Vitamin Supplement Use and Diabetes Mellitus Incidence among Adults in the United States

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In some studies, use of vitamin supplements has been inversely associated with the risk of several chronic diseases, but little is known about whether vitamin use affects the risk of diabetes mellitus. Using data from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study, the author examined whether vitamin use was related to diabetes incidence in a cohort of United States adults aged 25–74 years. In the analytic sample of 9,573 participants, 1,010 participants developed diabetes mellitus during about 20 years of follow-up. A smaller percentage of participants with incident diabetes (21.4%) reported using vitamins during the previous month at baseline compared with participants who remained free of this disease (33.5%) (p < 0.001). After multiple adjustment, the hazard ratios for participants using vitamin supplements were 0.76 (95% confidence interval (CI): 0.63, 0.93) for all participants, 0.70 (95% CI: 0.54, 0.92) for men, and 0.84 (95% CI: 0.64, 1.11) for women. Sex did not modify the association between vitamin use and diabetes incidence. Whether specific vitamins or other factors closely correlated with vitamin use account for this observation is unclear.

__MATERIALS AND METHODS__

Participants aged 25–74 years in the first National Health and Nutrition Examination Survey (NHANES I), conducted from 1971–1975, were followed through 1992 or 1993 (n = 14,407). The original sample was selected by using a complex sampling design to ensure that results would be representative of the noninstitutionalized civilian population. Details of the NHANES I and the NHANES I Epidemiologic Follow-up Study (NHEFS) have been published elsewhere (21–26).

Four attempts were made to contact participants or their surrogates in person, and during later follow-ups, by telephone, in 1982–1984, 1986 (participants aged ≥55 years only), 1987, and 1992–1993. Permission to obtain hospital records was requested. Deaths were identified through searches of the National Death Index, the Health Care Financing Administration enrollee files, and other tracing mechanisms. A participant was considered deceased only if a death certificate had been received or a proxy interview had been completed to verify the death. Death certificates have been obtained for 97 percent of deceased participants through 1993.

Participants were considered to have diabetes if: 1) they confirmed that they had ever been told by a doctor that they had diabetes during any of the four follow-up contacts, 2) a hospitalization record contained the International Classification of Diseases, Ninth Revision, Clinical Modification code 250 on any one of 10 diagnoses listed on...
the hospital discharge sheet, or 3) the death certificate included code 250. Participants with diabetes identified from their self-report were asked to report the year of onset. I designated the midpoint of that year as the date of onset. For participants who did not report a year of onset, I assigned the midpoint between the last date of known contact and the date of the most recent interview. The date of onset was chosen as the date on which the condition was first reported or recorded on institutional records or death certificates.

Participants who reported at baseline that they had ever been told that they had diabetes were considered as prevalent cases, as were participants who, during later follow-up contacts, reported a date of onset that occurred in their year of baseline interview or earlier. They were excluded from analysis.

Several questions about vitamin use were asked of participants at baseline. Before their phlebotomy, participants were asked, “Have you taken vitamins within the last 30 days?” (yes/no). In addition, as part of the dietary interview, participants were asked, “Are you taking vitamins or minerals?” Answers included no; yes, regularly; and yes, irregularly. Participants who answered yes were then asked to report in more detail what they were using. These categories included unknown or prescriptions; multiple vitamins, multiple vitamins with additional supplements; multiple vitamins and minerals, multiple vitamins with additional supplements; iron only; multiple vitamins with iron; iron with additional supplements—Geritol (GlaxoSmithKline, Research Triangle Park, North Carolina); vitamin E, vitamin E with additional supplements, vitamin A, vitamin A with additional supplements, vitamin D, vitamin D with additional supplements; vitamin C, vitamin C with additional supplements; calcium, calcium with additional supplements; dolomite—minerals with calcium and magnesium; vitamin B complex, vitamin B complex with additional supplements; and miscellaneous (cod liver oil; brewer’s yeast, kelp lecthin, yeast tablets, alfalfa tablets, liver tablets, potassium, folrume 24, iodine, bone meal, bone marrow, protein pills, amino acid pills, fluoride, and energol-wheat germ concentrate). In addition, during the first follow-up interview (1982–1984), participants were asked, “Are you now taking multivitamin pills including therapeutic and geriatric multivitamins and Geritol?” (yes/no).

