Higher Plasma Selenium Concentrations Are Associated with Increased Odds of Prevalent Type 2 Diabetes

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Abstract

Background: Selenium (Se), an essential trace element, has been investigated as a potential cancer prevention agent. However, several studies have indicated that Se supplementation may be associated with an increased risk of type 2 diabetes (T2D), although an equivocal relationship of this nature requires confirmation.

Objective: We examined the association between baseline plasma concentrations of Se and prevalence of T2D, as well as whether participant characteristics or intake of other antioxidant nutrients modified this relationship.

Methods: We conducted cross-sectional analyses of 1727 participants from the Selenium Trial, a randomized clinical trial of selenium supplementation for colorectal adenoma chemoprevention that had data for baseline Se plasma concentrations, T2D status, and dietary intake. Logistic regression modeling was used to evaluate the associations between plasma Se concentrations and prevalent T2D, adjusting for confounding factors. Heterogeneity of effect by participant characteristics was evaluated utilizing likelihood-ratio tests.

Results: Mean plasma Se concentrations for those with T2D vs. those without were 143.6 $\pm$ 28.9 and 138.7 $\pm$ 27.2 ng/ml, respectively. After adjustment for confounding, higher plasma Se concentrations were associated with higher prevalence of T2D, with ORs (95% CIs) of 1.25 (0.80-1.95) and 1.77 (1.16-2.71) for the second and third tertiles of Se, respectively, compared to the lowest tertile (*P*-trend=0.007). No statistically significant effect modification was observed for age, sex, BMI, smoking, or ethnicity. Increased odds of T2D were seen among those who were in the highest tertile of Se and the highest category of intake of β-cryptoxanthin (*P*-

trend=0.03) and lycopene (*P*-trend=0.008); however, interaction terms were not statistically significant.

Conclusions: These findings demonstrate that higher plasma concentrations of Se were statistically significantly associated with prevalent T2D among participants in a Se supplementation trial. Future work is needed to elucidate whether there are individual characteristics, such blood levels of other antioxidants, which may influence this relationship.

Keywords: selenium, supplementation, type 2 diabetes, antioxidants, trace elements

Introduction

Over the past two decades, the potential of the trace element selenium (Se) as a chemopreventive agent has been an area of intensive research. The first large randomized trial was the Nutritional Prevention of Cancer (NPC) Trial, in which 200 µg Se per day as brewers' yeast or a matched placebo was administered to evaluate whether it could reduce the risk of non-melanoma skin cancer[1]. While no effect of Se was observed for the primary endpoint of skin cancer, secondary analyses revealed a statistically significant 58% reduction in colorectal cancer and a 63% reduction in prostate cancer incidence among those receiving Se compared to placebo[1]. Since the findings for the NPC Trial were reported, Se supplementation has been tested in several large clinical trials to determine if it could prevent cancer or precancerous lesions, with generally null results for these endpoints[2,3].

In 2007, Stranges et al. published an analysis of data from the NPC trial which showed an increased risk for type 2 diabetes (T2D) among those in the Se intervention group as compared to those in the placebo arm[4]. In contrast, results from the large Selenium and Vitamin E Cancer Prevention Trial (SELECT) showed no significant increase in T2D risk after supplementation with 200 µg/d selenomethionine as compared to placebo[2]. Finally, the Selenium Trial, in which participants received either 200 µg/d of Se as selenized yeast or placebo, showed no overall increased risk for T2D with Se supplementation, but there was a significantly higher incidence of T2D among older participants receiving Se[3]. In addition to these clinical trials, several observational studies have been conducted to ascertain the potential influence of Se on diabetes[5-9] which generally provide evidence that supports a positive association between selenium concentrations and odds of T2D, though some studies found no relationship[10,11].

