Vitamin C and Hyperglycemia in the European Prospective Investigation Into Cancer—Norfolk (EPIC-Norfolk) Study

A population-based study

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OBJECTIVE — To examine the cross-sectional association between plasma vitamin C, self-reported diabetes, and HbA_{1c}.

RESEARCH DESIGN AND METHODS — Data from a population-based study of diet, cancer, and chronic disease were analyzed. A total of 2,898 men and 3,560 women 45–74 years of age who were registered with general practices in Norfolk, U.K., were recruited to the European Prospective Investigation Into Cancer—Norfolk study between 1995 and 1998.

RESULTS — Mean plasma vitamin C levels were significantly higher in individuals with HbA_{1c} levels <7% than in those with self-reported diabetes or prevalent undiagnosed hyperglycemia (HbA_{1c} ≥7%). An inverse gradient of mean plasma vitamin C was found in both sexes across quintiles of HbA_{1c} distribution <7%. The odds ratio (95% CI) of having prevalent undiagnosed hyperglycemia per 20 µmol/l (or 1 SD) increase in plasma vitamin C was 0.70 (0.52–0.95) (adjusted for sex, age, BMI, waist-to-hip ratio, tertiary education, any use of dietary supplements, vegetarian diet, alcohol consumption, physical activity, dietary vitamin E, dietary fiber, dietary saturated fat, and smoking history). The unadjusted change in HbA_{1c} per 20 µmol/l increase in vitamin C estimated by linear regression was −0.12% (−0.14 to −0.09) in men and −0.09% (−0.11 to −0.07) in women. After adjusting for the possible confounders, these values were −0.08% (−0.11 to −0.04) in men and −0.05% (−0.07 to −0.03) in women.

CONCLUSIONS — An inverse association was found between plasma vitamin C and HbA_{1c}. Dietary measures to increase plasma vitamin C may be an important public health strategy for reducing the prevalence of diabetes.

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Vitamin C is a water-soluble antioxidant vitamin that is thought to be important in preventing cellular damage from oxidative stress (1–3). People with diabetes are reported to have lower circulating vitamin C levels than nondiabetic subjects (4). Lower vitamin C levels in diabetic subjects may result from increased oxidative stress associated with the disease process (5,6) or may indicate a role of vitamin C in the risk of developing diabetes.

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Abbreviations: ANOVA, analysis of variance; EPIC-Norfolk, European Prospective Investigation Into Cancer—Norfolk; HPLC, high-performance liquid chromatography; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

A review of human studies regarding vitamin C status in diabetes concluded that these studies were generally based on small numbers of often highly selected cases from hospital clinics with limited information regarding possible confounders (4). We present data from a large population-based study to examine the association between plasma vitamin C and glucose tolerance.

RESEARCH DESIGN AND METHODS

Subjects and measurements

Subjects for this analysis were recruited between 1995 and 1997 as part of the East Anglian region component of the European Prospective Investigation Into Cancer—Norfolk (EPIC-Norfolk) study. EPIC-Norfolk is a multicenter international cohort study designed to investigate the relationships among diet, cancer, and chronic disease. The detailed design and operation of the study have been previously described (7,8).

At the baseline survey between 1993 and 1998, men and women 45–74 years of age were identified from general practice patient lists and were invited to participate in the study. Subjects who volunteered completed a detailed health and lifestyle questionnaire. They were asked about personal illness with the question "Has the doctor ever told you that you have any of the following?" Options included hypertension requiring treatment with drugs, hyperlipidemia, myocardial infarction, stroke, diabetes (excluding gestational diabetes), and cancer. Family history of diabetes was ascertained by a positive response to the diabetes option of the question "Have any of your immediate family had any of the following conditions?" Subjects recorded the approximate age at which diabetes first occurred in their mothers, fathers, and/or siblings.

Smoking history was derived from yes/no responses to the questions "Have you ever smoked as much as 1 cigarette a day for as long as a year?" and "Do you smoke cigarettes now?" The question "Did

you have any further education at college or university after you left school?" identified those who had tertiary education.

