Interrelation of vitamin C, infection, haemostatic factors, and cardiovascular disease

Kay-Tee Khaw, Peter Woodhouse

Abstract

Objective—To examine the hypothesis that the increase in fibrinogen concentration and respiratory infections in winter is related to seasonal variations in vitamin C status (assessed with serum ascorbate concentration).

Design—Longitudinal study of individuals seen at intervals of two months over one year.

Setting—Cambridge.

Subjects—96 men and women aged 65–74 years living in their own homes.

Main outcome measures—Haemostatic factors fibrinogen and factor VIIc; acute phase proteins; respiratory symptoms; respiratory function.

Results—Mean dietary intake of vitamin C varied from about 65 mg/24 h in winter to 90 mg/24 h in summer; mean serum ascorbate concentration ranged from 50 $\mu\text{mol/l}$ in winter to 60 $\mu\text{mol/l}$ in summer. Serum ascorbate concentration was strongly inversely related to haemostatic factors fibrinogen and factor VIIc as well as to acute phase proteins but not to self reported respiratory symptoms or neutrophil count. Serum ascorbate concentration was also related positively to forced expiratory volume in one second. An increase in dietary vitamin C of 60 mg daily (about one orange) was associated with a decrease in fibrinogen concentrations of 0.15 g/l, equivalent (according to prospective studies) to a decline of approximately 10% in risk of ischaemic heart disease.

Conclusion—High intake of vitamin C has been suggested as being protective both for respiratory infection and for cardiovascular disease. These findings support the hypothesis that vitamin C may protect against cardiovascular disease through an effect on haemostatic factors at least partly through the response to infection; this may have implications both for our understanding of the pathogenetic mechanisms in respiratory and cardiovascular disease and for the prevention of such conditions.

Introduction

Scurvy is a well recognised consequence of vitamin C deficiency; the role of vitamin C in prevention of other diseases, however, is more controversial. Pauling suggested that a high intake of vitamin C might prevent colds and influenza¹; more recently, studies have suggested that vitamin C protects against cardiovascular disease and cancer.^{2–4}

Most countries experience seasonal variations in mortality. Mortality in Britain is 20–30% higher in winter than during the rest of the year. Of the estimated 40 000 excess winter deaths annually, a third are attributed to respiratory disease and over half to cardiovascular disease, predominantly heart attacks and strokes.⁵ The cardiovascular risk factors blood pressure, cholesterol, and fibrinogen vary seasonally.^{6–8}

We recently reported that in men and women living in their own homes the observed winter rise in fibrinogen concentration was related to a winter increase in infection measured both by self reported respiratory symptoms and by biological markers including neutrophil count and α_1 antichymotrypsin.⁸ This provided a biologically plausible mechanism for the observed association between respiratory and cardiovascular disease in cross sectional and prospective studies. Why infections should occur more often in winter than in other seasons is not understood. We tested the hypothesis that vitamin C may influence the biological response to infection, concentration of haemostatic factors, and hence, risk of cardiovascular disease.

Methods

This study is described in detail elsewhere.⁸ Forty seven men and 49 women aged 65 to 74 years living in their own homes were recruited from a general practice in Cambridge. Each subject was visited at home by one investigator (PW) at intervals of two months from January 1991 to February 1992; visits were made on the same weekday and at the same time of day for a given individual to minimise the influence of circadian and weekday variation. At each visit the investigator administered a standard questionnaire that included a 24 hour dietary recall and questions on drug treatment, intake of vitamin supplements, and respiratory symptoms in the past fortnight. Forced expiratory volume in one second was determined with a pocket spirometer (Micro Medical, Kent). Blood was obtained without venostasis; subjects were not fasting. Full blood counts were measured on the same day (Coulter model STKS). Acute phase reactants C reactive protein and α_1 antichymotrypsin were estimated by immunoturbidimetry.⁹ Concentration of thrombin-clottable fibrinogen was measured with the method of Clauss¹⁰ and factor VIIc with a single stage assay with bovine adsorbed deficient plasma and rabbit brain thromboplastin that is sensitive to the more active, two chain form of factor VII.¹¹ A separate serum sample for ascorbate concentration was deproteinised with metaphosphoric acid. Total ascorbic acid concentration was measured with fluorometry. The intra-assay coefficient of variation was 2.7% and interassay coefficient of variation 3.8%.¹² The 24 hour dietary recall data were coded for specific foods and portion sizes, and the nutrient content was calculated with standard tables on food composition.¹³