The differences in these findings suggest that there may be patient characteristics that affect response to Se. However, there is a dearth of data regarding whether dietary intake of other antioxidant nutrients may influence any effect of Se on the development of T2D. The SELECT trial, the design of which was predicated in part on experimental evidence that the combination of Se and vitamin E might prevent prostate cancer more effectively than either agent alone, is an exception[12]. Therefore, we sought to conduct a cross-sectional study to ascertain whether baseline plasma concentrations of Se were associated with T2D in the Selenium Trial, as well as whether dietary intake of other antioxidant nutrients, including retinol, β-carotene, β-cryptoxanthin, lycopene, lutein/zeaxanthin, and α- and γ-tocopherol, modified this association.

Methods

Study Population

Participants for this study were drawn from the Selenium Trial. A total of 1727 participants had data for both baseline concentrations of Se and for T2D (**Figure 1**). As described in detail previously[3,13], the Selenium Trial was a randomized, double-blind, placebo-controlled trial designed to test the effect of 200 μg/d of Se as selenized yeast on the recurrence of colorectal adenomas. Briefly, healthy male and female participants between the ages of 40 and 80 years, and who had undergone total colonoscopy and complete removal of one or more colorectal adenomas with a diameter of 3 mm or more within the 6 months before registration, were eligible. Exclusion criteria included familial syndromes such as Lynch syndrome or familial adenomatous polyposis; and presence of uncontrolled hypertension or heart disease, uncontrolled diabetes, or renal insufficiency[3]. Participants were recruited from endoscopy clinics in Arizona, Colorado, Texas and New York. Study data and biospecimens were collected, managed, and archived at the University of Arizona Cancer Center (Tucson, AZ)[13]. The

University of Arizona Institutional Review Board (IRB) approved and oversaw the study protocol, and conduct of the trial was in accordance with requirements of the local IRB at each study site.

Exposure and Outcome Assessment

Plasma selenium concentrations were analyzed by the AAnalyst 600 atomic absorption spectrometer (Perkin-Elmer, Norwalk, CT), equipped with a THGA graphite furnace with Zeeman background correction and a selenium electrodeless discharge lamp. The furnace conditions were optimized for analytical sensitivity with the best signal-to-noise ratio and good linearity of the calibration curve. Prior to the analysis, each plasma sample was diluted with matrix modifiers containing 0.01% nickelous nitrate hexahydrate and 0.0043% magnesium nitrate hexahydrate in 0.4% nitric acid and 0.2% triton X-100. The method of additions was used to prepare the calibration standards. For each batch of analyses, quality control samples with known concentrations of selenium were included within every 10 samples, and triplicate readings were collected for each sample.

For the collection of dietary, sociodemographic, and medical history data, self-administered questionnaires were completed by all participants in the Selenium Trial at baseline. The Arizona Food Frequency Questionnaire (AFFQ) was employed for dietary data ascertainment. The AFFQ is a 113-item, semi-quantitative, scannable instrument that is a modification of the frequency section of the National Cancer Institute's Health Habits and History Questionnaire[14]. Participants were asked to report their intake of various foods for the prior year[15]. Response categories ranging from >3 times/day to rarely/never were employed for most items, although for frequently-consumed foods and beverages, the scale ranged from >6 times/day to rarely/never[15]. Total intake of each nutrient was calculated by multiplying the

frequency of each item's consumption by the nutrient composition of each food[15]. The presence of T2D was ascertained through self-report at clinic visits, reported use of diabetic medications, and participant medical record reports. This information was then confirmed via requests for medical records sent to participants' primary care physicians[13].

Statistical Analyses

Descriptive data for baseline characteristics by presence or absence of T2D, and by tertile of baseline Se concentration, were calculated with means and standard deviations for the continuous variables and frequencies and percentages for the categorical variables. Unconditional logistic regression modeling was used to evaluate the associations between Se concentrations and baseline T2D overall and stratified by baseline characteristics and dietary intake. Variables assessed for potential confounding in both models were age, body mass index (BMI), sex, race, ethnicity, education, smoking status, and dietary intake of energy, protein, carbohydrate, fat, and fiber. Variables that changed the point estimate by 10% or greater were included in the final multivariate logistic regression analyses of the association between plasma selenium concentrations and odds of T2D[16]. Heterogeneity of effect for variables such as age, sex, BMI, and dietary intake was assessed by employing an interaction term for tertile of Se status and the variable in question and evaluating with a likelihood-ratio test. All analyses were conducted using STATA statistical software package [version 13.1, Stata Corporation, College Station, TX].

