) (table 3). Analyses were repeated using cumulative cigarette consumption in pack-yrs as smoking exposure. Relative to never smokers, the adjusted OR (95% CI) for increasing tertiles of cumulative cigarette consumption were 0.78 (0.50–1.20), 1.31 (0.95–1.80) and 3.21 (2.42–4.27). There was a significant trend for risk of undiagnosed OAD with increasing consumption (p=0.0001). Plasma vitamin C was independently protective of sex, age, social class, residential area and tertiles of cumulative cigarette consumption. The OR (95% CI) for a 20 µmol·L⁻¹ increase was 0.87 (0.77–0.98) (p=0.025).

Table 4 shows the influence of smoking on risk of undiagnosed OAD in the quintiles of plasma vitamin C distribution. Relative to never smokers, individuals in the lowest quintile were consistently at highest risk, whatever their smoking exposure, compared to individuals in the higher four quintiles. The risk estimates for smoking exposures were similar in the highest four quintiles. They were, therefore, combined to test for interaction between smoking and vitamin C status as a binary variable, lowest quintile of vitamin C *versus* the others (table 5). Interaction terms for plasma vitamin C (binary) and smoking category (p=0.002), cumulative cigarette consumption (p=0.017) and time of smoking cessation (p=0.001) were highly significant. Among former smokers, plasma vitamin C status influenced the time taken since quitting for the risk of undiagnosed OAD to equal that of the never smokers (fig. 1).

Discussion

It was found that plasma vitamin C reduced the risk of undiagnosed OAD defined on the basis of predicted FEV₁ and FEV₁/FVC ratio. These findings are consistent with previous studies favouring a protective effect of plasma vitamin C on lung function independent of the effects of smoking [3–9]. The protective effect of plasma vitamin C on OAD risk was independent of smoking exposure, sex, age, social class and residential area. Within each smoking category, individuals who were in the lowest quintile of the plasma vitamin C distribution were at greatest risk of OAD. The results indicate that plasma vitamin C status may be an effect modifier of cigarette smoking on risk of OAD.

The present results are unlikely to have arisen due to chance, but several biases need to be considered. The EPIC-Norfolk study was designed as a prospective cohort study and the planned analysis aimed to make comparisons within the cohort cross-sectionally and over time. Although not primarily intended to give reliable population prevalence estimates, the distributions of BMI and blood pressure are similar to those of nationally representative samples [19, 24]. The within-population associations are, therefore, unlikely to be due to selection bias. Approximately 10% of subjects, whose spirometry measures may not have been reliable were excluded. Although they were older, there was no difference with respect to smoking category or mean plasma vitamin C concentration, the main exposures of interest. These exclusions are unlikely to have affected the results.

One potential limitation of cross-sectional analysis is the difficulty in establishing temporal relationships between associated factors. Changes in smoking behaviour and dietary vitamin C intake may occur after an individual is diagnosed with OAD. This possibility is supported by the finding that the risk of self-reported OAD in current smokers was attenuated in the present study, although the relation of plasma vitamin C to self-reported OAD and undiagnosed OAD were similar. Therefore, analyses were restricted to undiagnosed OAD to eliminate reverse causation as an explanation for the results. Participants were recruited through their doctors' practices and it is likely that

Table 2. — Characteristics of 3,714 males and 4,256 female, aged 45–74 yrs, of the EPIC-Norfolk cohort, 1993–1996 by obstructive airways disease (OAD) status

