

Original article

A case-control study of the relation between plasma selenium and asthma in European populations: a GA²LEN project*

Background: There is evidence that selenium levels are relatively low in Europe and may be falling. Low levels of selenium or low activity of some of the enzymes dependent on selenium have been associated with asthma.

Methods: The GA²LEN network has organized a multicentre case-control study in Europe to assess the relation of plasma selenium to asthma. The network compared 569 cases in 14 European centres with a diagnosis of asthma and reporting asthma symptoms in the last 12 months with 576 controls from the same centres with no diagnosis of asthma and no asthmatic symptoms in the last 12 months.

Results: All cases and controls were selected from the same population defined by age and place of residence. Mean plasma selenium concentrations among the controls ranged from 116.3 µg/l in Palermo to 67.7 µg/l in Vienna and 56.1 µg/l among the children in Oslo. Random effects meta-analysis of the results from the centres showed no overall association between asthma and plasma selenium [odds ratio (OR)/10 µg/l increase in plasma selenium: 1.04; 95% confidence interval (CI): 0.89–1.21] though there was a significantly protective effect in Lodz (OR: 0.48; 95% CI: 0.29–0.78) and a marginally significant adverse effect in Amsterdam (OR: 1.68; 95% CI: 0.98–2.90) and Ghent (OR: 1.35; 95% CI: 1.03–1.77).

Conclusion: This study does not support a role for selenium in protection against asthma, but effect modification and confounding cannot be ruled out.

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Asthma is a chronic inflammatory disease which is associated with increased oxidative stress (1). This is reflected in reduced levels of the anti-oxidant vitamins C and E and increased levels of oxidized glutathione in broncho-alveolar lavage fluid (2).

Defence against oxidative stress is partially dependent on diet, including intake of vitamins C, E and A, as well as other retinols and carotenes including α - and β -carotene, cryptoxanthin and lycopene and a wide variety of flavonoids and related anti-oxidant substances which are possibly responsible for the 'anti-asthmatic' effects of hard fruit, such as apples (3). Dietary selenium is necessary for the adequate function of the enzyme glutathione peroxidase, which in turn is necessary for reducing glutathione, an important anti-oxidant in the airway, and restoring its anti-oxidative effect. Selenium is also an important component of several other anti-oxidant enzymes (4), and has other immunomodulating actions (5, 6).

Selenium is of particular importance because its principal source is from soil, from which it is transferred into the food chain via crops. European soils are relatively poor sources of selenium compared with North American soils. The switch from North American to European sources of wheat is thought to have reduced the selenium intake over the past decades in some regions including the UK (7). The potential role of dietary selenium in asthma has been recently reviewed by the GA²LEN network (3). Selenium or glutathione peroxidase activity has been shown to be lower in asthmatic patients than in controls in a number of epidemiological studies (8–17). One study of selenium intake has also shown a lower intake of selenium associated with asthma (18). In one large pregnancy cohort low levels of selenium in umbilical cord have also been associated with persistent wheeze in children, the most common wheezing phenotype associated with asthma (19), and in another birth cohort low levels of selenium in maternal blood in pregnancy and in cord blood were associated with wheezing in early childhood (20).

A few studies have failed to confirm a link between low selenium levels and asthma later in life (21–23). One of these studies, however, suggested that young people exposed to environmental tobacco smoke may have some level of protection from a high serum selenium (22).

Until recently, there had only been one small trial of selenium in asthma and this showed clinical improvement but no significant change in the objective markers measured (24). As the current study was planned a further larger trial has provided no evidence of benefit from selenium supplementation in adult asthmatics in the UK who were mostly taking inhaled steroids (25).

The main aim of this study was to assess whether there is an association between the selenium blood levels of adults aged 20–45 years and asthma, and to describe the variation in selenium blood levels across several European centres. We included two paediatric centres where the participants were aged 7–14 years.