Baseline covariates included age, race or ethnicity (non-White, White), education (years), cigarette smoking (never, former, current), systolic blood pressure, use of antihypertensive medication (yes/no), serum cholesterol concentration (mg/dl), body mass index (kg/m²), recreational exercise (much, moderate, little, or no exercise), nonrecreational exercise (very active, moderately active, quite inactive), alcohol consumption (0, 1–2, ≥3 drinks per day), fruit and vegetable intake (servings per day), percent of calories consumed as fat, and total energy intake. For smoking, I used a variable constructed in part from responses obtained during the baseline interview and in part from the first follow-up interview (27, 28). Two questions were used to create the categories of smoking: “Have you smoked at least 100 cigarettes during your entire life?” and “Do you smoke cigarettes now?”

Cholesterol was measured by using a modification of the Abell-Kendall method. Fruit and vegetable intake and percent of calories consumed as fat were determined from a single 24-hour dietary recall questionnaire administered to 11,348 participants.

Two-sample comparisons of categorical and continuous variables were made using t tests. With the use of direct standardization, baseline characteristics and age-adjusted incidence rates were standardized to the age distribution from the 1980 census. Person-time was calculated for each participant from the time of entry into the study until one of the following conditions occurred: 1) the participant developed diabetes, 2) the participant died or left the study, or 3) follow-up was completed in 1993. The independent association between vitamin use at baseline and diabetes mellitus incidence was examined by using proportional hazard models. To account for the complex sampling design, I used the software SUDAAN (29) in all analyses except for evaluation of proportionality assumptions, which were done in SAS (30).

RESULTS

Of 14,407 participants in the NHEFS, 11,348 answered the dietary questionnaires. After deletion of persons who contributed no follow-up time, 10,925 participants remained. I excluded participants with a race or ethnicity other than White or African American (n = 172). Additional exclusions for incomplete information to establish diabetes incidence, diabetes prevalence, pregnancy, and missing data for covariates reduced the analytic sample to 9,573 participants, of whom 1,010 developed diabetes during the course of the study.

Participants who developed diabetes were older than those who remained free of the disease (table 1). After adjustment for age, participants who developed diabetes...
were less likely to be White, had fewer years of education, had a higher systolic pressure, had a higher serum cholesterol concentration, were heavier, were more likely to be sedentary, and consumed fewer fruits and vegetables compared with participants who remained free of diabetes. Only 21.4% of the participants who later developed diabetes reported using vitamins during the 30 days before their baseline interview compared with 33.5% of participants who remained free of diabetes (p < 0.001).

Using answers to the question “Have you taken vitamins within the last 30 days?”, I found that the age-adjusted incidence rate for diabetes mellitus was lower among participants who used vitamins than among those who did not (table 2). The proportional hazards model generally supported these patterns. After adjustment for age, race or ethnicity, education, cigarette smoking, systolic blood pressure, use of antihypertensive medication, serum cholesterol concentration, body mass index, recreational exercise, nonrecreational exercise, alcohol consumption, fruit and vegetable intake, percent calories from fat, and total energy intake, the hazard ratios for participants using vitamin supplements were 0.76 (95% confidence interval (CI): 0.63, 0.93, p = 0.007) for all participants, 0.70 (95% CI: 0.54, 0.92, p = 0.009) for men, and 0.84 (95% CI: 0.64, 1.11, p = 0.210) for women. The interaction term for sex and vitamin use was not significant (p = 0.405).