Seasonal variation was modelled on the assumption that the outcome variable would follow a sinusoidal curve with a period of one year (fig 1). The curve can be described mathematically in terms of three variables: the annual mean (a), increase in annual mean (b), and the decrease in annual mean (c), with the seasonal difference, being a function of b and c . The null

Clinical Gerontology Unit,
University of Cambridge
School of Clinical
Medicine, Addenbrooke's
Hospital, Cambridge
CB2 2QQ

Kay-Tee Khaw, professor
Peter Woodhouse, research
fellow

Correspondence to:
Professor Khaw.

BMJ 1995;310:1559–63

FIG 1—Seasonal curve for hypothetical outcome variable

hypothesis of no seasonal variation corresponds to both b and c being zero and may be tested with a Wald test.¹⁴ The expected value for the outcome variable on visit (v) is given by:

$$a + b \cdot \sin(2\pi(v-1)/6) + c \cdot \cos(2\pi(v-1)/6).$$

Measurements of the outcome variable at each visit would vary randomly about the expected curve. Repeated measurements throughout the year, however, would be correlated with each other and be accounted for by generalised estimating equations¹⁵ when estimating a , b , and c . The relation between serum ascorbate, haemostatic variables, and markers of infection was analysed by linear regression with generalised estimating equations, with adjustment for age, sex, and cigarette smoking. Analyses were repeated after exclusion of subjects who reported taking vitamin C supplements at any time during the year ($n=19$) and of cigarette smokers ($n=14$).

Results

Trends for men and women were similar, so pooled data are reported here. Table I shows the mean values for the 24 hour dietary intake of vitamin C, serum ascorbate concentration, haemostatic factors, markers of the acute phase response α_1 antichymotrypsin and C reactive protein, neutrophil count, self reported colds, and forced expiratory volume in one second, all of which varied significantly seasonally. While the mean values of carotene and vitamin E showed significant seasonal variations, the pattern of variation between winter (regarded as January to February) and summer (July to August) was not consistent. Other dietary variables—notably, total caloric and alcohol intake—did not show significant seasonal changes. Behavioural variables, including physical activity, cigarette smoking, and drug treatment, did not vary

seasonally (not shown here).⁸ Selected variables are plotted in figure 2. Serum ascorbate concentration was related to dietary intake of vitamin C calculated from the 24 hour dietary recall ($r=0.40$, $P<0.0001$).

Table II shows regression coefficients of biological variables on serum ascorbate concentration after the effects of age, sex, and smoking status were adjusted for. Serum ascorbate concentration was strongly inversely related to haemostatic factors fibrinogen and factor VIIC as well as to acute phase proteins but not to self reported respiratory symptoms or neutrophil count. Serum ascorbate concentration also related positively to forced expiratory volume in one second. Dietary vitamin E and carotene intake was not significantly related to either haemostatic factors or acute phase proteins, and the significant associations of serum ascorbate concentration with these factors remained after dietary vitamin E and carotene were adjusted for in multivariate analysis.