Methods

The study was a case-control study. Cases were aged 20–45 years, living in a defined area and had both a self-reported diagnosis of asthma and either wheezing, shortness of breath or waking at night with breathlessness in the previous 12 months (26). Controls lived in the same area, were aged 20- to 45-year old and had neither a diagnosis of asthma nor any of the three symptoms. In the first instance cases and controls were identified from a population-based survey, mostly through a simple screening questionnaire sent by post. However, these surveys were not always large enough to find adequate numbers of cases and further cases could be recruited from clinics providing that they met the criteria and were not being treated in the clinic for another atopic condition. In two centres (Athens and Oslo) paediatric populations were sampled and these were recruited from local schools in the age group 7–14 years.

Each centre was asked to recruit 50 cases and 50 controls. Once identified the subjects were invited to complete a longer administered questionnaire, had their height, weight and spirometric lung function measured and had skin prick tests to common allergens. Blood was drawn for estimation of plasma selenium levels.

Central training was given to staff in each centre prior to involvement with the main data collection. Instruction included adherence to standard protocols for administering questionnaires, undertaking skin prick tests and spirometry and handling specimens. Questionnaires used mostly questions that had been used in other surveys. The new questionnaires were forward and back translated and the original questionnaires and the back translations compared and reconciled. Socio-economic status was assessed from current or last occupation (of father in the case of children) and classified as professional, managerial, skilled, semi-skilled, unskilled or student. Smoking status was classified as never smoked and exposed to <1 h environmental tobacco smoke per day, never smoked and exposed to at least 1 h of environmental tobacco smoke per day, ex-smokers and current smokers. Dietary supplements were assessed by asking whether the subject took 'regular vitamin or mineral supplements'. For analysis the subjects were divided into two groups by severity, intermittent and mild persistent disease (night-time symptoms twice or less per month, trouble breathing less than once a day, forced expiratory volume in 1 s (at least 80% predicted and using at most a medium dose of inhaled steroid) and moderate or severe persistent disease who had more than these symptoms. Skin tests were undertaken using ALK-Abello (Hørsholm, Denmark) reagents against timothy grass, cat dander, *Dermatophagoides farinae*, olive, birch parietaria, alternaria and histamine (10 mg/ml) and diluent controls. Atopy was defined by the very sensitive criterion of any atopic wheal greater than the diluent control in the presence of a positive histamine control (27, 28). Vacutainer plastic blood collection tubes and 7-ml gel separator tubes with heparin were used to collect plasma. Samples were centrifuged at 1100–1300 g for 10 min within 2 h of collection and the plasma was stored at –20°C. Samples were subsequently shipped to Marburg for analysis on dry ice in compliance with EU regulations for the transport of human biological specimens.

All specimens were analysed for selenium in one accredited laboratory by atomic absorption spectroscopy using a Perkin Elmer 4110 ZL Zeeman graphite furnace atomic absorption spectrometer (29). All analysis reagents and modifiers were purchased from Merck, the standards used were Selenium Atomic Standard Solution (Sigma-Aldrich, St Louis, MO, USA), controls used were Chek-Control I and II (Recipe). All samples were measured in duplicate. Accuracy of selenium measurements was 6.0% intra-assay precision was 3.8%, inter-assay precision was 8.5%. The minimum detectable concentration was 0.02 $\mu\text{mol/l}$ (1.6 $\mu\text{g/l}$), normal values were within the reference range of 0.97–1.77 $\mu\text{mol/l}$ for

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Table 1. Numbers and characteristics of cases and controls recruited by centre – gender, age, smoking, supplement use