	Males			Females		
	Self-reported OAD	Prevalent undiagnosed OAD 216	No OAD	Self-reported OAD	Prevalent undiagnosed OAD	No OAD
Subjects n	594	216	2904	643	148	3465
Age yrs	59.9±8.9	63.2±8.3 ^{*,§}	59.6±8.5 [‡]	59.0±8.5	61.9±8.0 ^{*,§}	59.0±8.5 [‡]
Peak expiratory flow L·s ⁻¹	394.9±135.8	282.9±104.9 ^{*,§}	446.4±110.2 ^{*,‡}	292.0±81.4	173.6±76.1 ^{*,§}	305.3±74.3 ^{*,‡}
FVC L [#]	3.44±1.05	3.38±0.78	3.83±0.84 ^{*,‡}	2.51±0.69	2.46±0.56	2.75±0.59 ^{*,‡}
FEV1 L [#]	2.60±0.89	2.01±0.51 ^{*,§}	3.09±0.64 ^{*,‡}	2.02±0.57	1.47±0.36 ^{*,§}	2.24±0.45 ^{*,‡}
Predicted FEV1 (L)	3.25±0.44	3.16±0.40 ^{*,§}	3.27±0.42 [‡]	2.28±0.36	2.24±0.34	2.29±0.35
FEV1/FVC	0.76±0.14	0.60±0.09 ^{*,§}	0.81±0.08 ^{*,‡}	0.81±0.11	0.60±0.09 ^{*,§}	0.82±0.08 ^{*,‡}
Plasma vitamin C µmol·L ⁻¹	45.5±18.5	43.5±19.0	47.3±18.0 ^{*,‡}	56.4±18.8	53.9±18.8	58.7±19.8 ^{*,‡}
Never smokers % (n)	29.8 (175)	20.0 (43) ^{*,§}	36.3 (1051) ^{*,‡}	52.0 (333)	48.3 (71)	60.6 (2086) ^{*,‡}
Former smokers % (n)	59.0 (347)	57.2 (123)	53.5 (1547) [*]	35.5 (227)	27.2 (40)	29.0 (997) [*]
Current smokers % (n)	11.2 (66)	22.8 (49) ^{*,§}	10.2 (295) [‡]	12.5 (80)	24.5 (36) ^{*,§}	10.4 (357) [‡]
Cumulative smoking pack-yrs ⁺	20 (10–35)	30 (17.5–40)	20 (10–30)	17.5 (7.5–25)	22.5 (12.5–30.8)	11.5 (5–20.8)

Data are presented as mean±SD. ⁺: median (interquartile range). [#]: adjusted for body mass index. FVC: forced vital capacity; FEV1: forced expiratory volume in one second. ^{*}: p<0.05 versus self-reported OAD; [‡]: p<0.05 versus prevalent undiagnosed OAD; [§]: p<0.05 versus no OAD. Total prevalent OAD includes self-reported and undiagnosed OAD, prevalent is used to indicate that they are not newly discovered or diagnosed.

symptomatic individuals would have been diagnosed. Doctor-diagnosed OAD is probably a sensitive, if not specific, marker for true OAD. It is possible that some of the individuals classified as having undiagnosed OAD could have had symptoms and modified their lifestyle, but there are unlikely to be many in this situation.

The clinical definition of chronic OAD embraces emphysema, bronchitis and asthma [1]. These conditions may co-exist or be present independently in the same individual [1]. Chronic obstructive pulmonary disease is also associated with anatomical changes in the alveoli (emphysema) and airways (bronchitis). However, the presence of anatomical defects does not necessarily determine the clinical course or prognosis of the disease. It is the chronic limitation of expiratory airflow that characterizes the disease [1, 2]. The definition of undiagnosed OAD

used in the present study is likely to correctly identify individuals with airway obstruction but the possibility of misclassification using a single assessment of lung function cannot be excluded. Conversely, it is likely that subjects with acute airway obstruction would have been identified by research nurses and would not have been tested.

Guidelines for the measurement of lung function recommend a minimum of three measurements [25]. Only two measurements were performed in the present study. Although this may have affected the comparability of the findings with those of other studies, it is unlikely to have affected the internal validity of the results since a standard protocol was employed for all participants. Another possible limitation is that the equation used for predicted FEV1 [23] may lead to overestimation of this measure.