TABLE II—Linear regression of selected variables on serum ascorbate (per 10 $\mu\text{mol/l}$), with age, sex, and cigarette smoking controlled for, in 96 men and women by use of generalised estimating equations.¹⁵ Each variable was entered separately in the multiple regression together with age, sex, and smoking status

	Regression coefficient β (95% confidence interval)	P value
Fibrinogen (g/l)	-0.04 (-0.02 to -0.06)	<0.0001
Factor VIIC (fraction of 1)	-0.015 (-0.008 to -0.023)	<0.0001
Respiratory symptoms (any in fortnight)	-0.02 (0 to -0.04)	0.1
Neutrophil count ($\times 10^9/\text{l}$)	-0.03 (0.05 to -0.08)	0.4
α_1 Antichymotrypsin (g/l)	-0.014 (-0.008 to -0.026)	<0.0001
C reactive protein (mg/l)	-0.76 (-0.41 to -1.11)	<0.0001
Forced expiratory volume in 1 second (l/s)	0.008 (0.002 to 0.140)	0.02

The 14 subjects who were cigarette smokers had significantly lower serum ascorbate concentrations than non-smokers (38 $\mu\text{mol/l}$ and 56.1 $\mu\text{mol/l}$ respectively, $P=0.004$). Mean plasma fibrinogen concentrations in smokers and non-smokers were 3.02 g/l and 2.80 g/l respectively ($P=0.006$); and mean factor VIIC concentrations were 1.30 and 1.16 ($P=0.10$). The 19 subjects who reported taking vitamin C, or multivitamins that probably contained vitamin C, at any visit during the study had significantly higher mean serum ascorbate concentrations than subjects who did not take vitamin C (70.6 $\mu\text{mol/l}$ v 49.1 $\mu\text{mol/l}$, $P<0.001$); their mean plasma fibrinogen concentrations were 2.68 g/l and 2.87 g/l respectively ($P=0.06$), and factor VIIC concentrations were 1.07 and 1.20 respectively ($P=0.10$).

Table III shows regression analyses for fibrinogen and factor VIIC on serum ascorbate concentration after exclusion of cigarette smokers ($n=14$) and of subjects who took vitamin C supplements ($n=19$); results were similar to those for the whole cohort.

TABLE I—Biological variables and dietary intake of vitamin C, by month in 96 men and women between January 1991 and February 1992 (expressed as means)

	Visit							Annual mean (SD)	P value for seasonality
	1 (Jan or Feb)	2 (Mar or Apr)	3 (May or June)	4 (July or Aug)	5 (Sept or Oct)	6 (Nov or Dec)	7 (Jan or Feb)		
Biological variables:									
Plasma fibrinogen (g/l)	2.96	2.85	2.80	2.77	2.81	2.77	2.87	2.83 (0.49)	<0.01
Factor VIII (fraction of 1)	1.22	1.16	1.15	1.15	1.18	1.16	1.19	1.17 (34.7)	<0.05
Neutrophil count ($\times 10^9$ /l)	4430	4160	4000	3940	4090	4020	4260	4110 (1.32)	<0.01
α_1 antichymotrypsin (mg/l)	0.620	0.623	0.593	0.599	0.575	0.564	0.595	0.60 (0.17)	<0.01
C reactive protein (mg/l)	7.6	6.6	4.2	2.2	3.3	2.1	4.7	4.17 (11.3)	<0.01
Forced expiratory volume (l/s)	2.18	2.15	2.17	2.18	2.20	2.18	2.09	2.16 (0.56)	<0.0001
Serum ascorbate (μ mol/l)	53.2	49.7	49.7	60.2	57.3	53.5	50.5	53.5 (24.8)	<0.0001
Patients reporting a cold (%)	19.8	20.0	12.6	5.2	4.2	10.5	22.9	13.6	<0.0001
Reported dietary intake in past 24 hours:									
Total energy (kcal/24 h)	1885	1851	1944	1902	1879	2004	2045	1930 (578)	0.2
Vitamin C (mg/24 h)	65.8	76.7	84.8	90.7	71.2	69.8	73.2	76.0 (50.1)	<0.0001
Carotene (μ g/24 h)	3866	3859	2666	3155	3651	3793	3701	3527 (3459)	<0.01
Vitamin E (mg/24 h)	2.19	2.38	2.92	2.64	2.90	2.41	2.65	2.58 (1.78)	<0.05
Alcohol (g/24 h)	5.0	4.3	4.1	5.2	3.4	4.9	4.5	4.5 (10.3)	0.9

FIG 2—Mean (SEM) concentrations of selected variables by month in 96 men and women from January 1991 to February 1992