Centre	Numbers		% female		Mean age (years)		% current smokers		% supplement users		% atopic	
	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case
Ghent	59	76	56	61	32	29	17	27	28	25	40	85
Vienna	46	12	35	31	35	33	48	31	20	8	47	92
Odense	41	50	69	63	34	32	17	27	44	47	28	77
Berlin	33	18	27	38	39	38	46	54	22	38	19	81
Palermo	53	41	56	52	34	33	25	26	11	14	46	73
Rome	21	28	72	86	35	34	24	25	10	14	24	89
Amsterdam	38	38	59	78	35	33	17	13	22	35	44	90
Lodz	44	52	45	44	31	29	16	33	9	25	34	82
Coimbra	46	51	51	65	33	32	34	9	11	11	22	78
Barcelona	44	44	58	58	34	33	30	31	10	2	26	80
Stockholm	17	38	59	61	39	38	29	18	18	24	35	92
London	51	50	57	70	38	38	17	32	38	30	49	72
Athens	32	29	44	34	10	10	–	–	6	10	41	62
Oslo	51	42	50	47	9	9	–	–	56	51	25	60
Overall	576	569	52	58	35	33	26	26	23	25	35	79

adults (76–139 µg/l) and 0.46–1.42 µmol/l (36–112 µg/l) for children (> 6 years).

After examining the distributions of the variables logistic regression was used to estimate the risk of being a case in each centre. We estimated both the linear decrease in risk for each 10 µg/l increase in plasma selenium and the increase in risk if the selenium level was below a threshold of 80 µg/l. These analyses controlled for the possible confounders gender, age, smoking, socio-economic status, supplement use, paracetamol use and body mass index. After the initial within centre analyses the results were combined across centre using random effects meta-analysis. All analyses were undertaken in Stata (30).

We subsequently looked for interactive effects of other variables with plasma selenium levels. We tested specifically for effect modification by gender, atopy and smoking.

Local ethical committee approval was given in each centre and approval was given by the Norwegian Data Inspectorate. Each participant was provided with an information sheet explaining the study and signed a consent form prior to taking part.

Results

The centres recruited 576 cases and 569 controls. The groups were fairly similar with respect to various characteristics, with 52% female controls and 58% female cases, mean age of 35 years among the controls and 33 years among the cases, 26% smokers among both cases and controls and 23% supplement use reported by controls and 25% among cases. The proportion of controls that were atopic by our sensitive criterion ranged from 19% in Berlin to 49% in London among adults with a substantially higher prevalence in cases (Table 1). As is expected, differences between cases and controls were more variable within the centres where numbers are smaller.

Table 2 gives the severity of the asthma cases in each centre according to the GINA guidelines. Moderate and severe persistent asthma comprised 75% of the cases in

Table 2. Severity of asthma in the different centres as judged by the GINA guidelines [number (%) in each severity category]

	Intermittent	Persistent		
		Mild	Moderate	Severe
Ghent	33 (42)	13 (16)	24 (30)	9 (11)
Vienna	4 (31)	4 (31)	2 (23)	2 (15)
Odense	24 (47)	15 (29)	10 (20)	2 (4)
Berlin	11 (42)	6 (23)	8 (31)	1 (4)
Palermo	23 (55)	1 (2)	10 (24)	8 (19)
Rome	4 (14)	8 (29)	11 (40)	5 (18)
Amsterdam	4 (10)	6 (15)	18 (45)	12 (30)
Lodz	22 (42)	5 (10)	10 (19)	15 (29)
Coimbra	16 (30)	8 (15)	23 (43)	7 (13)
Barcelona	8 (17)	16 (33)	12 (25)	12 (25)
Stockholm	19 (50)	7 (19)	9 (24)	3 (8)
London	17 (34)	6 (12)	18 (36)	9 (18)
Athens	11 (42)	5 (19)	7 (27)	3 (12)
Oslo	7 (16)	13 (30)	19 (44)	4 (9)
Overall	203 (34.4)	113 (19.2)	182 (30.9)	92 (15.6)

Amsterdam and 24% of those in Odense. Overall 34% had intermittent asthma only, 19% had mild persistent asthma and 46% had moderate or severe persistent asthma.

