

# Serum Selenium and Diabetes in U.S. Adults

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**OBJECTIVE**— The purpose of this study was to examine the relationship between serum selenium levels and the prevalence of diabetes among U.S. adults.

**RESEARCH DESIGN AND METHODS**— We conducted a cross-sectional analysis of 8,876 adults  $\geq 20$  years of age who participated in the Third National Health and Nutrition Examination Survey. Diabetes was defined as the presence of a fasting plasma glucose  $\geq 126$  mg/dl, a self-report of a physician diagnosis of diabetes, or current use of insulin or oral hypoglycemic medication. Serum selenium was measured by atomic absorption spectrometry.

**RESULTS**— Mean serum selenium levels in participants with and without diabetes were 126.5 and 125.7 ng/ml, respectively. Age-, sex-, race-, and BMI-adjusted mean selenium levels were 126.8 ng/ml in participants with diabetes and 124.7 ng/ml in participants without diabetes (adjusted difference 2.1 ng/ml [95% CI 0.4–3.8];  $P = 0.02$ ). The multivariable adjusted odds ratio for diabetes comparing the highest to the lowest quintile of serum selenium was 1.57 [1.16–2.13]. However, the association between high serum selenium and the prevalence of diabetes was nonlinear, with no clear trend in quintiles 2–4.

**CONCLUSIONS**— In a probability sample of the U.S. population, high serum selenium levels were positively associated with the prevalence of diabetes. Until findings from prospective studies and randomized controlled trials are available, selenium intake, including selenium supplementation, should not be recommended for primary or secondary diabetes prevention in populations with adequate selenium status such as the U.S. population.

*Diabetes Care* 30:829–834, 2007

Oxidative stress reduces insulin secretion and increases insulin resistance in some experimental models and may thus play a causal role in the pathogenesis of diabetes (1–5). Selenium, an essential trace element, is involved in the complex system of defense against oxidative stress through selenium-dependent glutathione peroxidases and other selenoproteins (6,7). Because of its antioxidant properties, selenium might thus prevent the development of diabetes. In addition, selenate, an inorganic form of selenium, mimics insulin activity in experimental models (8,9).

Few population studies, however, have evaluated the association between selenium and diabetes. In a cross-sectional analysis of the Health Professionals Study, toenail selenium, a biomarker of selenium status, was inversely associated with diabetes (10). The reproducibility and generalizability of this inverse association to the adult U.S. population is unknown.

The objective of the present study was to assess the association between serum levels of selenium and the prevalence of diabetes in the Third National Health and Nutrition Examination Survey (NHANES

III). We hypothesized that serum selenium levels would be inversely associated with the prevalence of diabetes.

## RESEARCH DESIGN AND METHODS

NHANES III, conducted from 1988 to 1994 by the U.S. National Center for Health Statistics, used a complex multistage sampling design to obtain a probability sample of the civilian noninstitutionalized U.S. population (11). A total of 16,573 adults aged  $\geq 20$  years participated in the NHANES III interviews and physical examinations. The overall participation rate was 78%.

For the present study, we selected the 10,478 NHANES III participants aged  $\geq 20$  years who had fasted for  $\geq 8$  h before venipuncture or who reported a physician diagnosis of diabetes or current use of insulin or oral hypoglycemic medication. We then excluded 156 participants who were pregnant at the time of the survey, 379 with missing serum selenium data, and 1,067 with missing values on other variables of interest. The analyses were based on a total of 8,876 NHANES III participants.

The laboratory procedures and quality control methods for serum selenium measurement have been described in detail elsewhere (12). Whole blood was collected in containers previously screened for selenium contamination. After clotting and centrifugation, serum was collected, frozen at  $-20^{\circ}\text{C}$ , and shipped to the laboratory. Serum selenium was measured using atomic absorption spectrometry (12–14). The limit of detection was 8 ng/ml. The between-assay coefficients of variation for quality control pooled samples analyzed throughout the duration of the survey ranged from 4.0 to 6.4% (12).

The plasma glucose concentration was measured using a modified hexokinase enzymatic method (12). Prevalent diabetes was defined as a fasting plasma glucose  $\geq 126$  mg/dl, a self-report of a physician diagnosis of diabetes, or current use of insulin or oral hypoglycemic medication (15).

Information about age, sex, race/ethnicity, education, family income, menopausal status, smoking, alcohol consumption, physical activity, and use of vitamin/mineral supplements was based

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Received for publication 14 August 2006 and accepted in revised form 29 December 2006.