TABLE III—Linear regression of fibrinogen and factor VIIIc concentrations on serum ascorbate (per 10 μmol/l), with age, sex, and season controlled for, in men and women by use of generalised estimating equations,¹⁵ excluding smokers and subjects taking vitamin C supplements (units as in table I)

	Regression coefficient β (95% confidence interval)	P value
Excluding 14 cigarette smokers (n=82):		
Fibrinogen (g/l)	-0.05 (-0.03 to -0.07)	<0.0001
Factor VIIIc (fraction of 1)	-0.014 (-0.006 to -0.022)	<0.0001
Excluding 19 subjects taking vitamin C supplements (n=77):		
Fibrinogen (g/l)	-0.04 (-0.02 to -0.06)	<0.001
Factor VIIIc (fraction of 1)	-0.012 (-0.003 to -0.021)	<0.01

Discussion

Our findings indicate a relation between vitamin C status (measured with serum ascorbate concentration), biological markers of infection, and haemostatic factors and support the hypothesis that vitamin C may protect against cardiovascular disease through an effect on haemostatic factors at least partly through the response to infection.

That such a relation could be shown was surprising given the potentially large measurement error in estimating intake of vitamin C and vitamin C status—determined on the basis of the 24 hour dietary recall and a single blood sample at each visit. Unlike with many other dietary variables, however, the variation among subjects in vitamin C status is greater than the variation within a subject. In any case, random measurement errors are likely to obscure any underlying relation rather than produce a spurious association.

Low social class and smoking, both of which are associated with lower ascorbate concentrations, and higher concentrations of haemostatic factors are possible confounders in cross sectional studies, but as they were constant in these subjects over the year they do not account for the longitudinal seasonal variations observed. As expected, smokers had lower ascorbate

concentrations than non-smokers. The relation between ascorbate concentrations and haemostatic factors was consistent, however, when cigarette smokers were excluded from the analysis, indicating that this association is not explained by confounding by cigarette smoking.

The relation between fibrinogen, factor VIIIc, and ascorbate concentrations was also consistent after subjects who took vitamin C supplements at any time during the year were excluded, indicating that haemostatic factors were related to variability in vitamin C status within the normal dietary range and that differences were not accounted for by supplementation.

The inverse association between haemostatic factors and serum ascorbate concentration was strong and consistent. However, only biological markers of infection—that is, C reactive protein and α₁ antichymotrypsin concentrations, not respiratory symptoms—were significantly inversely related to serum ascorbate concentrations. Reduced ascorbate concentrations may result from, rather than cause, biological responses to infection. The strong relation between serum ascorbate concentration and dietary intake of vitamin C suggests, however, that serum concentrations largely reflect dietary intake. Our findings also accord with data from trials that indicate that vitamin C may not prevent respiratory infection but may modulate the biological response, resulting in a less severe infection.¹⁶ Our findings are also compatible with observations that dietary vitamin C has a protective effect on pulmonary function.¹⁷

PROTECTIVE EFFECT OF ANTIOXIDANTS ON CARDIOVASCULAR DISEASE

Our findings are of interest for several reasons. A protective role of antioxidants such as vitamins C and E, β carotene, and selenium in cardiovascular disease has been suggested. Several prospective studies have documented an inverse relation between intake of vitamin C and cardiovascular disease^{3 18}; however, the American male doctors' and the nurses' health studies, which found a strong protective effect of vitamin E supplementation for coronary heart disease, reported no independent relation between vitamin C and coronary heart disease after intake of vitamin E was adjusted for.^{19 20} These studies used self reported dietary intake, not biological determinations of vitamin C status, and measurement error—and hence lack of power—could account for the inconsistency between the studies. Two recent prospective studies from Switzerland and Finland that used blood ascorbate concentrations measured at baseline found that low vitamin C status predicted myocardial infarction.^{21 22} The Finnish study reported that low ascorbate concentration was associated with a 2.7-fold increase in risk of myocardial infarction independent of other risk factors.²² A secondary prevention trial of a Mediterranean diet showed a 70% reduction in myocardial infarction and mortality independent of an effect on blood pressure and lipids; though the intervention was primarily focused on oleic and α linolenic acid, intake of vitamin C, as well as plasma vitamin C concentrations, significantly increased in the active intervention group.²³ The traditional model is that any protective effect on heart disease of antioxidants such as vitamins C and E is mediated through oxidation of low density lipoprotein cholesterol; our results, however, suggest an alternative mechanism for vitamin C involving inflammation and haemostasis.

