Plasma Vitamin C Level, Fruit and Vegetable Consumption, and the Risk of New-Onset Type 2 Diabetes Mellitus

The European Prospective Investigation of Cancer–Norfolk Prospective Study

Anne-Helen Harding, PhD; Nicholas J. Wareham, FRCP, PhD; Sheila A. Bingham, PhD; KayTee Khaw, FRCP; Robert Luben, BSc; Ailsa Welch, PhD; Nita G. Forouhi, FFPH, PhD

**Background:** Epidemiologic studies suggest that greater consumption of fruit and vegetables may decrease the risk of diabetes mellitus, but the evidence is limited and inconclusive. Plasma vitamin C level is a good biomarker of fruit and vegetable intake, but, to our knowledge, no prospective studies have examined its association with diabetes risk. This study aims to examine whether fruit and vegetable intake and plasma vitamin C level are associated with the risk of incident type 2 diabetes.

**Methods:** We administered a semiquantitative food frequency questionnaire to men and women from a population-based prospective cohort (European Prospective Investigation of Cancer–Norfolk) study who were aged 40 to 75 years at baseline (1993-1997) when plasma vitamin C level was determined and habitual intake of fruit and vegetables was assessed. During 12 years of follow-up between February 1993 and the end of December 2005, 735 clinically incident cases of diabetes were identified among 21,831 healthy individuals. We report the odds ratios of diabetes associated with sex-specific quintiles of fruit and vegetable intake and of plasma vitamin C levels.

**Results:** A strong inverse association was found between plasma vitamin C level and diabetes risk. The odds ratio of diabetes in the top quintile of plasma vitamin C was 0.38 (95% confidence interval, 0.28-0.52) in a model adjusted for demographic, lifestyle, and anthropometric variables. In a similarly adjusted model, the odds ratio of diabetes in the top quintile of fruit and vegetable consumption was 0.78 (95% confidence interval, 0.60-1.00).

**Conclusions:** Higher plasma vitamin C level and, to a lesser degree, fruit and vegetable intake were associated with a substantially decreased risk of diabetes. Our findings highlight a potentially important public health message on the benefits of a diet rich in fruit and vegetables for the prevention of diabetes.

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ONE OF THE KEY DIETARY recommendations for the prevention of chronic disease is to eat at least 5 portions of fruits and vegetables a day.1 Although the prevalence of diabetes mellitus has reached epidemic proportions,2 few studies3-5 have examined the association between fruit and vegetable consumption and the risk of type 2 diabetes. These studies provide some evidence that fruit and vegetable consumption is protective against diabetes, but the evidence is inconclusive. This may, in part, be because of the impact of measurement error in the assessment of fruit and vegetable consumption on the association with diabetes.6 Use of a biomarker of fruit and vegetable consumption would help to resolve this issue.

Plasma vitamin C level is a good candidate to act as a biomarker for fruit and vegetable consumption because in Western diets fruit and vegetable consumption is the main source of vitamin C.6 Plasma vitamin C level is more strongly related to fruit and vegetable intake than is the level of plasma carotenoids or vitamin E.7 Several cross-sectional studies have reported lower levels of plasma vitamin C in diabetic individuals compared with healthy individuals (discussed by Will et al8). However, these studies cannot establish the temporal sequence of events to establish whether low vitamin C level precedes diabetes or whether low plasma vitamin C level is a consequence of diabetes. To our knowledge, the only published prospective study9 has investigated the association between dietary vitamin C intake and diabetes risk and...
found no significant association. To our knowledge, no published studies have examined the association of plasma vitamin C level and incident diabetes.

The aim of this study was to investigate the prospective association between plasma vitamin C level and the risk of developing type 2 diabetes in a population of middle-aged men and women. An additional aim was to examine the relationship between fruit and vegetable intake and incident diabetes.