Mean plasma selenium concentrations among the controls ranged from 116.3 µg/l in Palermo to 67.7 µg/l in Vienna and 56.1 µg/l among the children in Oslo (Table 3). In Amsterdam cases had on average 5.7 µg/l more selenium than controls, whereas in Lodz cases had 9.7 µg/l less selenium than controls. Other centres showed differences in between these two extremes. Overall there was no difference in mean plasma selenium between cases (85.7 µg/l) and controls (85.4 µg/l) ($P = 0.81$).

Table 4 shows the results of the logistic regressions together with the results of the meta-analyses. After controlling for gender, age, socio-economic status,

Table 3. Plasma selenium concentrations ($\mu\text{g/l}$) by centre mean, SD, range, number

Centre	Control	Case	Difference in selenium concentration ($\mu\text{g/l}$) (<i>P</i> -value)
Ghent	82.7 (16.0) (53.7–124.8) 59	85.9 (17.5) (60.0–131.9) 76	–3.12 (0.29)
Vienna	67.7 (13.1) (35.5–112.1) 46	66.7 (10.2) (56.1–89.2) 12	0.96 (0.81)
Odense	76.4 (11.5) (60.0–99.5) 41	79.2 (11.3) (56.1–101.9) 50	–2.79 (0.25)
Berlin	82.4 (15.2) (60.8–114.5) 33	87.0 (9.7) (70.3–105.1) 18	–4.67 (0.24)
Palermo	116.3 (17.5) (82.1–148.4) 53	113.0 (19.8) (72.6–153.2) 41	3.21 (0.41)
Rome	88.6 (13.0) (64.7–112.1) 21	88.5 (11.3) (69.5–115.3) 28	0.10 (0.98)
Amsterdam	82.0 (11.9) (64.0–120.8) 38	87.7 (15.8) (58.4–138.2) 38	–5.69 (0.08)
Lodz	79.2 (14.8) (44.2–113.7) 44	69.5 (15.1) (34.0–110.5) 52	9.67 (0.002)
Coimbra	95.7 (11.0) (68.7–114.5) 46	94.5 (13.9) (54.5–124.8) 51	1.26 (0.63)
Barcelona	102.1 (13.4) (79.0–135.0) 44	100.0 (16.1) (74.2–138.2) 44	2.19 (0.49)
Stockholm	79.89 (8.5) (63.2–101.0) 17	79.5 (11.6) (52.9–99.5) 38	0.39 (0.90)
London	99.0 (17.8) (62.4–142.1) 51	97.2 (19.9) (48.2–151.6) 50	1.79 (0.63)
Athens	80.3 (13.1) (56.1–120.0) 30	82.7 (10.9) (56.1–109.8) 27	–2.37 (0.46)
Oslo	56.1 (9.6) (37.9–86.1) 51	56.4 (9.4) (39.5–75.0) 42	–0.34 (0.87)
Overall	85.4 (21.0) (35.5–148.4) 574	85.7 (20.3) (34.0–153.2) 567	–0.30 (0.81)

supplement use, paracetamol use and body mass index, a 10 $\mu\text{g/l}$ increase in plasma selenium was associated with a 52% decrease in risk of asthma in Lodz (OR: 0.48; 95% CI: 0.29–0.78) and a 35% increase in risk in Ghent (OR: 1.35; 95% CI: 1.03–1.77), with a 68% increase in risk in Amsterdam (OR: 1.68; 95% CI: 0.98–2.90). Overall there was no effect of selenium on the risk of asthma (OR/10 $\mu\text{g/l}$: 1.04; 95% CI: 0.89–1.21). The effect of the adjustment was to strengthen marginally both the positive and the negative associations. Looking at the threshold dose of 80 $\mu\text{g/l}$, the adverse effects in Ghent and Amsterdam are no longer significant though in the

Table 4. Odds of being a case at different levels of selenium and if plasma selenium is <80 $\mu\text{g/l}$