**Abbreviations:** NHANES III, Third National Health and Nutrition Examination Survey.

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

DOI: 10.2337/dc06-1726

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Table 1—Characteristics of the study population by presence or absence of diabetes

	Diabetes	No diabetes	P
n	1,379	7,497	
Age (years)*	58.3 (0.5)	42.8 (0.4)	<0.001
Male sex (%)	45.6 (2.3)	49.8 (0.7)	0.08
Race (%)			0.01
Non-Hispanic white	73.7 (2.0)	77.2 (1.4)	
Non-Hispanic black	13.5 (1.2)	10.3 (0.6)	
Mexican American	6.0 (0.5)	5.2 (0.5)	
High school education (%)	60.0 (2.6)	76.8 (1.1)	<0.001
BMI (kg/m <sup>2</sup> )*	30.3 (0.3)	26.3 (0.1)	<0.001
Current smoking (%)	19.1 (1.8)	28.8 (0.9)	<0.001
Current alcohol consumption (%)	38.7 (2.8)	64.8 (1.4)	<0.001
Hypertension (%)	60.9 (2.0)	28.6 (1.0)	<0.001
Hypercholesterolemia (%)	50.1 (2.2)	28.4 (0.9)	<0.001
Vitamin/mineral supplement use (%)	42.1 (1.9)	40.6 (1.1)	0.48
C-reactive protein (mg/l)*	6.8 (0.4)	3.8 (0.1)	<0.001
Serum selenium concentration (ng/ml)*	126.5 (1.0)	125.7 (1.0)	0.41

Data are % (SE) or \*means (SE).

on interview questionnaires (11). Nutrient intake data were obtained from a 24-h dietary recall questionnaire. BMI was calculated by dividing weight in kilograms by the square of height in meters. Hypertension was defined as systolic blood pressure  $\geq 140$  mmHg, diastolic blood pressure  $\geq 90$  mmHg, a self-report of a physician diagnosis, or a self-report of current medication use for hypertension. Hypercholesterolemia was defined as a serum total cholesterol  $\geq 240$  mg/dl, a self-report of a physician diagnosis, or current medication use. Glomerular filtration rate was estimated by the Modifi-

cation of Diet and Renal Disease formula (16,17). Methods for other laboratory determinations are available elsewhere (12).

#### Statistical methods

Participants were divided in quintiles of serum selenium concentration based on the weighted population distribution. Odds ratios (ORs) and 95% CIs of diabetes were computed by comparing the four highest quintiles of serum selenium to the lowest one using multivariable logistic regression. To further explore the shape of the relationship between serum selenium and diabetes, we used restricted quadratic

splines with knots at the 5th, 35th, 65th, and 95th percentiles of the serum selenium distribution (18).

The association between serum selenium and diabetes prevalence was determined for subgroups defined by sex, age, race/ethnicity, smoking status, alcohol consumption, BMI, and vitamin/mineral supplement use. P values for the interactions were obtained from likelihood ratio tests comparing models with and without the interaction terms.

The data were analyzed using svy commands in STATA (version 9.0; Research Triangle Institute, Research Triangle Park, NC) to account for the NHANES III weights and complex survey design.

**RESULTS**— On average, participants with diabetes were older, had a higher BMI, were less likely to be high school educated, and were more likely to have hypertension or hypercholesterolemia compared with participants without diabetes (Table 1). Participants in the highest quintile of serum selenium were more likely to be male, non-Hispanic white, and high school educated and to have hypercholesterolemia (Table 2). Serum selenium levels were inversely associated with the prevalence of smoking.

Mean selenium levels were 126.5 ng/ml in participants with diabetes and 125.7 ng/ml in those without diabetes ( $P = 0.41$ ). Age-, sex-, race-, and BMI-adjusted mean selenium levels were 126.8 ng/ml in participants with diabetes

Table 2—Characteristics of the study population by quintile of serum selenium levels