Results

Characteristics for diabetic (n=172) and non-diabetic (n=1,555) participants are presented in **Table 1**. Those who were diabetic were slightly older than those without T2D (64.8, SD: 8.0 vs.

62.9, SD: 9.0, respectively); were more likely to be male (72.7% vs 63.8%, respectively); and had a higher BMI (64.0% with a BMI >30 vs. 33.5%, respectively). There was a higher proportion of Black, Asian, and Hispanic participants with T2D than without; however, participant numbers were small and lacked precision. Smoking status and education level did not differ substantially between diabetics and non-diabetics. For dietary intake, those with T2D had higher consumption of energy and all other macronutrients compared to those without diabetes.

Table 2 presents participant characteristics stratified by tertile of baseline plasma selenium concentrations. Age and race were similar across the three tertiles, as was education and intake of energy and macronutrients. Those in the highest tertile of baseline Se compared to the lowest were more likely to be male (66.6% vs. 62.9%) and had a higher percentage with a BMI of 25 to <30 (46.2% vs. 43.0%) or a BMI $\geq$ 30 (36.1% vs. 34.4%). There were fewer current smokers and more former smokers in the group with T2D compared to those without.

Adjusted odds ratios for the association between baseline plasma selenium concentration and T2D are presented in **Table 3** by total population and stratified by baseline characteristics. Those in the highest tertile of baseline plasma selenium concentrations had the highest odds of prevalent T2D (OR 1.77; 95% CI 1.16-2.71). Among those less than 63 years of age, a baseline selenium value in either the second or third tertile was associated with a significantly higher odds of T2D, with ORs (95% CIs) of 2.54 (1.07-6.04) and 3.04 (1.32-7.02), respectively (*P*-trend=0.01). This association was not statistically significant among those aged 63 years and older, although an interaction term for age and Se concentrations was not statistically significant (*P*=0.18). There was a statistically significant trend for increased odds of prevalent T2D with increasing tertile of Se for men (*P*-trend=0.01), but not women (*P*-trend=0.09), although the

interaction term for sex was not significant (*P*=0.87). No material differences were observed for the association between Se and T2D by BMI category. Current smokers in the third tertile of baseline Se concentrations were determined to be at a greater odds of prevalent T2D relative to current smokers in the lowest tertile (OR 7.04; 95% CI 1.04-47.55), which was not observed among former or never smokers. However, the interaction term was not statistically significant (*P*=0.43), and the estimate for current smokers lacked precision. Among Non-Hispanics/Latinos, only those in highest tertile of baseline selenium had significantly increased odds of T2D prevalence (OR 1.75; 95% CI 1.12-2.73) (*P*-trend=0.01); while for Hispanics/Latinos, those in the highest tertile vs. the lowest had an OR (95% CI) of 0.63 (0.06-6.54), but the interaction term for ethnicity was not statistically significant (*P*=0.12).

Adjusted odds ratios for the association between baseline plasma Se concentration and T2D, stratified by dietary intake of other nutrients, are presented in **Table 4**. No effect modification was observed for intake of energy, protein, carbohydrate, total fat, or total fiber. In addition, there were no material differences in the magnitude of the association between Se and T2D by retinol, β-carotene, lutein, α-tocopherol, or ᵞ-tocopherol intake. However, among those with both the highest concentration of Se and the highest intake tertiles of β-cryptoxanthin and lycopene, the odds of T2D were highest, with ORs (95% CIs) of 3.03 (1.15-7.98) for β-cryptoxanthin (*P*-trend=0.03) and 2.66 (1.25-5.67) for lycopene (*P*-trend=0.008). No interaction terms for these antioxidants by Se concentrations were statistically significant.