Subjects were classified as vegetarians if they gave a positive response to the vegetarian option of the question "Do you follow any particular diets?" and as supplement takers if they answered "yes" to the question "Have you taken any vitamin, minerals, or other food supplements regularly during the past year (such as vitamin C, vitamin D, iron, calcium, fish oils, primrose oil, beta carotene, etc.)?" Data on dietary intake of saturated fat, vitamin E, and fiber and on alcohol consumption were obtained from food frequency questionnaires (8,9).

Subjects were asked to choose among four options to describe the type and amount of physical activity involved in their work. These options were sedentary (mostly sitting), standing (mostly standing or walking but no intense physical activity), physical work (handling heavy objects and use of tools), or heavy manual work (very vigorous physical activity). A validation study showed that this question was a valid measure of usual energy expenditure (10). Subjects also recorded the hours spent each week on leisure-time physical activity during the summer and winter, and the average was calculated (11)

For the purpose of identifying subjects who may have consciously altered their lifestyles, we defined subjects with "known diabetes" as those who reported themselves as either being told by a physician that they have diabetes or who responded positively to the diabetes option of the question "Have you modified your diet in the past year (give reasons)?"

After completing the questionnaire, the subjects were invited to attend the general practice surgery where research nurses performed a health check. Height and weight were measured with subjects in light clothing and with their 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. These were used to calculate the BMI as weight in kilograms divided by height in meters squared. Waist circumference was measured at the smallest circumference between the ribs and iliac crest to the nearest 0.1 cm, and hip circumference was measured as the maximum circumference between the iliac crest and the crotch to the nearest 0.1 cm. These measurements were used to calculate the waist-to-hip ratio (WHR).

Consent to have blood taken was obtained from 95% of subjects who had blood taken after the health check. Plasma vitamin C levels were measured from blood drawn into citrate bottles. The blood was stored overnight in a dark box in a refrigerator at 4–7°C and then spun at 2,100*g* for 15 min 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 estimated using a fluorometric assay within 1 week of sampling (12). The coefficient of variation was 5.6% at the lower end of the range (mean 33.2 μmol/l) and 4.6% at the upper end of the range (mean 102.3 μmol/l).

Beginning in November 1995, a sample of EDTA-anticoagulated blood was taken for HbA_{1c} measurement. The blood was stored in a refrigerator at 4–7°C until it was transported at an ambient temperature within a week of sampling to be assayed. The HbA_{1c} assays were carried out using high-performance liquid chromatography (HPLC) on a Bio-Rad Diamat (Richmond, CA) (13). The coefficient of variation was 3.6% at the lower end of the range (mean 4.94%) and 3.0% at the upper end of the range (mean 9.76%).

Statistical analysis

Subjects who had completed the health and lifestyle questionnaire and health check, had given blood for HbA_{1c} determinations and vitamin C measurement, and had complete data entry by July 1998 formed the study population. Of the 10,242 subjects recruited after November 1995, 6,596 met these criteria. This population was divided into 3 groups: self-reported diabetes (physician diagnosis or dietary modification because of diabetes), prevalent previously undiagnosed hyperglycemia ($HbA_{1c} \geq 7\%$ and no treatment for diabetes), and others (classified as having normal glucose tolerance [$HbA_{1c} < 7\%$ and no history of diabetes]). A cutoff point of 7% was chosen because only 4% of individuals would be misclassified as having normal glucose tolerance above this level (14). Comparisons were made separately for the sexes among the 3 groups for plasma vitamin C, HbA_{1c}, and possible confounding factors. The subjects were then divided into quintiles based on plasma vitamin C level after excluding those with self-reported diabetes. Comparisons were made separately for men and women using common quintiles.

Statistical analysis was performed using SAS Version 6.12 (SAS Institute, Cary, NC). Significance testing was done using analysis of variance (ANOVA) with a post-ANOVA *t* test comparison for means and the χ^2 test for proportions. A value of $P < 0.05$ was used for statistical significance. The risk of prevalent undiagnosed hyperglycemia was analyzed using logistical regression. Adjustment for possible confounders of the association between plasma vitamin C and HbA_{1c} was performed using linear regression.