Centre	Per 10 $\mu\text{g/l}$ increase unadjusted	Per 10 $\mu\text{g/l}$ increase adjusted*	Se <80 $\mu\text{g/l}$ adjusted*
Ghent	1.12 (0.91–1.37)	1.35 (1.03–1.77)	0.45 (0.18–1.10)
Vienna	0.94 (0.55–1.59)	0.87 (0.47–1.61)	2.92 (0.23–37.28)
Odense	1.24 (0.86–1.80)	1.10 (0.68–1.79)	0.81 (0.26–2.48)
Berlin	1.30 (0.84–2.00)	1.34 (0.75–2.37)	0.51 (0.10–2.59)
Palermo	0.91 (0.73–1.14)	1.02 (0.73–1.42)	Too few data
Rome	0.99 (0.62–1.60)	1.09 (0.52–2.28)	1.29 (0.20–8.34)
Amsterdam	1.36 (0.96–1.93)	1.68 (0.98–2.90)	0.42 (0.11–1.64)
Lodz	0.64 (0.47–0.87)	0.48 (0.29–0.78)	3.79 (1.24–11.53)
Coimbra	0.92 (0.67–1.27)	0.81 (0.49–1.33)	3.00 (0.52–17.50)
Barcelona	0.90 (0.68–1.20)	0.98 (0.66–1.46)	0.98 (0.12–8.28)
Stockholm	0.97 (0.56–1.66)	0.62 (0.27–1.40)	1.08 (0.22–5.27)
London	0.95 (0.77–1.17)	1.08 (0.82–1.40)	1.91 (0.49–7.52)
Athens	1.21 (0.78–1.86)	1.16 (0.66–2.01)	0.80 (0.23–2.83)
Oslo	1.04 (0.67–1.60)	1.19 (0.71–2.01)	Too few data
All centres (meta-analysis)	1.00 (0.90–1.10)	1.04 (0.89–1.21)	1.04 (0.68–1.52)
Heterogeneity: <i>Q</i> (d.f.) <i>P</i> -value	17.39 (13) 0.18	20.29 (13) 0.088	14.14 (11) 0.23

*Controlling for gender, age, smoking, socio-economic status, supplement use, paracetamol use and body mass index.

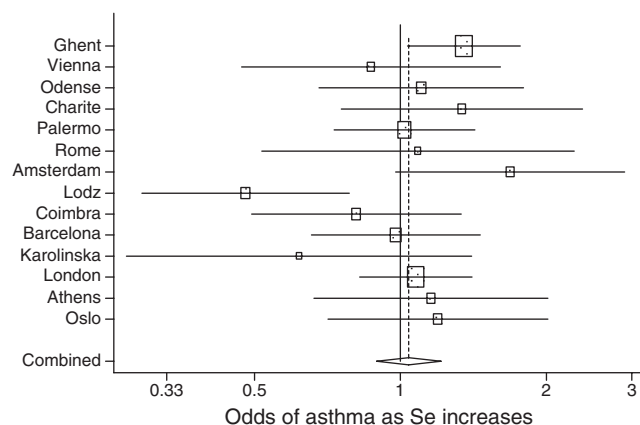


Figure 1. Graph showing meta-analysis of odds of asthma as plasma selenium increases linearly per 10 $\mu\text{g/l}$. Effects are adjusted for gender, age, smoking, socio-economic status, supplement use, paracetamol use and body mass index.

same direction as before but the protective effect in Lodz was strong and still significant. In the absence of a strong threshold effect this is expected to be a less powerful analysis. The data for the linear effects are given as a Forest plot in Fig. 1. Both analyses give some evidence for heterogeneity of the effects between the centres.