Discussion

The results of this cross-sectional study demonstrated that higher baseline plasma concentrations of Se were statistically significantly associated with prevalent T2D among

participants in a clinical trial of selenium supplementation. The relationship appeared to be stronger among younger individuals, current smokers, and non-Hispanic whites; however, none of the interactions were statistically significant. In addition, the sample sizes for these stratified analyses limited the precision of the point estimates. Consumption of macronutrients did not appear to modify the relationship between Se and T2D; however, those who were in the highest tertile of plasma Se concentration and who also consumed the highest quantities of the antioxidant nutrients β-cryptoxanthin and lycopene had the highest prevalence of T2D, though interaction terms did not reach statistical significance. These findings are the first to indicate that intake of other antioxidant nutrients may modify the effect of selenium supplementation, though this relationship requires further examination, including measurement of blood levels of antioxidants.

The overall findings of this report are in agreement with the majority of observational studies which have reported positive associations between blood levels of Se and T2D[5,7-9]. Two studies utilized NHANES data to examine whether Se was related to T2D among participants in the United States[7,8]. Together, these reports encompassed over 9000 individuals, and both found that higher concentrations of Se were associated with higher rates of T2D, with ORs (95% CIs) of 1.57 (1.16-2.13)[8] and 7.64 (3.34-17.46)[7] for those in the highest quantiles for serum Se as compared to those in the lowest. Stranges et al.[9] employed data from the Italian Olivetti Heart Study and demonstrated that there was a higher proportion of individuals with diabetes in the highest tertile of baseline Se concentrations compared to the lowest. Zhang et al. compared levels of several trace elements among diabetic Chinese participants with those with no history of diabetes, and observed that those in the highest quartile of Se had an OR (95% CI) of 2.69 (1.31-3.49) compared to those in the lowest[5]. In contrast to these studies which found positive

associations for Se and T2D, two studies among participants in the Nord-Trøndelag Health Survey (HUNT-3) in Norway found no relationship[10,11]. Simic et al.[10] reported an OR (95% CI) of 1.13 (0.65-1.96) for prevalent diabetes among those in the highest tertile of whole blood concentrations of Se vs. the lowest; while Hansen restricted this population to early-stage diabetes and reported an OR (95% CI) of 0.93 (0.50–1.74)[11].

The reasons for the differential findings of the studies conducted in Norway as compared to the present work are unclear; however, the median measured blood concentrations of Se in the Norwegian work was in the range of 100-105 ng/ml[10,11]. These levels are substantially lower than those of the present study, wherein the overall mean Se concentration was 139.2 ng/ml, with a median of 135 ng/ml. Stranges et al.[4] reported that the increased odds for T2D in the NPC Trial were confined to those who entered the trial with blood levels of Se at or above 121.6 ng/ml. This suggests that the Se concentrations in the Norwegian studies were below those in which an increased risk for T2D would be observed. However, a larger proportion of individuals with T2D among those in the highest tertile of Se was reported in the study conducted in Italy, in which the mean Se concentration was only 95.5 ng/ml[9]. Therefore, although four of the six observational studies reported significantly increased odds for diabetes among those with the highest category of blood selenium levels compared to the lowest, it remains unclear whether there is a specific threshold of Se concentrations that may affect risk for T2D. It is possible that another, as-yet unidentified confounding variable affects this association. Results from clinical intervention trials therefore must be considered.

Although findings from observational studies suggest that there is a direct association between higher blood Se concentrations and T2D, data from completed clinical trials of Se supplementation are less consistent. Secondary analyses of the Nutritional Prevention of Cancer

(NPC) Trial revealed a hazard ratio (HR) and 95% confidence interval for the development of T2D among those supplemented with Se vs. placebo of 1.55 (1.03-2.33)[4]. Among more than 35,000 participants in the SELECT trial, the HR (95% CI) was 1.07 (0.94-1.22)[2]; while for the Selenium Trial, it was 1.25 (0.74-2.11)[3]. In the latter trial, a statistically significantly increased odds for T2D was observed for those aged >63 years, with an OR (95% CI) of 2.21 (1.04-4.67)[3]. Taken together, these results suggest that there may be a modest increase in the odds of T2D with higher circulating Se concentrations or with Se supplementation for chemoprevention.