INFECTION AND HAEMOSTASIS AND CARDIOVASCULAR DISEASE

Fibrinogen and factor VIIIc are well recognised risk factors for myocardial infarction and stroke.²⁴⁻²⁶ Evidence also exists that chronic and acute infection

and a raised white cell count are risk factors for cardiovascular disease.²⁷⁻²⁹ Infection may contribute towards inflammatory processes occurring in atherosclerosis.³⁰ Fibrinogen, C reactive protein, and α_1 antichymotrypsin are all acute phase proteins that are synthesised by hepatocytes in increased amounts during inflammatory processes. This synthesis is mediated mainly by interleukin 6, produced by monocytes and macrophages.³¹ Increased concentrations of fibrinogen provide a biologically plausible mechanism by which acute or chronic infection could increase cardiovascular risk.

HYPOTHESIS: ROLE OF VITAMIN C

While haemostatic factors, infections, and intake of vitamin C have separately been implicated as risk factors for cardiovascular disease, our results support the hypothesis that they may share a common biological pathway. This may give clues as to possible biological mechanisms involving antioxidants, inflammation, haemostasis, and atherosclerosis. Thus a winter reduction in dietary intake of vitamin C, leading to lower serum ascorbate concentrations, may be related to increased susceptibility to infection in winter and subsequently to an increase in levels of haemostatic factors and increased cardiovascular mortality.

This hypothesis may also provide an explanation for several disparate observations. While deaths from influenza contribute only a small proportion of the total excess winter mortality, the size of the winter excess in cardiovascular mortality in different years is closely related to influenza epidemics,⁵ suggesting that a high prevalence of infection is directly associated with increased cardiovascular risk in the general population. Additionally, respiratory and cardiovascular health are closely related: poor respiratory function is a strong predictor of subsequent cardiovascular mortality, independent of cigarette smoking.³² The pronounced social class gradient in coronary heart disease, independent of classic risk factors such as blood pressure, cigarette smoking, and lipid concentrations,³³ may be better explained by the higher levels of chronic and acute infection and of fibrinogen,³⁴ and lower intake of vitamin C³⁵ in individuals of low socioeconomic status.

HEALTH IMPLICATIONS

These observations also have clinical and public health implications. The important determinants of vitamin C status were dietary food sources, not supplements. The estimated average intake of vitamin C (mean 77 mg daily) and corresponding concentration of serum ascorbate (mean 54 $\mu\text{mol/l}$) were relatively low and the seasonal variation modest. Variations in haemostatic variables and infection markers were apparent within this range. Our findings suggest that large doses of vitamin C (several grams daily, as recommended by Pauling¹) may not be necessary. Even increasing mean daily intake of vitamin C from food sources within the usual seasonal dietary range from 65 mg to 90 mg or an increase in mean serum ascorbate concentration from 50 $\mu\text{mol/l}$ to 60 $\mu\text{mol/l}$ had a measurable impact on risk factors. On the basis of estimates from our study, an increase in dietary vitamin C of 60 mg daily (about one orange) was associated with a decrease in fibrinogen concentration of 0.15 g/l, equivalent to a decline of about 10% in risk of ischaemic heart disease.²³ This estimate is compatible with data from population studies that show that increasing daily intake of fruit or vegetables (the major source of vitamin C) by two to three servings is associated with a 20-40% decline in risk of stroke and 25% decline in risk of ischaemic heart disease.³⁶⁻³⁸