METHODS

The European Prospective Investigation of Cancer–Norfolk (EPIC-Norfolk) study is a population-based cohort study, described in detail previously. The study is part of a 10-country European collaboration that was originally initiated to examine the prospective association between diet and cancer; the scope of the study was broadened to include other end points, such as diabetes and coronary heart disease. Men and women aged 40 to 75 years who lived in Norfolk, England, and were identified from general practice age-sex registers (n = 35 participating practices) were eligible for participation. Of 77,754 mailed invitations, 25,639 participants (33.0% participation rate) attended the first health checkup between February 1993 and the end of 1997. Since the baseline visit, 3 study follow-ups have been performed, 2 of which were by postal questionnaire (at 18 and 36 months) and 1 of which was a study follow-up (second) health checkup visit at 3 to 5 years (January 1998 to October 2000). Follow-up for the diabetes end point has included these 3 follow-up phases and follow-up through record linkage to external sources to the end of 2005 (see the “Case Ascertainment” subsection of this section). The EPIC-Norfolk study was approved by the Norfolk Local Research Ethics Committee, and all volunteers gave written informed consent.

At baseline, study participants completed a detailed health and lifestyle questionnaire that included questions relating to family history of diabetes, smoking status, occupational social class, educational level, and physical activity. A 4-point physical activity index incorporating occupational and nonoccupational physical activity was used as a measure of physical activity to categorize individuals as sedentary, moderately active, active, and very active. Participants were invited to attend a health checkup at the study clinic. Anthropometric measurements, including height, weight, and waist and hip circumferences, were taken according to a standard protocol, and venous blood samples were obtained by trained study nurses. Measurement of hemoglobin A_1c (HbA_1c) was added to the protocol halfway through the baseline visit in February 1995 and was available in approximately half of the cohort. The HbA_1c was measured with high-performance liquid chromatography on a Bio-Rad Diamat (Bio-Rad, Hercules, Richmond, California), on a sample of EDTA-anticoagulated blood.

PLASMA VITAMIN C

Plasma vitamin C concentrations were measured in blood samples drawn into citrate bottles, placed in dark boxes, and refrigerated overnight at 4°C to 7°C. Blood was then centrifuged at 2100g for 15 minutes at 4°C. The plasma was stabilized in a standardized volume of metaphosphoric acid and stored at −70°C. Within 1 week of sampling, a fluorometric assay was used to estimate the plasma vitamin C concentration. The coefficient of variation was 5.6% (mean, 0.58 mg/dL [to convert to micromoles per liter, multiply by 56.78]) at the lower end of the range and 4.6% (mean, 1.80 mg/dL) at the upper end of the range.

DIETARY ASSESSMENT

At baseline, participants completed a 130-item semiquantitative food frequency questionnaire (FFQ). The questionnaire related to food consumption during the past year and was based on the questionnaire developed for the US Nurses’ Health Study. The lists of foods were modified to reflect important sources of nutrients in the average British diet and included 11 questions related to fruit intake and 26 questions related to vegetable intake. The FFQ was validated in a British sample against 16-day weighed food records. Food and nutrient intakes (in grams per day) were estimated from the reported food intake and in-house databases.

CASE ASCERTAINMENT

Cases of diabetes prevalent at baseline were identified by self-report of physician diagnosis, diabetes medication, or diabetes diet in the health and lifestyle questionnaire and excluded from follow-up for clinically incident diabetes. Clinically incident cases of diabetes were ascertained using multiple sources of information. Sources internal to the study included any self-report of diabetes diagnosed by a physician and of diabetes-specific medication at follow-up. Record linkage with external sources ascertained clinically incident diabetes from general practice diabetes registers, the local hospital diabetes register, hospital admissions data for diabetes-related admissions among study participants, and Office for National Statistics mortality data with coding for diabetes. Identification of cases through external sources of information was independent of the health checkup and questionnaire follow-up. Possible cases based solely on self-report, and not confirmed by another data source, did not qualify as a confirmed case of diabetes. Cases ascertained up to December 31, 2005, were included in the study.