	Quintile 1 ( $<111.62$ ng/ml)	Quintile 2 (111.62–120.17 ng/ml)	Quintile 3 (120.18–128.25 ng/ml)	Quintile 4 (128.26–137.65 ng/ml)	Quintile 5 ( $\geq 137.66$ ng/ml)	$P_{\text{trend}}$
Age (years)*	44.5	44.7	44.4	43.8	45.0	0.93
Male sex	40.5	42.7	49.1	50.9	53.4	<0.001
Race						
Non-Hispanic white	70.1	76.7	78.0	82.6	84.6	<0.001
Non-Hispanic black	19.8	12.8	9.8	7.3	6.9	<0.001
Mexican American	4.7	4.7	5.4	4.5	3.9	0.37
High school education	67.9	70.7	74.8	73.9	77.0	<0.001
BMI (kg/m <sup>2</sup> )*	27.2	26.5	26.8	26.9	26.4	0.19
Current smoking	39.1	32.3	29.3	30.3	21.4	<0.001
Current alcohol consumption	66.1	67.2	66.1	72.3	68.6	0.30
Hypertension	27.0	27.4	28.6	30.1	31.5	0.14
Hypercholesterolemia	24.0	30.5	31.3	34.6	38.4	<0.001
Vitamin/mineral supplement users	38.8	41.2	40.9	38.3	41.9	0.69
C-reactive protein (mg/l)*	2.8	2.1	1.5	1.7	1.4	<0.001

Data are % or \*means, adjusted for age, sex, and race/ethnicity.

Table 3—ORs (95% CI) for diabetes by quintile of serum selenium levels

	Quintile 1 (<111.62 ng/ml)	Quintile 2 (111.62– 120.17 ng/ml)	Quintile 3 (120.18– 128.25 ng/ml)	Quintile 4 (128.26– 137.65 ng/ml)	Quintile 5 (≥137.66 ng/ml)
Cases/noncases	285/1,708	306/1,669	251/1,545	226/1,309	311/1,266
Model 1	1.00 (reference)	1.22 (0.87–1.72)	1.03 (0.75–1.42)	1.13 (0.83–1.53)	1.43 (1.02–2.01)
Model 2	1.00 (reference)	1.40 (0.99–1.98)	1.05 (0.74–1.48)	1.12 (0.81–1.55)	1.60 (1.18–2.16)
Model 3	1.00 (reference)	1.40 (0.97–2.00)	1.03 (0.73–1.47)	1.15 (0.82–1.62)	1.57 (1.16–2.13)

Model 1 was adjusted for age (continuous), sex (male or female), and race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, or other). Model 2 was further adjusted for education (≥12 years of school completed or <12 years of school completed), family income (≥\$20,000 or <\$20,000), postmenopausal status for women (yes or no), cigarette smoking (current, former, or never), serum cotinine (continuous), alcohol consumption (current, former, or never), physical activity (0, 1–2, or ≥3 times per week), BMI (continuous), C-reactive protein (≥1.0, 0.3–0.9, or <0.3 mg/dl), hypercholesterolemia (yes or no), serum triglycerides (continuous), hypertension (yes or no), glomerular filtration rate (continuous), vitamin/mineral supplement use (yes or no), and intake of β-carotene (continuous), vitamin C (continuous), and vitamin E (continuous). Model 3 was further adjusted for serum levels of albumin (continuous), α-carotene (continuous and log-transformed), β-carotene (continuous and log-transformed), β-cryptoxanthin (continuous and log-transformed), lutein/zeaxanthin (continuous and log-transformed), lycopene (continuous and log-transformed), uric acid (continuous), vitamin C (continuous and log-transformed), and vitamin E (continuous and log-transformed).

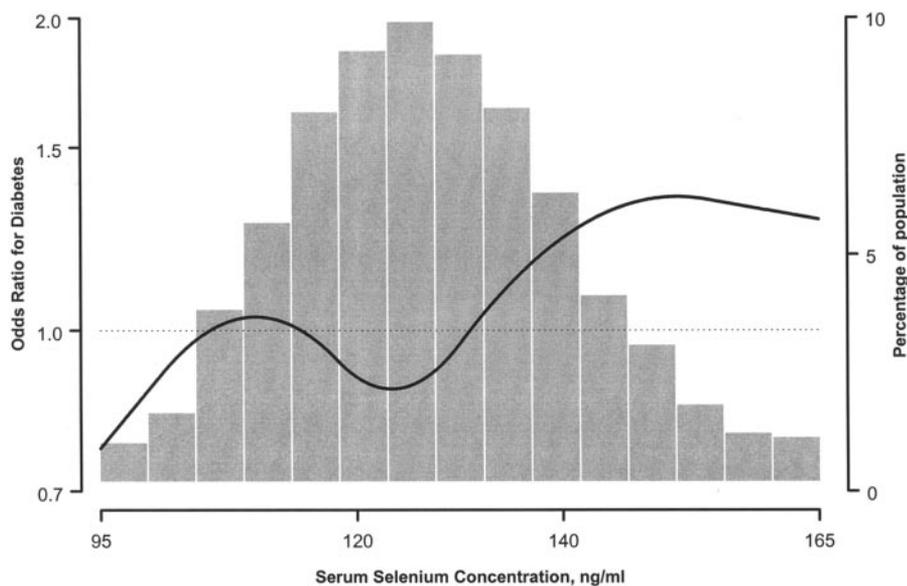
and 124.7 ng/ml in participants without diabetes (adjusted difference 2.1 ng/ml [95% CI 0.4–3.8];  $P = 0.02$ ). The multivariable-adjusted OR for diabetes comparing the highest to the lowest quintile of serum selenium was 1.57 [1.16–2.13] (Table 3). No clear trend was evident in quintiles 2–4. The spline regression model showed an increase in the odds for diabetes at >130 ng/ml serum selenium, which reached a plateau at >150 ng/ml (Fig. 1). The positive association between high serum selenium levels and the prevalence of diabetes was consistent for all subgroups examined except for participants with BMI <25 kg/m<sup>2</sup> (Fig. 2).