Table 3. — Risk of prevalent undiagnosed obstructive airways disease (OAD) (n=364), in 3,120 males and 3,613 females aged 45–74 yrs, EPIC-Norfolk cohort, 1993–1996 (self-reported OAD excluded)

	Smoking category (never smokers)		Sex (male)	Age (per 10 yrs)	Residence (rural postcode)	Social class* (I)		Plasma vitamin C (per 20 µmol·L ⁻¹)
	Category	Risk				Class	Risk	
Model 1	Current	3.63 2.69–4.89	0.64 0.51–0.81	1.65 1.44–1.88				
	Former	1.43 1.11–1.85						
Model 2	Current	3.26 2.38–4.45	0.62 0.49–0.78	1.61 1.41–1.84	0.93 0.70–1.24	II	1.05 0.63–1.73	
	Former	1.34 1.03–1.74				III NM	1.32 0.78–2.25	
						III M	1.19 0.71–2.00	
						IV	1.36 0.79–2.33	
						V	0.65 0.26–1.59	
Model 3	Current	3.06 2.22–4.21	0.66 0.52–0.84	1.59 1.39–1.82	0.93 0.70–1.25	II	1.05 0.63–1.73	0.89 0.79–1.00
	Former	1.34 1.03–1.73				III NM	1.31 0.77–2.23	
						III M	1.16 0.69–1.96	
						IV	1.32 0.77–2.27	
						V	0.62 0.25–1.52	

Data are presented as odds ratio (95% confidence interval). Age and plasma vitamin C concentration were modelled as continuous variables. Reference categories are given in parenthesis. ^{*}: social class: I: professional occupations (reference category); II: managerial and technical occupations; III NM: nonmanual skilled occupations; III M: manual skilled occupations; IV: partly skilled occupations; V: unskilled occupation.

Table 4. — Risk of prevalent undiagnosed OAD (n=364), in 3,120 males and 3,613 females, aged 45–74 yrs, EPIC-Norfolk cohort, 1993–1996 by quintiles of plasma vitamin C distribution (self-reported OAD excluded)

	Quintile				
	1	2	3	4	5
Subjects n	1406	1318	1327	1313	1369
OAD cases n	107	79	67	62	49
Vitamin C $\mu\text{mol}\cdot\text{L}^{-1}$ *	25.5 $\pm$ 8.6 (3–37)	43.9 $\pm$ 3.4 (38–49)	54.1 $\pm$ 2.6 (50–58)	63.1 $\pm$ 2.8 (59–68)	80.2 $\pm$ 12.2 (69–174)
Smoking category					
Never	1	1	1	1	1
Current	5.93 (3.03–11.61)	2.41 (1.21–4.78)	1.91 (0.80–4.60)	4.27 (2.10–8.67)	2.65 (0.94–7.47)
Former	3.25 (1.73–6.14)	0.88 (0.51–1.53)	1.08 (0.61–1.92)	1.26 (0.68–2.31)	1.04 (0.53–2.05)
Cumulative smoking among ever smokers					
Never smoker	1	1	1	1	1
Lowest tertile	1.66 (0.65–4.29)	0.61 (0.23–1.62)	0.50 (0.17–1.45)	0.69 (0.26–1.84)	0.85 (0.31–2.30)
Middle tertile	3.21 (1.58–6.51)	0.85 (0.42–1.69)	1.07 (0.53–2.18)	1.72 (0.84–3.53)	0.51 (0.17–1.55)
Highest tertile	6.25 (3.28–11.92)	2.24 (1.25–4.02)	3.02 (1.55–5.87)	3.38 (1.69–6.75)	3.31 (1.52–7.23)

Data are presented as odds ratio (95% confidence interval). *: mean $\pm$ SD (range). Odds ratios were adjusted for sex, age, residence and social class. Cumulative smoking: lowest tertile: <10 pack-yrs; middle tertile: 10–23 pack-yrs; highest tertile: >23 pack-yrs.

This could attenuate the results because of inclusion of some individuals with less severe FEV₁ reduction than the equation suggests in the group with undiagnosed OAD.

Plasma vitamin C concentration is a short-term measure of vitamin C intake and may be prone to acute fluctuations. In the present study, participants were not sampled with respect to their vitamin C intake, smoking or OAD status. Acute fluctuations in plasma vitamin C concentration would, therefore, be random and have the effect of attenuating the true association because of regression dilution bias. A single measure of plasma vitamin C might misclassify individuals with respect to long-term status. Leukocyte vitamin C concentration is thought to be a longer-term marker of vitamin C status [26] but is expensive and complex to measure [27]. Furthermore, plasma vitamin C concentration has been shown to be highly correlated with buffy-coat (leukocyte) vitamin C concentration and was an equally good index of long-term status over 18 months [28]. In addition, in the same study, a single measure of vitamin C concentration ranked individuals as well as the mean of

six measures taken over the 18-month period and plasma vitamin C concentration correlated well with the long-term intake of vitamin C in that study [28].