RESULTS — We present data on all 2,898 men and 3,560 women who comprised 98% of the subjects who were recruited to the EPIC-Norfolk study between 1995 and 1997 and had complete data available by July 1998. Data on HbA_{1c} measurement were missing in 138 (2%) subjects. No differences were evident regarding age, BMI, and plasma vitamin C level between the population defined for this analysis and the entire EPIC-Norfolk cohort ($P > 0.5$ for each variable).

The distribution of variables by glycemic status is shown in Table 1. Of the 176 individuals classified as having self-reported diabetes, 137 reported having a physician's diagnosis, and 39 indicated that they had modified their diets as a result of diabetes without reporting a physician's diagnosis of diabetes. Of these 39 individuals, 28 reported that they were taking medication for diabetes or had an HbA_{1c} level ≥7%. Subjects with self-reported diabetes or an HbA_{1c} level ≥7% were significantly older and heavier than their counterparts who were classified as normoglycemic. Mean plasma vitamin C levels were significantly higher in men and women with an HbA_{1c} level <7% than in subjects with self-reported diabetes or an HbA_{1c} level ≥7% ($P < 0.001$). Among women, vitamin C levels were similar in subjects with self-reported diabetes compared with subjects with undiagnosed hyperglycemia. In men with undiagnosed hyperglycemia, vitamin C levels were lower than in men with self-reported diabetes, but this difference was not statistically significant ($P = 0.11$). After adjusting for covariates (Table 1) in men and women, the difference in mean plasma vitamin C concentrations between normoglycemic and hyperglycemic subjects remained significant ($P = 0.001$ men, $P < 0.001$ women).

Women with an HbA_{1c} level <7% were significantly more likely to take supplements than women with hyperglycemia ($P = 0.005$). No significant differences were

Table 1—*Characteristics of the 2,898 men and 3,560 women 45–74 years of age in the EPIC-Norfolk cohort (1995–1997) by glycemic status (self-reported diabetes, prevalent previously undiagnosed hyperglycemia, and others)*

	Men			Women		
	Self-reported diabetes	Prevalent undiagnosed hyperglycemia	Others	Self-reported diabetes	Prevalent undiagnosed hyperglycemia	Others
n	103	44	2,751	73	30	3,457
HbA_{1c} (%)	8.08 ± 1.88	8.27 ± 1.34	5.31 ± 0.55*	8.41 ± 2.12	8.65 ± 1.85†	5.29 ± 0.55*
Age (years)	65.9 ± 7.2	66.2 ± 7.5	59.1 ± 9.2*	64.4 ± 7.4	66.1 ± 7.4	58.5 ± 9.3*
BMI (kg/m^2)	28.4 ± 3.8	28.5 ± 3.4	26.6 ± 3.3*	29.4 ± 5.56	30.8 ± 5.8	26.1 ± 4.2*
WHR	0.96 ± 0.06	0.97 ± 0.06	0.93 ± 0.06*	0.85 ± 0.07	0.86 ± 0.06	0.79 ± 0.06*
Current smokers‡	7.9	9.5	13.0§	5.6	20.0	11.4
College or university education	35.0	31.8	40.5	19.2	37.9§	33.6§
Taking any dietary supplements	34.3	35.7	36.3	40.3	35.7	52.2§
Following a vegetarian diet	1.9	4.6	4.2	8.2	6.7	6.6
Occupational physical activity among workers (% sedentary)‡	50.9	55.0	38.0	57.1	35.7	36.7
Plasma vitamin C (μmol/l)	40.6 ± 17.1	35.7 ± 16.7	46.2 ± 19.5‖	47.1 ± 16.8	47.5 ± 17.6	57.8 ± 20.3*
Age-adjusted mean plasma vitamin C (μmol/l)	41.5	36.6	46.1*	47.6	48.1	57.8*
Adjusted mean plasma vitamin C (μmol/l)	41.8	38.5	46.2*	49.0	55.0	57.9§