**CONCLUSIONS**— Contrary to our initial hypothesis, this large cross-sectional study conducted in a probability sample of the U.S. population identified a positive association between serum selenium levels and the prevalence of diabetes. This association was nonlinear. Subjects in the highest quintile of serum selenium had a statistically significant in-

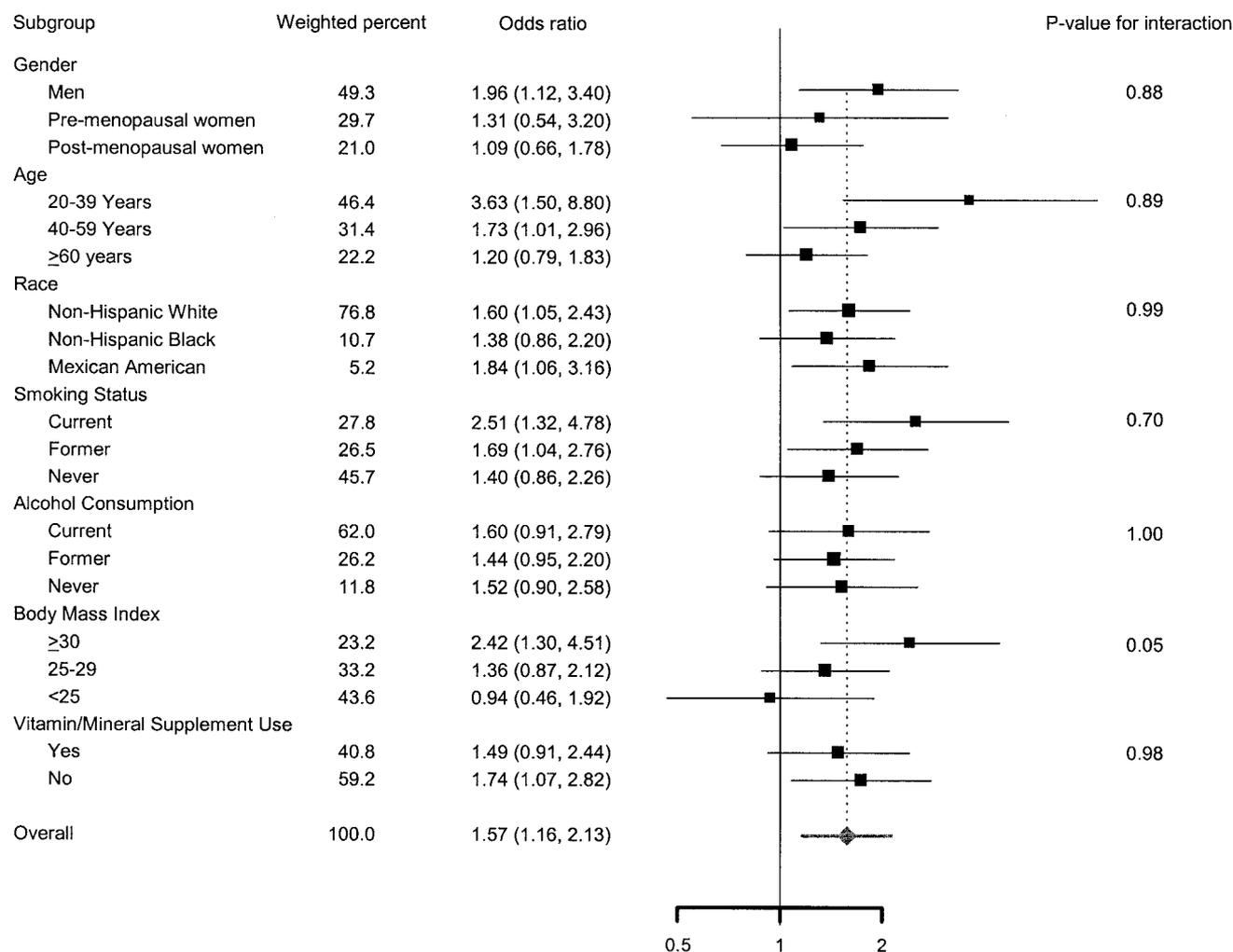
creased prevalence of diabetes compared with those in the first quintile, whereas there was no clear dose-response pattern in the three middle quintiles. Age, race, sex, risk factors for diabetes, or levels of other antioxidants did not explain this association.