The potential mechanism of action for any link between Se and T2D may be mediated in part via the selenoprotein glutathione peroxidase-1 (GPx-1)[17]. Saturation of GPx-1 occurs at comparatively low blood concentrations of Se[18], and findings in experimental animal models suggest that prolonged activation of GPx-1 may result in dysregulation of insulin signaling[19,20]. Overexpression of GPx-1 causes obesity and insulin resistance in experimental animal models[19], while reduced GPx-1 expression appears to reduce the manifestation of these outcomes[20]. Another possible mechanism that has been put forth is related to oxidative stress, via increased production of reactive oxygen species (ROS) under conditions of high concentrations of selenite and the Se metabolite methyselenol, which in turn may adversely affect pancreatic β-cells[8,17]. However, further work is required to elucidate the mechanism of action, as well as whether there is heterogeneity of treatment effect among study participants by variables such as age or intake of antioxidant nutrients in addition to Se, which themselves may impact oxidative stress.

Results from the present study suggest that there may be effect modification by other antioxidants in relation to T2D risk, although these findings were not statistically significant, and may be due to chance. We observed that odds for T2D were highest for those in the highest tertile of plasma Se concentrations who were also in the highest tertile for intake of β-

cryptoxanthin and lycopene. These findings are in contrast to recent work indicating that a high antioxidant capacity was associated with a reduced risk for T2D in the French E3N-European Prospective Investigation into Cancer and Nutrition (EPIC) cohort[21]. However, it remains unclear whether a balance of antioxidants may be key to scavenging ROS and thus protection against oxidative stress, or indeed whether antioxidants may also exhibit pro-oxidant activity at higher concentrations[22,23].

The results of the present study indicated that there was a stronger association for baseline Se concentrations and prevalent T2D among those who were <63 years of age, although the interaction term was not statistically significant. These results are in accordance with the two other observational studies that presented results stratified by age and where no statistically significant interactions were observed[7,8]. In the parent clinical trial for the present study, the Selenium Trial, a significantly increased risk for incident T2D was observed in those $\geq$ 63 years of age, but not in the younger age group, with a statistically significant interaction term[3]. It is possible that the differences in these findings may result from imprecise estimates due to lower numbers of events occurring in stratified analyses.

The strengths of this study include the large sample size and the detailed data available for participant characteristics and dietary intake. However, limitations to the work must be acknowledged. First, this was a cross-sectional analysis of blood Se concentrations and T2D, and as such no interpretations in regard to causality can be made. It is possible that a diagnosis of T2D alters dietary habits such that different food choices are made, and more antioxidant nutrients are consumed post-diagnosis[17]. Next, dietary data were ascertained via the AFFQ[15], which is a validated instrument; however, we did not capture data for blood concentrations of antioxidants other than Se. Therefore, future work will require measurement of these levels in

order to determine the degree to which bioavailability and utilization of these nutrients may affect these findings. Finally, although this was a large study, we were unable to determine whether there were differences in the association between Se and T2D among different racial and ethnic groups, which will be key to fully understanding whether Se may in fact increase the risk of this disease.

In conclusion, the results of this cross-sectional analysis support previously-published observational studies showing a positive association between Se and odds of T2D. To our knowledge, these are the first findings to suggest that intake of other antioxidant nutrients may modify the effects of Se supplementation. Future work is needed in measuring blood concentrations of other antioxidant nutrients, as well as clarifying whether there may be variation in this association by other individual characteristics such as race or ethnicity.