Key messages

- Mortality from respiratory and cardiovascular causes increases by about 20% in winter in most countries
- A winter increase in fibrinogen concentration has been associated with a winter increase in respiratory infection
- Vitamin C status is related to fibrinogen and factor VIIc concentrations as well as markers of infections including acute phase proteins and to respiratory function
- Maintaining adequate vitamin C intake—for example, by eating an extra orange daily—may reduce some of the seasonal variation in mortality
- Differences in vitamin C status, infection, and fibrinogen concentration might explain some of the observed socioeconomic differential in respiratory and cardiovascular disease

The hypothesis that vitamin C may protect against cardiovascular disease through an effect on haemostatic factors at least partly through the response to infection needs further investigation and may have implications both for our understanding of the pathogenetic mechanisms in respiratory and cardiovascular disease and for the prevention of such conditions. The limitations of observational studies are well recognised, and insufficient evidence exists to support widespread use of vitamin C supplements. Nevertheless, these findings further support the public health advice to increase intake of fruit and vegetables and suggest that maintaining intake in winter may be of particular value.

We thank the participants and the doctors of the general practice in this study, which was supported by the Medical Research Council (SPG 8913493).

- 1 Pauling L. Vitamin C and the common cold and the flu. San Francisco: W H Freeman, 1970.
- 2 Simon JA. Vitamin C and cardiovascular disease: a review. *J Am Coll Nutr* 1992;11:107-25.
- 3 Enstrom JE, Kanim LE, Klein MA. Vitamin C intake and mortality among a sample of the United States population. *Epidemiology* 1992;3:194-202.
- 4 Block G. Vitamin C and cancer prevention: the epidemiologic evidence. *Am J Clin Nutr* 1991;53:270-82S.
- 5 Curwen M. Excess winter mortality: a British phenomenon? *Health Trends* 1991;22:169-75.
- 6 Woodhouse P, Khaw KT, Plummer M. Seasonal variation in blood pressure in relation to temperature in elderly men and women. *J Hypertens* 1993;11:1267-74.
- 7 Gordon DJ, Hyde J, Trost DC, Whaley FS, Hannan PJ, Jacobs DR, Ekelund LG. Cyclic seasonal variation in plasma lipid and lipoprotein levels: the Lipid Research Clinics Coronary Primary Prevention Trial Placebo Group. *J Clin Epidemiol* 1988;41:679-89.
- 8 Woodhouse PR, Khaw KT, Meade TW, Stirling Y, Plummer M. Seasonal variations of plasma fibrinogen and factor VII activity in the elderly: winter infections and death from cardiovascular disease. *Lancet* 1994;343:435-9.
- 9 Calvin J, Price CP. Measurement of serum α_1 antichymotrypsin by immunoturbidimetry. *Ann Clin Biochem* 1986;23:206-9.
- 10 Clauss A. Gerinnungsphysiologische Schnellmethode zur Bestimmung des Fibrinogens. *Acta Haematol* 1957;17:237-46.
- 11 Miller GJ, Walter SJ, Stirling Y, Thompson SG, Esnouf MP. Assay of factor VII activity by two techniques: evidence for increased conversion of VII to α VIIa in hyperlipidaemia, with possible implications for ischaemic heart disease. *Br J Haematol* 1985;59:249-58.
- 12 Vuilleumier JP, Keck E. Fluorometric assay of vitamin C in biological materials using a centrifugal analyser with fluorescence attachment. *Journal of Micronutrient Analysis* 1989;5:25-34.
- 13 Paul AA, Southgate DAT. *McCance and Widdowson's the composition of foods*. 4th ed. London: HMSO, 1978.
- 14 Rao CR. *Linear statistical inference and its applications*. 2nd ed. New York: Wiley, 1973:418-9.
- 15 Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;42:121-30.
- 16 Hemila H. Vitamin C and the common cold. *Br J Nutr* 1992;67:3-16.
- 17 Schwartz J, Weiss ST. Relationship between dietary vitamin C intake and pulmonary function in the first national health and nutrition examination survey (NHANES I). *Am J Clin Nutr* 1994;59:110-4.
- 18 Vollset SE, Bjelke E. Does consumption of fruit and vegetables protect against stroke? *Lancet* 1983;ii:742.
- 19 Rimm EB, Stampfer MJ, Ascherio A, Giovannucci E, Colditz GA, Willett WC. Vitamin E consumption and the risk of coronary heart disease in men. *N Engl J Med* 1993;328:1450-9.