Data are *n*, means ± SD, %, or means. Plasma vitamin C was adjusted for age, BMI, WHR, supplement taking, smoking history, vegetarian diet, physical activity, alcohol consumption, dietary vitamin E, dietary fiber, and dietary saturated fat. *$P < 0.05$ compared with both self-reported diabetes and prevalent undiagnosed glucose intolerance; †$P < 0.05$ compared with both self-reported diabetes and others; ‡smoking history in each sex is compared for proportion of current, former, and never smokers in each of the glucose tolerance categories; §$P < 0.05$ compared with self-reported diabetes only; ‖$P < 0.05$ compared with prevalent undiagnosed glucose intolerance only.

noted in men ($P = 0.7$). Men and women with self-reported diabetes were less likely to be current smokers, but the differences were not statistically significant ($P = 0.14$ men, $P = 0.12$ women). Women with self-reported diabetes were more likely to be sedentary than women with an HbA_{1c} level <7% ($P = 0.01$).

When the subjects with an HbA_{1c} level <7% were divided into quintiles of HbA_{1c} distribution, a gradient was found in mean plasma vitamin C levels in both men and

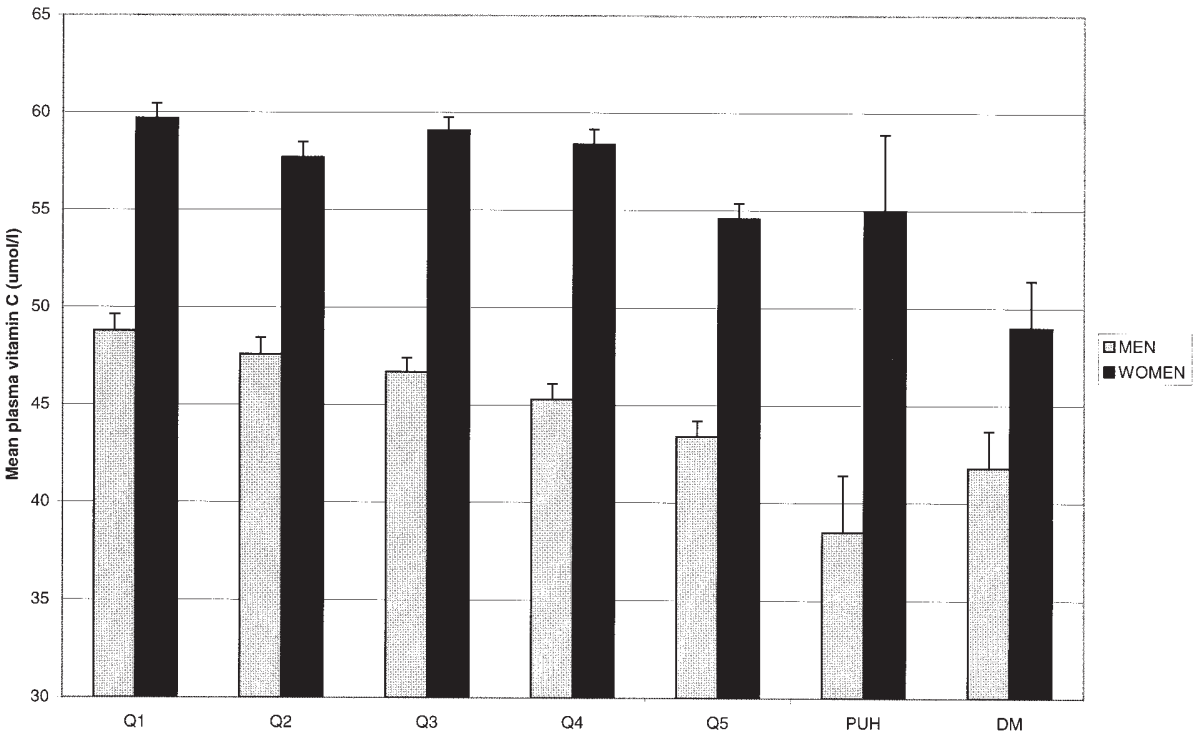

Figure 1—*Adjusted mean plasma vitamin C levels by glycemic status in 3,237 men and 3,965 women 45–74 years of age, EPIC-Norfolk cohort 1995–1997. DM, self-reported diabetes; PUH, prevalent undiagnosed hyperglycemia; Q1–Q5, quintiles of HbA_{1c} distribution <7%. Bars represent SEM.*