Examination of the characteristics of the centres did not give a clear idea of any systematic difference that might explain the differences between the centres. There was no evidence of any interactions between atopy or gender and selenium. However, there was some evidence

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Table 5. Effect modification of the associations between plasma selenium and smoking exposures by centre

Centre	Odds ratio (95% confidence limits) of asthma/10 µg/l increase in plasma selenium				
	Nonsmokers	Passive smokers	Ex-smokers	Current smokers	Difference between groups
Ghent	1.05 (0.71–1.55)	0.90 (0.54–1.51)	1.30 (0.63–2.70)	1.45 (0.75–2.82)	$\chi^2 = 2.70$, $P = 0.44$
Vienna	0.88 (0.39–1.97)	0.08 (0.001–7.12)	0.60 (0.11–3.37)	1.47 (0.43–5.00)	$\chi^2 = 2.37$, $P = 0.50$
Odense	1.24 (0.66–2.32)	1.03 (0.39–2.76)	0.78 (0.26–2.30)	1.37 (0.43–4.41)	$\chi^2 = 0.72$, $P = 0.87$
Berlin	1.33 (0.54–3.25)	–	1.22 (0.27–5.61)	0.87 (0.30–2.54)	$\chi^2 = 0.26$, $P = 0.88$
Palermo	1.03 (0.57–1.89)	0.67 (0.32–1.40)	1.28 (0.46–3.55)	1.05 (0.49–2.25)	$\chi^2 = 3.04$, $P = 0.38$
Rome	1.66 (0.35–7.98)	0.42 (0.07–2.56)	0.84 (0.13–5.56)	0.58 (0.10–3.46)	$\chi^2 = 1.39$, $P = 0.71$
Amsterdam	157 (0.95–2.58)	0.48 (0.04–5.32)	0.49 (0.20–1.17)	2.94 (0.49–17.80)	$\chi^2 = 4.95$, $P = 0.18$
Lodz	0.98 (0.53–1.80)	0.39 (0.15–1.04)	0.83 (0.38–1.81)	0.48 (0.16–1.42)	$\chi^2 = 4.64$, $P = 0.20$
Coimbra	0.80 (0.33–1.94)	0.99 (0.37–2.69)	3.05 (0.54–17.14)	2.87 (0.60–13.66)	$\chi^2 = 4.12$, $P = 0.25$
Barcelona	1.09 (0.59–2.01)	0.54 (0.22–1.30)	0.74 (0.33–1.66)	1.32 (0.48–3.67)	$\chi^2 = 3.52$, $P = 0.32$
Stockholm	1.57 (0.60–4.13)	–	0.30 (0.06–1.48)	0.25 (0.04–1.65)	$\chi^2 = 3.27$, $P = 0.20$
London	1.39 (0.88–2.18)	0.61 (0.35–1.09)	0.84 (0.32–2.22)	0.56 (0.30–1.05)	$\chi^2 = 4.10$, $P = 0.25$
Athens	1.18 (0.58–2.41)	1.06 (0.42–2.69)	–	–	$\chi^2 = 0.01$, $P = 0.91$
Oslo	1.03 (0.64–1.68)	1.29 (0.39–4.26)	–	–	$\chi^2 = 0.17$, $P = 0.68$
Overall controlling for centre	1.06 (0.94–1.19)	0.80 (0.69–0.93)	1.08 (0.88–1.32)	0.95 (0.80–1.13)	$\chi^2 = 12.14$, $P = 0.007$

(Table 5) of a protective effect of plasma selenium in nonsmokers exposed to environmental tobacco smoke (χ^2_3 for difference between smoking categories = 12.14; $P = 0.007$).

Comparing moderate and severe persistent asthma with intermittent and mild persistent asthma, selenium was associated with less severe asthma (OR: 0.37/10 µg/l increase in selenium (95% CI: 0.15–0.88)) in Lodz. Again, however, the evidence was inconsistent and the effect went the other way in Coimbra (OR: 2.00; 95% CI: 0.99–4.01) and overall the effect was minimal (OR: 0.95; 95% CI: 0.68–1.32) with significant heterogeneity between the centres [$Q = 20.908$ on 11 degrees of freedom ($P = 0.034$)]. Secondary analyses looking at the effect of selenium on lung function showed no difference in lung function after adjusting for confounders or stratifying for case-control status.