- 20 Stampfer MJ, Hennekens CH, Manson JE, Colditz GA, Rosner B, Willett WC, *et al.* Vitamin E consumption and the risk of coronary heart disease in women. *N Engl J Med* 1993;328:1444-9.
- 21 Gey KF, Stahelin HB, Eichholzer. Poor plasma status of carotene and vitamin C is associated with higher mortality from ischemic heart disease and stroke: Basel prospective study. *Clin Invest* 1993;71:3-6.
- 22 Nyyssonen K, Parvianen MT, Salonen R, Korpela H, Tuomilehto J, Salonen JT. Vitamin C deficiency is associated with high risk of myocardial infarction in eastern Finnish men. *Eur Heart J* 1994;15(suppl):168.
- 23 De Lorgeril M, Renaud S, Mamelle N, Salen P, Martin JL, Monjaud I, *et al.* Mediterranean α linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 1994;343:1454-9.
- 24 Meade TW, Mellowes S, Brozovic M, Chakraborti RR, Haines AP, Imeson JD, *et al.* Haemostatic function and ischaemic heart disease: principal results of the Northwick Park heart study. *Lancet* 1986;iii:533-7.
- 25 Wilhelmsen L, Svardstudd K, Korsan-Bengtson K, Larsson B, Welin L, Tibblin G. Fibrinogen as a risk factor for stroke and myocardial infarction. *N Engl J Med* 1984;311:501-5.
- 26 Qizilbash N, Jones L, Warlow C, Mann J. Fibrinogen and lipid concentrations as risk factors for transient ischaemic attacks and minor ischaemic strokes. *BMJ* 1991;303:605-9.
- 27 Syrjanen J, Valtonen VV, Iivanainen M, Kaste M, Huttunen JK. Preceding infection as an important risk factor for ischaemic brain infarction in young and middle aged patients. *BMJ* 1988;296:1156-60.
- 28 Spodick DH, Flessas AP, Johnson MM. Association of acute respiratory symptoms with onset of acute myocardial infarction: prospective investigation of 150 consecutive patients and matched control patients. *Am J Cardiol* 1984;53:481-2.
- 29 Kannel WB, Anderson K, Wilson WF. White blood cell count and cardiovascular disease. *JAMA* 1992;267:1253-6.
- 30 Alexander RW. Inflammation and coronary artery disease. *N Engl J Med* 1994;331:468-9.
- 31 Akira S, Kishimoto T. IL-6 and NF-IL6 in acute phase response and viral infection. *Immunol Rev* 1992;127:25-50.
- 32 Strachan DP. Ventilatory function, height and mortality among lifelong non-smokers. *J Epidemiol Community Health* 1992;46:66-70.
- 33 Marmot MG, Rose G, Shipley M, Hamilton PJS. Employment grade and coronary heart disease in British civil servants. *J Epidemiol Community Health* 1978;32:244-9.
- 34 Wilson TW, Kaplan GA, Kauhanen J, Cohen RD, Wu M, Salonen R, *et al.* Association between plasma fibrinogen concentration and five socioeconomic indices in the Kuopio ischemic heart disease risk factor study. *Am J Epidemiol* 1993;137:292-300.
- 35 Gregory J, Foster K, Tyler H, Wiseman M. *The dietary and nutritional survey of British adults*. London: HMSO, 1990:126-52.
- 36 Khaw KT, Barrett-Connor E. Dietary potassium and stroke associated mortality. *N Engl J Med* 1987;316:235-40.
- 37 Khaw KT, Barrett-Connor E. Dietary fiber and reduced ischaemic heart disease mortality rates in men and women: a 12 year prospective study. *Am J Epidemiol* 1987;126:1093-102.
- 38 Gillman M, Cupples L, Gagnon D, Posner B, Ellison R, Castelli W, *et al.* Protective effect of fruits and vegetables on development of stroke. *Am J Epidemiol* 1994;139:547.