Table 2—*Characteristics of 2,795 men 45–74 years of age in the EPIC-Norfolk cohort (1995–1997) by quintiles of plasma vitamin C (excluding self-reported diabetes)*

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P*
Plasma vitamin C (μmol/l)	23.0 ± 8.3 (4–35)	42.3 ± 3.7 (36–48)	52.9 ± 2.6 (49–57)	62.3 ± 3.2 (58–68)	80.7 ± 14.5 (69–175)	—
n	809	690	569	435	292	—
Age (years)	60.3 ± 9.3	59.1 ± 9.0	58.6 ± 9.5	59.1 ± 9.0	58.3 ± 9.3	0.002
BMI (kg/m^2)	27.0 ± 3.6	27.0 ± 3.2	26.6 ± 3.1	26.1 ± 3.1	25.7 ± 2.9	<0.001
WHR	0.94 ± 0.06	0.94 ± 0.05	0.93 ± 0.06	0.92 ± 0.05	0.91 ± 0.05	<0.001
Current smokers	23.3	9.3	8.6	7.7	9.4	0.001*
College or university education	32.9	39.2	43.7	48.5	45.3	0.001
Taking any dietary supplements	24.4	33.9	39.8	42.8	58.7	0.001
Following a vegetarian diet	2.7	3.6	4.4	4.6	8.9	0.001
Occupational physical activity among workers (% sedentary)	34.1	38.9	39.5	41.1	39.6	0.08†
Prevalence of undiagnosed hyperglycemia	2.8 (23)	1.6 (11)	1.1 (6)	0.7 (3)	0.3 (1)	0.006
HbA_{1c} (%)	5.52 ± 0.77	5.38 ± 0.68	5.27 ± 0.63	5.27 ± 0.63	5.20 ± 0.49	<0.001
Age-adjusted mean HbA_{1c} (%)	5.50	5.38	5.28	5.27	5.21	<0.001
Adjusted mean HbA_{1c} (%)	5.47	5.38	5.30	5.28	5.22	<0.001

Data are *n*, means ± SD (ranges), %, % (*n*), or means. HbA_{1c} was adjusted for age, BMI, WHR, supplement taking, smoking history, vegetarian diet, physical activity, alcohol consumption, dietary vitamin E, dietary fiber, and dietary saturated fat. *Comparison of proportion by 3 categories of smoking history (never, former, and current); †comparison of proportion by 4 categories of occupational physical activity among workers (sedentary, standing, physical work, and heavy manual work).

women. Subjects in the lowest quintile of HbA_{1c} level had the highest mean plasma vitamin C levels, and subjects in the highest quintile of HbA_{1c} level had the lowest mean plasma vitamin C levels. The means were significantly different across quintiles in both sexes ($P = 0.0001$) (Fig. 1).

The relationship between HbA_{1c} and plasma vitamin C levels with possible confounding factors is shown in Tables 2 and 3 for men and women, respectively. The distribution of these factors across the quintiles of plasma vitamin C concentration was similar in both sexes. Subjects in the lowest quintile of plasma vitamin C level had the highest mean HbA_{1c} level but were also older and heavier than subjects in the highest quintiles. Subjects in the lowest quintile were the most likely to be current smokers and the least likely to take supplements.

Prevalent undiagnosed hyperglycemia ($n = 74$) was the dependent variable in logistical regression, and subjects with self-reported diabetes were excluded from the analysis. An increase of 20 μmol/l (or 1 SD) in plasma vitamin C level (approximately equivalent to 1 orange daily) was associated with a reduction in the risk of having prevalent undiagnosed hyperglycemia. The odds ratio (95% CI) was 0.70 (0.52–0.95) and was independent of sex, age, BMI, supplement taking, smoking history, a vegetarian diet, physical activity, alcohol consumption, dietary vitamin E, dietary fiber, and dietary saturated fat.

The association between HbA_{1c} and plasma vitamin C was further investigated with linear regression. An inverse relationship was found in both men and women and was demonstrated in all subgroups analyzed. The unadjusted change in HbA_{1c} per 20-μmol/l increase in vitamin C was −0.12% (−0.14 to −0.09) in men and −0.09% (−0.11 to −0.07) in women. After adjusting for the possible confounders, these values were −0.08% (−0.11 to −0.04) in men and −0.05% (−0.07 to −0.03) in women.