Our findings are in contrast with a cross-sectional analysis of the Health Professionals Study, which showed an inverse association between toenail selenium and diabetes prevalence (10). Among male health professionals, the OR for prevalent diabetes comparing the highest to the lowest quartile of toenail selenium was 0.43 [95% CI 0.28–0.64], with a clear inverse dose-response relationship ( $P_{\text{trend}} = 0.001$ ) (10). In NHANES III, diagnosis of diabetes was based on fasting glucose levels and participant self-reports, whereas in the Health Professionals Study, diagnosis of diabetes was based only on self-reports. On the other hand, the Health Professionals Study used toenail selenium as a biomarker of exposure, whereas NHANES III used serum selenium. Although both biomarkers reflect selenium intake, toenail selenium provides a better assessment of long-term intake than serum selenium (10,19). It is unclear whether the differences in exposure and outcome assessment between NHANES III and the Health Professionals Study explain the different direction in the association between selenium and diabetes in both studies.

In a smaller cross-sectional study of a representative sample of Asians residing in Singapore, 126 participants with diabetes and 530 participants without diabetes had similar mean serum selenium levels (120.7 vs. 121.4 ng/ml, respectively;  $P = 0.68$ ) (20). This study, how-



**Figure 1**—ORs for diabetes by serum selenium levels. The curve represents adjusted ORs based on restricted quadratic splines with knots at the 5th, 35th, 65th, and 95th percentiles of the serum selenium distribution. The reference value (OR = 1) was set at the 10th percentile of the serum selenium distribution (105.7 ng/ml). ORs were adjusted for age, sex, race-ethnicity, education, income, menopausal status, cigarette smoking, serum cotinine, alcohol consumption, physical activity, BMI, C-reactive protein, total serum cholesterol, serum triglycerides, hypertension, glomerular filtration rate, vitamin/mineral supplement use, intake of β-carotene, vitamin C and vitamin E, and serum levels of albumin, α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin, lycopene, uric acid, vitamin C, and vitamin E. The histogram represents the frequency distribution of serum selenium in the study sample.



**Figure 2**—ORs for diabetes comparing the highest to the lowest quintile of serum selenium in selected population subgroups. The area of each square is proportional to the inverse of the variance of the log ORs. Horizontal lines represent 95% CIs. Results were adjusted for age, sex, race-ethnicity, education, income, menopausal status, cigarette smoking, serum cotinine, alcohol consumption, physical activity, BMI, C-reactive protein, total serum cholesterol, serum triglycerides, hypertension, glomerular filtration rate, vitamin/mineral supplement use, intake of  $\beta$ -carotene, vitamin C, and vitamin E, and serum levels of albumin,  $\alpha$ -carotene,  $\beta$ -carotene,  $\beta$ -cryptoxanthin, lutein/zeaxanthin, lycopene, uric acid, vitamin C, and vitamin E.

ever, did not report a detailed dose-response analysis.

Our findings were consistent with an observational analysis conducted within the Supplementation with Antioxidant Vitamins and Minerals (SU.VI.MAX) trial, in which baseline plasma selenium levels were positively associated with combined fasting plasma glucose at baseline and after 7.5 years of follow-up ( $P < 0.0001$ ) (21). Incidence of diabetes in this study by baseline selenium levels was not reported.