STUDY POPULATION ANALYZED

Altogether 25,639 men and women attended the baseline health checkup. Those with diabetes at baseline (n = 855) were excluded from the analysis. An additional 2259 men and women who reported having cancer, myocardial infarction, or stroke at baseline were also excluded because they may have altered their diet as a result of their condition. In addition, 644 individuals who had missing anthropometric or lifestyle data and 50 individuals who reported a total energy intake greater than or less than 3 SDs of the log-transformed mean were excluded from the analysis. This left 21,831 individuals (9815 men, and 12,016 women) for the analysis. Of these individuals, 19,246 had plasma vitamin C data available.

STATISTICAL ANALYSES

Sex-specific quintiles of plasma vitamin C level and fruit and vegetable intake were generated. The relationships between baseline population characteristics and quintiles of plasma vitamin C levels were examined using a nonparametric trend test for continuous variables and χ² tests for categorical variables. A variable that indicated the season in which the plasma vitamin C level was assessed was generated because seasonal variation in fruit and vegetable availability might potentially affect their intake. The univariate odds ratios (ORs) of diabetes associated with potential confounding variables were calculated. These variables were age, sex, total energy intake, fat intake, alcohol consumption (5 categories, including nondrinkers plus sex-specific quartiles of alcohol consumption), educational level (<11 vs ≥11 years), occupational socioeconomic status, body mass index, physical activity, smoking status, hip circumference, presence of chronic diseases, and diabetes medication at follow-up.
class (manual vs nonmanual), physical activity (4 categories, ranging from sedentary to active), smoking status (never, former, or current), vitamin supplementation (yes vs no), and season (winter [December through February], spring [March through May], summer [June through August], and autumn [September through November]). The variables that were associated with both plasma vitamin C concentrations and the risk of developing diabetes in univariate analysis were included in the multiple logistic regression model. Waist circumference and body mass index (calculated as weight in kilograms divided by height in meters squared), which may be mediators of the association, were included in the final multiple logistic regression model. The interaction between plasma vitamin C level and explanatory variables was tested. All regression models were tested for goodness of fit. The OR for trend was obtained by fitting the quintiles as a continuous variable. A similar analytical approach was used to investigate the association of fruit and vegetable intake with diabetes risk. A quantitative estimate of the effect of plasma vitamin C levels on diabetes risk was obtained by fitting the full multiple logistic regression model (model 6) using plasma vitamin C level as a continuous variable. To investigate the possibility that the results were biased by undiagnosed cases of diabetes in the cohort, the analysis was repeated for those with an HbA1c level of less than 7% (to convert to proportion of total hemoglobin, multiply by 0.01) in the subsample with HbA1c data. All analyses were undertaken using Stata statistical software, version 9.2 (Stata Corporation, College Station, Texas).

RESULTS

The mean (SD) age of the study population was 58.0 (9.2) years. The mean (SD) BMI was 26.0 (3.3) in men and 26.0 (4.3) in women. Plasma vitamin C levels were higher in women (mean [SD], 1.04 [0.35] mg/dL) than in men (mean [SD], 0.84 [0.33]). Table 1 indicates that, among both men and women, the plasma vitamin C level was inversely associated with age, BMI, waist circumference, total energy intake, and fat intake and was positively associated with fruit, vegetable, and fiber intakes. Compared with the lowest quintile of plasma vitamin C, more of those in the top quintile consumed alcohol, had more than 11 years of education, had nonmanual occupations, were physically active, had never smoked, and took vitamin supplements. Mean plasma vitamin C levels were lowest in spring and highest in autumn. The mean (SD) plasma vitamin C concentrations were 0.89 (0.38) mg/dL in spring and 0.99 (0.32) mg/dL in autumn.

Among the 21,831 men and women included in the analysis, 735 clinically incident cases of diabetes (in 423 men and 312 women) were identified during the 12-year follow-up (incidence, 3.2%). Of these individuals, plasma vitamin C data were available for 638 with diabetes. With 4 exceptions, the covariates listed herein were associated with diabetes in univariate logistic regression (OR range, 0.49-1.26; P < .01 for all). Season, total energy intake, and fat and fiber intakes were not associated with diabetes (OR range, 0.85-1.00; P > .30 for all) and consequently were unlikely to be acting as confounders in this population.