Results were similar when using answers to the question “Are you taking vitamins or minerals?” Compared with participants who did not use vitamins or minerals, adjusted odds ratios for all participants were 0.86 (95% CI: 0.62, 1.20) for those who used vitamins irregularly and 0.75 (95% CI: 0.60, 0.94) for regular vitamin or mineral users (n = 9,665). For men, the adjusted hazard ratios were 0.74 (95% CI: 0.43, 1.27) and 0.68 (95% CI: 0.48, 0.97) for those who used vitamins irregularly and regular vitamin users, respectively (n = 3,874). For women, the adjusted hazard ratios were 0.98 (95% CI: 0.66, 1.45) and 0.83 (95% CI: 0.62, 1.11), respectively (n = 5,791). The interaction term for sex and vitamin or mineral use was not significant (p = 0.523). Using the more detailed use data (n = 9,512), the adjusted hazard ratios for all participants were 0.89 (95% CI: 0.62, 1.29) for users of multiple vitamins or multiple vitamins with additional supplements; 0.67 (95% CI: 0.41, 1.10) for users of multiple vitamins and minerals or multiple vitamins and minerals with additional supplements; 1.19 (95% CI: 0.58, 2.43) for users of iron only; 0.74 (95% CI: 0.48, 1.14) for users of multiple vitamins with iron or iron with additional supplements—Geritol; 0.87 (95% CI: 0.65, 1.17) for users of vitamin E, vitamin E with additional supplements, vitamin A, vitamin A with additional supplements, vitamin D, or vitamin D with additional supplements; and 1.13 (95% CI: 0.55, 2.32) for users of vitamin C or vitamin C with additional supplements. Because the numbers of participants using calcium or related products with or without other products, vitamin B with or without additional supplements, or miscellaneous products were less than 100, I eliminated these subjects from the above analysis. Furthermore, because the sample size for some of the usage categories was small, I did not stratify these analyses by sex.

To estimate the risk of developing diabetes in function of reported vitamin use from the baseline (“Are you taking vita-

<table>
<thead>
<tr>
<th>Vitamin use</th>
<th>No. of cases</th>
<th>Person-years</th>
<th>Unadjusted incidence per 100,000 person-years*</th>
<th>Age-adjusted incidence per 100,000 person-years*</th>
<th>Unadjusted incidence</th>
<th>Age-adjusted incidence</th>
<th>Multiple-adjusted† incidence</th>
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</thead>
<tbody>
<tr>
<td>Total sample (1,010 persons with diabetes/9,573 in sample)</td>
<td></td>
<td></td>
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<td>Yes</td>
<td>232</td>
<td>48,101</td>
<td>420.6</td>
<td>397.9</td>
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<td>0.53</td>
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<td>103,427</td>
<td>662.8</td>
<td>663.2</td>
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<td>Men (411 persons with diabetes/3,829 in sample)</td>
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<tr>
<td>Yes</td>
<td>88</td>
<td>15,202</td>
<td>442.8</td>
<td>430.2</td>
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<td>709.5</td>
<td>718.8</td>
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<td>Women (599 persons with diabetes/5,744 in sample)</td>
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<td>Yes</td>
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<td>622.1</td>
<td>616.7</td>
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</table>

* Weighted estimate.
† Adjusted for age, race, or ethnicity, education, cigarette smoking, systolic blood pressure, use of antihypertensive medication, serum cholesterol concentration, body mass index, recreational exercise, nonrecreational exercise, alcohol consumption, fruit and vegetable consumption, percent calories from fat, and total energy intake.
‡ HR, hazard ratio; CI, confidence interval.

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Vitamin Use and Diabetes Incidence

Little is known about whether vitamin use or vitamin status may have a protective effect on diabetes mellitus. The findings from the NHEFS that vitamin use may be associated with lower risks for diabetes mellitus are intriguing. Although the reduction in risk of diabetes associated with the use of vitamins was significant only among men, the smaller reduction observed among women was not inconsistent with the results among men. The findings that participants who used vitamins regularly had a larger reduction in risk than those who used vitamins irregularly and that participants who reported using vitamins both at baseline and during the first-follow-up interviews had larger reductions in risk than those who either started or stopped vitamin use during that period suggest dose-response relations.