CONCLUSIONS — Our findings in this study confirm the observation that subjects with diabetes have lower plasma vitamin C levels than subjects without diabetes. We also demonstrated reduced plasma vitamin C levels in subjects who were likely to have undiagnosed diabetes. These results are not likely because of chance and support the hypothesis that the association between diabetes and vitamin C is not because of behavioral or dietary change resulting from the diagnosis. In addition, we demonstrated an inverse relationship between plasma vitamin C and HbA_{1c} levels in both men and women. This association was independent of age, BMI, WHR, educational status, supplement taking, smoking history, alcohol consumption, physical activity, dietary vitamin E, dietary fiber, dietary saturated fat, and self-reported vegetarianism.

We chose a sensitive definition of diabetes to exclude individuals who may have changed their behavior and diet as a result of having diabetes. Although no validation of the diagnoses was done, subjects were recruited through general practices, and therefore a report of physician-diagnosed diabetes is likely to be correct. Of the subjects who reported only modifying their diet because of diabetes, 72% were also taking diabetic medication or had an HbA_{1c} measurement >7%.

The EPIC-Norfolk study was designed as a prospective cohort study and was not primarily intended to give reliable population prevalence estimates. The planned analysis aimed to examine comparisons within the cohort cross-sectionally and over time (8). Nevertheless, the distributions of BMI and blood pressure are similar to those from nationally representative samples (8,15). The within-population associations are not likely to be because of selection bias.

Seasonality could be a possible confounder because seasonal trends have been described with various measures of glucose tolerance (16,17). However, we found no seasonal trend in HbA_{1c} in our study. Dietary intake of vitamin C may be one of

Table 3—*Characteristics of 3,487 women 45–74 years of age in the EPIC-Norfolk cohort (1995–1997) by quintiles of plasma vitamin C (excluding self-reported diabetes)*

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P*
Plasma vitamin C (μmol/l)	23.3 ± 7.9 (5–35)	42.8 ± 3.6 (36–48)	53.2 ± 2.6 (49–57)	62.9 ± 3.2 (58–68)	80.8 ± 14.0 (69–242)	—
n	457	540	653	884	953	—
Age (years)	59.6 ± 9.7	59.7 ± 9.4	58.2 ± 9.3	58.0 ± 9.1	58.4 ± 9.1	0.001
BMI (kg/m^2)	27.1 ± 4.8	27.0 ± 4.8	26.5 ± 4.2	26.0 ± 4.2	25.1 ± 3.5	<0.001
WHR	0.82 ± 0.06	0.81 ± 0.06	0.80 ± 0.06	0.79 ± 0.06	0.78 ± 0.06	<0.001
Current smokers	28.8	13.0	10.1	8.0	6.6	0.001*
College or university education	24.7	30.9	31.5	34.8	39.9	0.001
Taking any dietary supplements	37.7	47.6	50.7	55.8	64.0	0.001
Following a vegetarian diet	4.8	6.1	7.2	6.8	7.2	0.46
Occupational physical activity among workers (% sedentary)	34.2	34.7	35.5	37.4	36.6	0.043†
Prevalence of undiagnosed hyperglycemia	1.3 (6)	2.2 (12)	0.6 (4)	0.5 (4)	0.4 (4)	0.002
HbA_{1c} (%)	5.53 ± 0.74	5.41 ± 0.76	5.32 ± 0.62	5.26 ± 0.56	5.22 ± 0.63	<0.001
Age-adjusted mean HbA_{1c} (%)	5.51	5.39	5.33	5.27	5.23	<0.001
Adjusted mean HbA_{1c} (%)	5.43	5.34	5.32	5.27	5.26	<0.001

Data are *n*, means ± SD (ranges), %, % (*n*), or means. HbA_{1c} was adjusted for age, BMI, WHR, supplement taking, smoking history, vegetarian diet, physical activity, alcohol consumption, dietary vitamin E, dietary fiber, and dietary saturated fat. *Comparison of proportion by 3 categories of smoking history (never, former, and current); †comparison of proportion by 4 categories of occupational physical activity among workers (sedentary, standing, physical work, and heavy manual work).

the mediators of the social class gradient sometimes observed for diabetes (18–21). Consequently, social class may be causally related to plasma vitamin C and therefore not a true confounder. Physical activity was not found to be an important confounder in this study. However, we cannot exclude the possibility of residual confounding resulting from measurement error in the assessment of this variable and in the assessment of dietary variables.