The mean (SD) plasma vitamin C concentration in men and women with diabetes was lower than in those without diabetes (0.76 [0.32] mg/dL vs 0.95 [0.35] mg/dL). Plasma vitamin C level was inversely associated with diabetes risk in the logistic regression model (Table 2). In the unadjusted model, the OR of diabetes in the top quintile compared with the bottom quintile was 0.23 (P < .001), and a significant trend was seen across the quintiles (OR, 0.69; P < .001). This association was materially unchanged when adjusted for age, sex, family history of diabetes, alcohol intake, physical activity, smoking status, educational level, occupational social class, and vitamin supplements (models 1-5). Adjusting additionally for BMI and waist circumference attenuated the association (OR for top quintile, 0.38; 95% confidence interval [CI], 0.28-0.52; model 6), but it remained statistically significant (P < .001). The inverse trend across the quintiles (OR, 0.78) also remained statistically significant (P < .001) in the final model. No evidence was found of interaction between plasma vitamin C and any of the explanatory variables (P > .05). When plasma vitamin C was fitted as a continuous variable (in model 6), a 29% reduction was found in diabetes risk per SD change (0.33 mg/dL) in vitamin C level.

In the subsample of men and women who had a measure of HbA1c at baseline and had an HbA1c level of less than 7% (n=8446) and, thus, were likely to be nondiabetic according to biochemical criteria, the OR for those in the top quintile of plasma vitamin C was 0.46 (95% CI, 0.25-0.84) and the linear trend across quintiles of plasma vitamin C was 0.80 (P < .001) in the final adjusted multiple logistic regression model.

The overall partial correlation coefficient, adjusted for age, between plasma vitamin C level and fruit and vegetable intake was 0.26 (P < .001) in men and 0.24 (P < .001) in women without diabetes. The correlation was strongest in the bottom quintile of plasma vitamin C (0.19 in men and 0.25 in women; P < .001) and weakest in the fourth quintile of plasma vitamin C (~0.009 in men and ~0.0005 in women; P > .70). The median daily number of portions of fruit and vegetables (80 g per portion) consumed was 3 in men and 4 in women in the bottom quintile of plasma vitamin C and 5 in men and 6 in women in the top quintile of plasma vitamin C.

The series of multiple logistic regression models of incident diabetes on plasma vitamin C level was repeated, with quintiles of dietary fruit and vegetable intake replacing quintiles of plasma vitamin C in the models. The OR of diabetes in the top quintile of fruit and vegetable intake was 0.87 (95% CI, 0.69-1.11) in the unadjusted model and 0.78 (95% CI, 0.60-1.00) in the final adjusted model. Modeling total fruit and total vegetable intake separately showed that the association with diabetes risk was stronger for fruit than for vegetables (top quintile vs bottom quintile of fruit intake: OR, 0.70 [95% CI, 0.54-0.90]; OR for trend in model 6, 0.92 [95% CI, 0.86-0.98]; top quintile vs bottom quintile of vegetable intake: OR, 0.80 [95% CI, 0.62-1.03]; and OR for trend in model 6, 0.94 [95% CI, 0.89-1.00]).

The Figure compares the association of incident diabetes with plasma vitamin C level and fruit and vegetable intake and indicates that the strongest association was for plasma vitamin C level. There appeared to be a dose-response effect for plasma vitamin C level but not for fruit and vegetable intake.
The correlation between plasma vitamin C level and fruit and vegetable intake was relatively low, given the fact that in this Western population approximately 90% of vitamin C is estimated to be obtained from fruit and vegetable consumption.6 The lack of relationship between plasma vitamin C level and fruit and vegetable intake in the higher quintiles of plasma vitamin C, the weaker association of fruit and vegetable intake with incident diabetes, and the lack of a dose-response relationship suggest that measurement error in ascertaining dietary intake may have attenuated the association substantially. Furthermore, the FFQ is known to overestimate fruit and vegetable consumption when compared to other methods.7,8