Discussion

Taking the data from Lodz alone there would have been a convincing case for suggesting that selenium was protective against asthma. There is a relatively strong protective effect which is even stronger after adjusting for controlling for gender, age, smoking, socio-economic status, supplement use, paracetamol use and body mass index. In addition, when asthmatics are looked at separately even in this relatively small sample those with more severe asthma have lower levels of selenium than the milder cases. However, in this multi-centre study of plasma selenium and asthma there was little overall evidence of a protective effect from plasma selenium levels. The study is a large and powerful study with standardization of the definition of cases and controls and of research methods and centralized measurement of selenium levels in a single laboratory. The data do, however, suggest variation in

the association between the sites and this may be important. Heterogeneity between the centres could be as a result of chance, to negative or positive confounding in some of the areas or to effect modification.

The possibility that the variability in the findings between the centres is because of chance cannot be discounted. The heterogeneity evident in the data is of only marginal significance ($P = 0.088$ in the most powerful of the analyses). Significance, however, in this context is not an overwhelming argument as this depends on the power of the study. The study gives some evidence that the relation of plasma selenium to asthma varies from place to place.

Animal models have suggested that any association between selenium and airway responsiveness may not be linear (6). We explored different nonlinear options and found that none of them fitted the data better than the models shown here. This may seem strange where there is good reason to predict a threshold effect. Threshold effects in individuals, however, do not necessarily lead to clear thresholds in populations (31).

Modification of the effect of plasma selenium on asthma status by other factors is plausible. Selenium has, for instance, been shown to act synergistically with vitamin E in some of its biological actions (32). We were unable to show convincing evidence of effect modification by either gender or atopy. However, there was some evidence for differences in the effect of plasma selenium according to smoking status. The protective effect of selenium in nonsmokers exposed to environmental tobacco smoke was more consistent than in other groups, was significant overall and the associations of plasma selenium with asthma were significantly different between the different smoking exposure groups. Although this finding was not a primary hypothesis in this study it is in agreement with another study which found a substantial, though not significant, protective effect in those exposed

to environmental tobacco smoke (22). The finding must still be treated with some scepticism until it has been replicated.

Apart from effect modifiers the negative or positive effects in some centres could be as a result of uncontrolled confounding. It is never possible to exclude this in an observational study. Anything associated with both plasma selenium and asthma could act as a confounder and could produce either a spurious positive or negative effect or a spurious lack of association. We have accounted for place of residence, gender, age, smoking, socio-economic status, body mass index and use of supplements, and these have had relatively little effect on the estimated effects and both the negative and the positive effects associated with raised plasma selenium levels increased after this adjustment. This argues against confounding by these variables at least. Nevertheless, there are many other potential confounders and many of these have not been measured. This is particularly likely with other dietary variables which are known to be strongly correlated with each other (3) and which may interact with selenium in biological processes (32).

The plasma selenium levels among the controls are very variable and tend to be highest in the southern centres. The values are generally higher than those reported recently (4), particularly in Poland, but in this context the important fact is that the measurements were all made in a single laboratory accredited according to ISO/IEC 17025 standards and that the controls were drawn from the same populations as the controls.

The results reported here are compatible with the results of two more recent randomized trials which failed to show a benefit from supplementation of the diet of asthmatic adults with selenium (25, 33), although average plasma selenium levels in the first of these studies were such that a substantial proportion of subjects are likely to have had optimal or near optimal, glutathione peroxidase activity at the beginning of the trial. Taken together these results suggest that selenium, at levels reported in this study, is not critical in determining the prevalence of asthma. This does not, however, exclude the possibility that it is involved in specific sub-groups of patients or under specific conditions. Given the strong theoretical grounds for believing that selenium levels might influence asthma, pursuing more specific hypotheses might still be justifiable. It also does not imply that the low levels of selenium in Europe are a matter for complacency. Even in the USA, where levels are generally much higher, randomized trials have shown beneficial effects in other conditions, notably cancer (34).

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Appendix

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