Another possibility is that the relationship results from interference by vitamin C on the assay of HbA_{1c} (22). Weykamp et al. (23) investigated the effect of vitamin C supplementation for 12 weeks on the assay of glycosylated hemoglobin using 4 methods: HPLC, electrophoresis, affinity chromatography, and immunoassay. They concluded that no interference occurred in the assay and that vitamin C did not affect in vivo glycosylation of hemoglobin.

Some researchers have postulated that diabetes may result in decreased plasma vitamin C (4) through several mechanisms, including loss of vitamin C in the urine (24,25) and increased oxidative stress (26,27). However, in this study, we found a gradient of mean plasma vitamin C levels across quintiles of subjects who are not likely to have diabetes with no apparent threshold. The relationship therefore seems to exist even in nondiabetic individuals. This suggests that vitamin C may protect against impaired glucose regulation. Support for this hypothesis comes from a study by Feskens et al. (28) in which past dietary intake of vitamin C was inversely related to 2-h plasma glucose levels at 20-year follow-up in Finnish and Dutch men. Frequent consumption of salad vegetables (a source of dietary vitamin C) was found to decrease risk of type 2 diabetes in another population-based study (29).

Will et al. (30) found that serum vitamin C concentrations were lower in subjects with newly diagnosed diabetes than in subjects without diabetes. After adjusting for covariates including dietary intake of vitamin C, the difference was no longer significant. An important difference between the groups was that subjects who did not develop diabetes had a much higher mean intake of supplemental vitamin C than subjects who developed diabetes. This result is consistent with a protective role of vitamin C intake on the risk of diabetes.

Dietary vitamin C is a determinant of serum vitamin C concentration. Serum or plasma vitamin C reflects short-term vitamin C intake but also is positively correlated with the habitual intake of fresh fruit and vegetables (31). When Will et al. (30) adjusted for dietary vitamin C in their study, they may have attenuated the relationship between serum vitamin C and diabetes because dietary vitamin C and serum vitamin C are causally related.

Vitamin C may act as a marker of some other dietary or lifestyle factors that are protective against diabetes (31). Nevertheless, oxidative stress is known to impair insulin action (32,33), and vitamin C may play a role in ameliorating insulin resistance because of its antioxidant function (34). A population-based study did not find an association between dietary intake of vitamin C and vitamin E as assessed by food frequency questionnaire and insulin sensitivity (35). This may be because of the measurement error in the assessment of dietary intake thus attenuating the true effect (9). In contrast, Salonen et al. (36) found that low plasma vitamin E levels were associated with an increased risk of type 2 diabetes after 4 years of follow-up in a prospective study of Finnish men.

Reducing free radical damage to β-cells (37,38) may be another mechanism by which vitamin C protects against diabetes. Vitamin C was found in to be important for insulin secretion in animal studies (39,40), and further research may uncover a similar role in humans. In the presence of diabetes, vitamin C is potentially important in reducing complications mediated through free radical damage from autooxidation of glucose and glycosylation of structural proteins (41).

Microvascular complications of diabetes are associated with the concentration of glycosylated hemoglobin (42,43). If vitamin C is indeed protective (and this will require confirmation by longitudinal studies and randomized controlled trials), then it is of considerable clinical and public health importance. We found that an increase in plasma vitamin C levels of 20 µmol/l was associated with a reduction in the risk of undiagnosed hyperglycemia by almost one-third. This increase in plasma vitamin C is achievable by dietary means and would be another benefit of increased regular intake of fresh fruit and vegetables (44–47). Such an intervention could be an effective prevention strategy in individuals at high risk for developing diabetes.

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