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**Table 1. Population Characteristics at Baseline by Sex and Quintiles of Plasma Vitamin C: European Prospective Investigation of Cancer–Norfolk Study**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin C, range, mg/dL</td>
<td>&lt;0.56</td>
<td>0.57-0.77</td>
<td>0.78-0.93</td>
<td>0.94-1.09</td>
<td>≥1.10</td>
<td>1.10</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>59.9 (9.4)</td>
<td>59.0 (9.2)</td>
<td>58.2 (9.1)</td>
<td>58.1 (8.9)</td>
<td>58.3 (9.2)</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>26.7 (3.6)</td>
<td>26.8 (3.3)</td>
<td>26.5 (3.0)</td>
<td>26.1 (3.0)</td>
<td>25.7 (2.9)</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>Waist, mean (SD), cm</td>
<td>96.8 (10.0)</td>
<td>96.6 (9.5)</td>
<td>95.5 (9.2)</td>
<td>94.1 (9.1)</td>
<td>92.8 (8.8)</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>Total energy intake, mean (SD), cal/d</td>
<td>2248 (645)</td>
<td>2207 (631)</td>
<td>2248 (637)</td>
<td>2181 (597)</td>
<td>2176 (604)</td>
<td>0.003a</td>
</tr>
<tr>
<td>Fat intake, mean (SD), % of energy</td>
<td>34.7 (5.4)</td>
<td>33.7 (5.4)</td>
<td>33.0 (5.6)</td>
<td>32.6 (5.5)</td>
<td>31.6 (5.7)</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>Saturated</td>
<td>13.9 (3.3)</td>
<td>13.1 (3.1)</td>
<td>12.8 (3.1)</td>
<td>12.5 (3.1)</td>
<td>12.1 (3.2)</td>
<td>&lt;0.01b</td>
</tr>
<tr>
<td>Polyunsaturated</td>
<td>5.9 (2.0)</td>
<td>6.2 (2.0)</td>
<td>6.1 (1.9)</td>
<td>6.2 (2.0)</td>
<td>6.2 (2.0)</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>Monounsaturated</td>
<td>12.5 (2.3)</td>
<td>12.0 (2.2)</td>
<td>11.8 (2.2)</td>
<td>11.5 (2.2)</td>
<td>11.1 (2.2)</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>Carbohydrate intake, mean (SD), % of energy</td>
<td>45.8 (6.5)</td>
<td>46.5 (6.9)</td>
<td>47.2 (6.2)</td>
<td>47.2 (6.0)</td>
<td>47.7 (6.5)</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>Protein, mean (SD), % of energy</td>
<td>15.7 (2.8)</td>
<td>16.0 (2.8)</td>
<td>15.9 (2.8)</td>
<td>16.1 (2.7)</td>
<td>16.3 (2.6)</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>Fruit and vegetable intake, mean (SD), g/d</td>
<td>289 (180)</td>
<td>370 (198)</td>
<td>412 (215)</td>
<td>424 (221)</td>
<td>459 (251)</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>Fiber intake, mean (SD), g/d</td>
<td>16.0 (5.9)</td>
<td>17.4 (5.8)</td>
<td>18.5 (6.0)</td>
<td>18.7 (6.1)</td>
<td>19.3 (6.5)</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>Alcohol drinkers, No. (%)</td>
<td>1452 (82.8)</td>
<td>1503 (87.5)</td>
<td>1519 (88.2)</td>
<td>1541 (89.8)</td>
<td>1461 (88.5)</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>Educational level &amp;11 y, No. (%)</td>
<td>978 (53.8)</td>
<td>1094 (61.0)</td>
<td>1107 (64.9)</td>
<td>1126 (66.6)</td>
<td>1139 (69.5)</td>
<td>&lt;0.01b</td>
</tr>
<tr>
<td>Nonmanual OSC, No. (%)</td>
<td>858 (47.4)</td>
<td>1049 (56.8)</td>
<td>1058 (59.3)</td>
<td>1091 (63.0)</td>
<td>1097 (64.9)</td>
<td>&lt;0.01b</td>
</tr>
<tr>
<td>Active physical activity, No. (%)</td>
<td>1174 (64.6)</td>
<td>1247 (69.5)</td>
<td>1286 (72.2)</td>
<td>1224 (74.0)</td>
<td>1294 (77.0)</td>
<td>&lt;0.01b</td>
</tr>
<tr>
<td>Use of vitamin supplements, No. (%)</td>
<td>485 (26.7)</td>
<td>588 (32.8)</td>
<td>643 (36.3)</td>
<td>655 (39.6)</td>
<td>853 (50.8)</td>
<td>&lt;0.01b</td>
</tr>
<tr>
<td>Incident diabetes mellitus, No. (%)</td>
<td>132 (7.3)</td>
<td>94 (5.2)</td>
<td>68 (3.8)</td>
<td>46 (2.8)</td>
<td>34 (2.0)</td>
<td>&lt;0.01b</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, not applicable; OSC, occupational social class.