Several limitations of this study need to be recognized. Persons who use vitamins differ in known and unknown ways from those who do not (31). Although I adjusted for various factors that are related to vitamin use, other unknown factors or residual confounding could account for some or all of the observed association. Unfortunately, limited information about the types, dosage, frequency, and duration of vitamin use was requested from the participants. Thus, it was impossible to assess whether particular vitamins or vitamin use patterns were responsible for the observed association. The endpoint of diabetes incidence was based on self-reports, hospital diagnoses, and death certificates; this information is often incomplete and may underreport the diagnosis of diabetes mellitus. The vast majority of cases were very likely to have been type 2 diabetes mellitus, however. About 95 percent of the participants who developed diabetes were aged 40 years or more when they did so.

The antioxidant effects of vitamin C or E could account for the observed association between vitamin use and incidence of diabetes mellitus. Some research has suggested that oxidation and attendant free radical damage contribute to the pathogenesis of diabetes mellitus, although the mechanisms are unclear (37, 38). Beta cells are thought to be highly susceptible to damage from reactive oxygen species (39) and are characterized by low concentrations of radical scavengers (40). Vitamin E has been shown to block the formation of malondialdehyde, an end product of lipid peroxidation (41). Although some studies have suggested that vitamin E has favorable effects on insulin action (42, 43) and could help maintain residual beta cell function in persons with insulin-dependent diabetes mellitus (44), not all studies have produced similar results (45). In at least one study, vitamins E and C were not significantly associated with insulin sensitivity (46).

Only a few studies have prospectively examined the relations between dietary intakes or physiologic concentrations of vitamins and diabetes incidence. In a 20-year follow-up of 338 men of the Finnish and Dutch cohorts of the Seven Country Study, vitamin C intake was inversely related to the incidence of diabetes (n = 26) and impaired glucose tolerance (n = 71) (17). Plasma vitamin E concentration was inversely related to the incidence of diabetes mellitus (n = 45) in a cohort of 944 men aged 42–60 years who were followed for 4 years in Finland (15). In a Finnish nested case-control study of 106 persons who developed diabetes and were matched to 201 controls, serum alpha-tocopherol was not significantly related to diabetes incidence after adjustment for a number of risk factors (16).

Research suggests that some of the contents of mineral supplements such as chromium and magnesium may lower the risk for developing this disease. Chromium has been shown to improve insulin sensitivity in humans and animals and may improve glycemic control in patients with diabetes (47). Several studies have suggested that dietary magnesium intake is inversely related to diabetes incidence (48, 49) and insulin resistance (50, 51). Furthermore, magnesium supplementation may improve glycemic control (52).

Supplements containing iron did not appear to affect the risk for diabetes mellitus significantly in this study. Because iron is a prooxidant and because some evidence suggests that oxidation may play a role in the pathogenesis of diabetes mellitus, an increase in the risk for developing diabetes might have been expected. Hemochromatosis, a condition of iron overload, is associated with an increased risk of diabetes, and this has suggested to some that lower concentrations of excess iron might also increase the risk for diabetes.
A few cross-sectional and prospective studies have shown associations between various indicators of elevated iron stores and diabetes (53, 54).

The NHIFS is one of only a few studies to suggest that vitamin use or vitamin status may have a beneficial effect on the incidence of diabetes mellitus. If future studies support the findings of this study, the vitamins responsible for any protective effect will need to be identified and mechanisms for such effects unraveled. Diabetes mellitus is the seventh leading cause of mortality in the United States. With 16 million Americans thought to have diabetes (55) and the incidence and prevalence of this disease increasing (56–58), new approaches to primary and secondary prevention need to be explored. Perhaps the judicious use of vitamins may play a role in the prevention of this disease.

REFERENCES

Vitamin Use and Diabetes Incidence