Although the effect of plasma vitamin C status on OAD risk was independent of smoking and other potential confounders, this analysis may underestimate its importance. Smoking increases the demand for vitamin C because of increased oxidative stress [15, 16]. Since smoking is an important determinant of plasma vitamin C status, simultaneously adjusting for both factors may attenuate the effect of vitamin C. Therefore, individuals were stratified into quintiles of plasma vitamin C distribution and the effect of smoking in these quintiles investigated. This analysis would avoid the attenuation that might result from adjustment since some of the effect of vitamin C may be mediated through counteracting the oxidative effects of smoking.

Stratification also provided more information regarding the role of vitamin C in OAD risk than the adjusted OR. The adjusted OR indicated that, for a 20 $\mu\text{mol}\cdot\text{L}^{-1}$ (or 1 SD) increase in plasma vitamin C concentration, there was a modest 13% reduction in risk. However, stratifying the risk of undiagnosed OAD from smoking by quintiles of vitamin C concentration suggests that there may be modification by plasma vitamin C status of the adverse effects of smoking. The risk of OAD due to smoking was greatest in those in the lowest quintile and the greatest reduction in risk was observed between the first (lowest) and second quintiles. Furthermore, the risk was similar in each of the highest four quintiles.

These results support the effect of an interaction between plasma vitamin C level and smoking exposures on risk of OAD. Interaction terms included in statistical models were highly significant. In order to achieve adequate power to detect interaction, the sample size needs to be at least four times that required to detect main effects of the same magnitude [29]. Other studies failed to detect interaction [3–7]. This may be due not only to lack of statistical power but also to dietary assessment not reflecting true vitamin C status. This measurement error could lead to underestimation of effect modification. The present results also suggest that the effect modification would be detected at the lowest end of the plasma vitamin

Table 5. — Risk of prevalent undiagnosed OAD (n=364) in the lowest quintile of plasma vitamin C concentration compared to the other quintiles, in 3,120 males and 3,613 females, aged 45–74 yrs, EPIC-Norfolk cohort, 1993–1996 (self-reported OAD excluded)

	Quintile	
	1	2–5
Smoking category		
Never	1	1
Current	5.93 (3.03–11.61)	2.84 (1.92–4.19)
Former	3.25 (1.72–6.14)	1.06 (0.78–1.43)
Cumulative smoking pack-yrs		
0	1	1
<10	1.66 (0.65–4.29)	0.65 (0.39–1.07)
10–23	3.21 (1.58–6.51)	1.04 (0.71–1.52)
>23	6.25 (3.28–11.92)	2.84 (2.04–3.97)

Data are presented as odds ratio (OR) (95% confidence interval). ORs were adjusted for sex, age, residence and social class. CI: confidence interval.

Fig. 1. – Risk of undiagnosed obstructive airways disease (OAD) among former smokers by time since smoking cessation with respect to quintiles (Qs) of plasma vitamin C concentration (—: Q1 (lowest); - - - - : Q2–5) in 2,754 males and 3,194 females aged 45–74 yrs, EPIC-Norfolk cohort, 1993–1996 (self-reported OAD excluded). OR: odds ratio; CI: confidence interval.

C distribution. If few individuals have sufficiently low plasma vitamin C concentrations, the interaction may be undetectable.

Measures to increase plasma vitamin C concentration, whether by increased fruit and vegetable intake or vitamin C supplementation, may reduce the risk of obstructive airways disease from smoking. This benefit may be greatest in those who have the lowest levels of plasma vitamin C. Vitamin C may play a protective role in the aetiology of obstructive airways disease and may act as an important effect modifier of smoking on the risk of obstructive airways disease.

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