Nonparametric test for trend across the quintiles.

aχ² Tests.
parried with more detailed methods for assessing diet. These factors may in part explain the inconsistent associations between fruit and vegetable consumption and diabetes risk reported previously. Fruit consumption was associated with a slightly stronger (protective) association than was vegetable consumption. However, the actual vitamin C content of individual components of fruit and vegetable intake was not available in our study, although it is plausible that the effect on diabetes risk may be related to the intake of specific fruits and vegetables. Nevertheless, our findings re-endorse the public health message of the beneficial effect of increasing total fruit and vegetable intake.

The cases of diabetes in this study were diagnosed in the community and are likely to be typical of newly diagnosed cases in the general population. They were identified through self-report of diagnosis by a physician or of type 2 diabetes–specific medication, as well as from their general practice and local hospital diabetes registers, through hospital admissions data, and through death certificates. This was an important strength of the study because new cases of diabetes were identified through sources of data that did not depend on a participant returning a follow-up questionnaire or attending a follow-up health checkup. However, people may have diabetes for many years before it is diagnosed. The presence of any undiagnosed cases in the cohort may reduce the number of new cases and, hence, have the effect of attenuating any observed associations. A similar magnitude of association was observed in the subsample of participants who had HbA1c levels of less than 7%, thus excluding those with potentially undiagnosed diabetes at baseline. The relatively low incidence rate (3%) during the follow-up period may be a result of the fact that this was not a high-risk population and that individuals who agree to participate in studies are often healthier than those who do not take part. The EPIC-Norfolk cohort had a lower proportion of smokers (12%) than the average for England and Wales (approximately 27% in 1998) but was similar to nationally representative samples with respect to important anthropometric and clinical characteristics.

The list of variables that were considered as potential confounders of the association between plasma vitamin C level and fruit and vegetable intake, adjusted for age and sex, European Prospective Investigation of Cancer–Norfolk Study. For plasma vitamin C analysis, the sample size was 19246. For fruit and vegetable analysis, the sample size was 21831. Error bars indicate 95% confidence intervals.

### Table 2. Logistic Regression of Incident Diabetes Mellitus on Plasma Vitamin C: European Prospective Investigation of Cancer–Norfolk Study

<table>
<thead>
<tr>
<th>Model</th>
<th>OR (95% CI) by Quintiles of Plasma Vitamin C</th>
<th>Linear Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>0.64 (0.51-0.79)</td>
<td>0.23 (0.17-0.31)</td>
</tr>
<tr>
<td>1</td>
<td>0.66 (0.53-0.81)</td>
<td>0.31 (0.24-0.42)</td>
</tr>
<tr>
<td>2</td>
<td>0.66 (0.53-0.81)</td>
<td>0.31 (0.24-0.41)</td>
</tr>
<tr>
<td>3</td>
<td>0.66 (0.53-0.82)</td>
<td>0.32 (0.24-0.42)</td>
</tr>
<tr>
<td>4</td>
<td>0.66 (0.54-0.83)</td>
<td>0.33 (0.25-0.44)</td>
</tr>
<tr>
<td>5</td>
<td>0.67 (0.54-0.83)</td>
<td>0.33 (0.25-0.44)</td>
</tr>
<tr>
<td>6</td>
<td>0.71 (0.57-0.89)</td>
<td>0.43 (0.32-0.58)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.