(Accepted 15 May 1995)

Vitamin C and risk of death from stroke and coronary heart disease in cohort of elderly people

Catharine R Gale, Christopher N Martyn, Paul D Winter, Cyrus Cooper

Abstract

Objectives—To determine whether vitamin C status, as measured by dietary intake and plasma ascorbic acid concentration, is related to mortality from stroke and coronary heart disease in people aged 65 and over.

Design—A 20 year follow up study of a cohort of randomly selected elderly people living in the community who had taken part in the 1973-4 Department of Health and Social Security nutritional survey and for whom dietary and other data had been recorded.

Setting—Eight areas in Britain (five in England, two in Scotland, and one in Wales).

Subjects—730 men and women who had completed a seven day dietary record and who had no history or symptoms of stroke, cerebral arteriosclerosis, or coronary heart disease when examined by a geriatrician in 1973-4.

Results—Mortality from stroke was highest in those with the lowest vitamin C status. Those in the highest third of the distribution of vitamin C intake had a relative risk of 0.5 (95% confidence interval 0.3 to 0.8) compared with those in the lowest third, after adjustment for age, sex, and established cardiovascular risk factors. The relation between vitamin C intake and stroke was independent of social class and other dietary variables. A similar gradient in risk was present for plasma ascorbic acid concentrations. No association was found between vitamin C status and risk of death from coronary heart disease.

Conclusion—In elderly people vitamin C concentration, whether measured by dietary intake or plasma concentration of ascorbic acid, is strongly related to subsequent risk of death from stroke but not from coronary heart disease.

Introduction

Antioxidant vitamins may be important in protecting low density lipoproteins from oxidation by free radicals.^{1,2} Because oxidative modification of low density lipoproteins may enhance their atherogenic potential,³ dietary antioxidants have a potential role in the prevention of cardiovascular disease. The most

important dietary antioxidant in terms of intake is vitamin C, and evidence from ecological studies links low intake of this vitamin with increased rates of cardiovascular disease. In Britain, for example, rates of stroke and coronary heart disease are highest in regions where consumption of fruit and vegetables is lowest.^{4,5}

During 1973-4 the Department of Health and Social Security surveyed random samples of people aged 65 and over living in eight areas of Britain (five in England, two in Scotland, and one in Wales) to assess the nutritional state of the elderly population. The areas were chosen so that the socioeconomic characteristics of the study sample were representative of non-institutionalised elderly people in Britain. We examined the association between vitamin C status, as measured by either dietary intake or plasma ascorbic acid concentration, and mortality from stroke and coronary heart disease in a 20 year follow up study of this national sample.

Subjects and methods

During 1973 and 1974, 1775 people were randomly sampled in eight areas of the country from family practitioner committee lists of all patients aged 65 and over. The areas were Islington, Harrow, Hastings, Bristol, Salford, Rutherglen, Angus, and Merthyr Tydfil. Stratified sampling was used to obtain equal numbers of men and women aged 65 to 74 and 75 and over.

Of those selected, 1688 were living in the community and were asked to take part in the study; 1419 (84%) agreed. Of those who participated, 983 (69%) agreed to be examined by a geriatrician (58% of those originally selected took part).

Participants kept a diary of every item of food or drink consumed over a week. They were provided with a set of scales to weigh each item. An interviewer visited them at least four times. If the participants were unable to cope with the weighing procedure, the interviewer used the food diary to quantify their consumption; food purchases were used as a cross check. Nutrient intake was calculated by using a food composition table

MRC Environmental Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton SO16 6YD
Catharine R Gale, research student
Christopher N Martyn, clinical scientist
Paul D Winter, computing manager
Cyrus Cooper, clinical scientist

Correspondence to: Dr Martyn.

BMJ 1995;310:1563-6