Although prospective studies with diabetes incidence as the outcome are needed to establish a causal role of selenium on diabetes risk, our findings provide a stark reminder that selenium exposure can be harmful. Indeed, the potential benefits of increased selenium in

populations with adequate selenium intake, such as the U.S., are unclear. Selenium is incorporated in selenoproteins as selenocysteine (7,22). Selenoproteins are responsible for the biological functions of selenium, and specific selenoproteins such as glutathione peroxidase, selenoprotein P, and thioredoxin reductase are important antioxidant enzymes (7,23). Although increased selenium intake may increase serum selenium, serum selenoprotein concentration and activity are maximized at plasma selenium levels between 70 and 90 ng/ml. Above these levels, increases in serum selenium do not reflect increases in selenoprotein levels or activity but rather reflect the nonspecific incorporation of selenomethionine replacing methionine in albumin and other serum proteins (6,23,24). Because 99% of

NHANES III participants had serum selenium levels  $>95$  ng/ml (23), selenium levels in our study population probably reflect selenomethionine intake but not selenoprotein activity.

In addition to its antioxidant effects, selenium has been reported to have strong antidiabetic and insulin-mimetic effects (8,9,25). In animal experiments, selenate decreased the activity of protein tyrosine phosphatase, a negative regulator of insulin signal transmission, by 50% and effectively reduced insulin resistance (8). This antidiabetic effect of selenium, however, is limited to selenate and does not hold for any other form of selenium (8,25). Even for selenate, the effect was only present at very high doses, e.g., half the lethal dose in rats (25). Given the toxicity of selenium (26), the implications of

these experimental effects of selenate for selenium nutrition in humans are uncertain.

The relatively narrow therapeutic range of selenium and its toxicity are partly related to the ability of some selenium compounds to generate reactive oxygen species (26–28). In the presence of reduced glutathione, selenite and methylselenol (a metabolite of selenomethionine and a likely intermediate in the selenium elimination pathway) (29,30) continuously generate superoxide ( $O_2^{\cdot-}$ ) in vitro (27). Under conditions of oxidative stress, reactive oxygen species may increase insulin resistance and affect pancreatic  $\beta$ -cell function (1–5). It is thus theoretically possible that high serum and body selenomethionine paradoxically result in oxidative stress and increased diabetes risk.

Probably the main limitation of our data is the inability to determine the direction of the observed association, as increased serum selenium may be a consequence rather than a cause of diabetes. For instance, participants with diabetes may have changed their health-related behaviors such as smoking, diet, and supplement use after learning that they have diabetes. In our study, this may have happened for smoking, since the prevalence of smoking was lower in participants with diabetes compared with those without diabetes (Table 1), even though smoking is an established risk factor for diabetes. To evaluate whether our findings were the result of changes in health behaviors after diabetes was diagnosed, we conducted a sensitivity analysis to assess the association of smoking and selenium with A1C, a well-established measure of glycemic control. We expected that if behavioral changes were the driving force behind our findings, the participants with the best-controlled diabetes would have more favorable health behaviors, including a lower prevalence of smoking and a higher selenium intake through diet and supplements. Indeed, lower A1C was associated with lower odds of smoking among participants with diabetes. However, lower A1C was also associated with lower serum selenium levels. This sensitivity analysis, however, cannot completely exclude reverse causation through behavioral changes. It is also possible that physiopathological changes in diabetes result in an increased serum selenium level, which would be an important finding for selenium research. Potential mechanisms for increased selenium levels in diabetes patients need to be identified and evaluated.

In addition, because participants with the highest selenium levels among those with diabetes also had the poorest glycemic control, it is possible that other subjects with diabetes and high serum selenium may have died or developed diabetes-related morbidity and would not be included in our study. As a consequence, this prevalence-incidence bias may have underestimated the association between selenium and diabetes in our data.

Our study had several strengths. These include the rigorous methodology and the detailed quality control procedures of NHANES III and the large sample size.

In summary, in a probability sample of the U.S. population, subjects in the highest serum selenium quintile had an increased prevalence of diabetes compared with those in the first quintile. These results are based on U.S. adults, a population with adequate selenium status, and cannot be extrapolated to populations with low selenium intake and status. Prospective studies are needed to confirm this association. In addition, ongoing randomized controlled trials of selenium supplements (31,32) should monitor diabetes incidence in study participants. Until the findings of these studies are available, selenium intake, including selenium supplementation, should not be recommended for diabetes prevention in populations with adequate selenium status. Furthermore, diabetic patients should avoid selenium supplements until randomized controlled trials show objective benefits on mortality or morbidity end points.

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