*Model 1 includes plasma vitamin C level, age, and sex; model 2, model 1 plus family history of diabetes; model 3, model 2 plus alcohol consumption, physical activity, and smoking; model 4, model 3 plus educational level and occupational social class; model 5, model 4 plus vitamin supplements; model 6, model 5 plus body mass index and waist circumference. Categorical variables were entered as family history of diabetes (yes vs no), alcohol consumption (nondrinkers plus sex-specific quartiles of alcohol consumption), educational level (<11 vs ≥11 years), occupational social class (manual vs nonmanual), physical activity (4 categories, ranging from sedentary to active), smoking status (never, former, or current), and vitamin supplementation (yes vs no).
Plausible mechanisms for a beneficial effect of increased fruit and vegetable intake or plasma vitamin C levels on diabetes risk exist. Fruit and vegetable consumption may be protective for diabetes risk, at least partially, through its effect on obesity. In this context, Bell et al reported a clinical trial that investigated the effect of energy density on total energy intake. They found that individuals ate the same weight of food and reported a similar degree of satiety whether on a high- or a low-energy-density diet. Many fruits and vegetables are rich in dietary fiber. The low energy density of fruits and vegetables and the feeling of fullness promoted by a high-fiber diet may prevent the passive overconsumption associated with an energy-dense diet and the resulting gain in weight. In this context, the lack of association of fruit and vegetable fiber with diabetes risk but the protective effect of cereal fiber for diabetes risk reported in a recent meta-analysis is noteworthy and may suggest that it is not the fiber content of fruit and vegetables per se that contributed to the reduced risk for diabetes in our study. Fruits and vegetables are also rich sources of vitamins, minerals, and biologically active phytochemicals. Many of these, including vitamin C, have antioxidant properties that may be protective against diabetes. Oxidative stress, the situation in which an imbalance between the levels of reactive oxygen species and antioxidants exists, can lead to disturbed glucose metabolism and hyperglycemia. Oxidative stress is consistently observed in patients with diabetes, and the degree of oxidative stress tends to be greater in those with microalbuminuria and more diabetic complications. Obesity, one of the strongest risk factors for diabetes, may promote oxidative stress. In a cross-sectional study of this EPIC-Norfolk population, plasma vitamin C concentrations were inversely related to waist-hip ratio, independent of BMI. A diet rich in fruit and vegetables and, hence, rich in antioxidants, including vitamin C, may help to prevent oxidative stress.

The inverse association observed between plasma vitamin C and diabetes risk in this prospective study suggests that low levels of vitamin C are present before the onset of diabetes. The subsample analysis in which men and women with HbA1c levels greater than 7% were excluded demonstrated that this association was not explained by the presence of previously undiagnosed cases of diabetes at baseline. Our findings of a striking inverse association between the risk of diabetes and plasma vitamin C or fruit and vegetable intake should be confirmed in other prospective studies in different settings and in specifically designed clinical trials. However, the strong independent association observed in this prospective study, together with biological plausibility, provides persuasive evidence of a beneficial effect of vitamin C and fruit and vegetable intake on diabetes risk. Because fruit and vegetables are the main sources of vitamin C, the findings suggest that eating even a small quantity of fruit and vegetables may be beneficial and that the protection against diabetes increases progressively with the quantity of fruit and vegetables consumed.

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Correspondence: Nita G. Forouhi, FFPH, PhD, Medical Research Council Epidemiology Unit, Institute of Metabolic Science, Addenbrooke’s Hospital, PO Box 285, Hills Road, Cambridge CB2 0QQ, England (nita.forouhi@mrc-epid.cam.ac.uk).

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