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Table 1. Baseline characteristics of study participants overall and stratified by baseline diabetes status.[1]

Characteristic	Total population *n*=1727	No diabetes *n*=1555	Diabetes *n*=172
Age, years	63.1 ± 8.9	62.9 ± 9.0	64.8 ± 8.0
Male, *n* (%)	1117 (64.7)	992 (63.8)	125 (72.7)
BMI in kg/m^2, *n* (%)[2]			
<25	344 (19.9)	334 (21.4)	10 (5.8)
25 to <30	752 (43.6)	700 (45.1)	52 (30.2)
≥ 30	630 (36.5)	520 (33.5)	110 (64.0)
Race, *n* (%)[3]			
White	1625 (94.2)	1474 (94.8)	151 (88.3)
Black	49 (2.8)	42 (2.7)	7 (4.1)
Asian	17 (1.0)	13 (0.8)	4 (2.3)
American Indian/Alaskan	8 (0.5)	7 (0.5)	1 (0.6)
Mixed or Other	26 (1.5)	18 (1.2)	8 (4.7)
Hispanic ethnicity, *n* (%)[4]	77 (4.5)	59 (3.8)	18 (10.5)
Cigarette smoking status, *n* (%)[5]			
Never	706 (41.8)	642 (42.2)	64 (38.1)
Former	828 (49.0)	739 (48.5)	89 (53.0)
Current	156 (9.2)	141 (9.3)	15 (8.9)
Education[6]			
< High school	32 (1.9)	27 (1.7)	5 (2.9)

High school or GED	337 (19.5)	299 (19.2)	38 (22.1)
Some college	510 (29.6)	448 (28.8)	62 (36.1)
Bachelor's degree	365 (21.2)	335 (21.6)	30 (17.4)
Graduate/professional	482 (27.8)	445 (28.7)	37 (21.5)
Dietary intake			
Energy (kcal/d)	1864 ± 890	1859± 871	1913± 1050
Protein (g/d)	76 ± 38	75 ± 36	82 ± 50
Carbohydrate (g/d)	248 ± 127	248 ± 125	254 ± 140
Total fat (g/d)	62 ± 35	61 ± 34	66 ± 43
Total fiber (g/d)	21 ± 12	21 ± 12	23 ± 13
Baseline plasma Se (ng/ml)	139.2 ± 27.2	138.7 ± 27.2	143.6 ± 28.9

[1]Values are means ± SDs or n (%). BMI, body mass index; Se, selenium.
[2] *n*=1726
[3] *n*=1725
[4] *n*=1725
[5] *n*=1690
[6] *n*=1726

Table 2. Baseline characteristics of study participants stratified by tertile of baseline plasma selenium concentrations (*n*=1714)[1].

	Tertile of plasma selenium level at baseline (mean ± sd, ng/ml)		
Characteristic	113.5 ± 9.7 *n*=572	135.4 ± 5.9 *n*=571	168.7 ± 23.4 *n*=571
Age, years	63.0 ± 9.3	63.3 ± 9.0	63.0 ± 8.8
Male, *n* (%)	360 (62.9)	374 (65.5)	380 (66.6)
BMI in kg/m^2, , *n* (%)			
<25	129 (22.6)	110 (19.3)	101 (17.7)
25 to <30	246 (43.0)	236 (41.4)	264 (46.2)
≥ 30	197 (34.4)	224 (39.3)	206 (36.1)
Race, , *n* (%)			
White	540 (94.6)	534 (93.7)	538 (94.2)
Black	18 (3.2)	19 (3.3)	12 (2.1)
Asian	2 (0.4)	5 (0.9)	10 (1.8)
American Indian/Alaskan	4 (0.7)	2 (0.4)	2 (0.4)
Mixed or Other	7 (1.2)	10 (1.8)	9 (1.6)
Hispanic ethnicity (yes) [1]	21 (3.7)	27 (4.8)	29 (5.1)
Cigarette smoking status, , *n* (%)[1]			
Never	236 (42.1)	237 (42.5)	226 (40.4)
Former	266 (47.5)	266 (47.7)	292 (52.1)
Current	58 (10.4)	55 (9.9)	42 (7.5)

Education[1]			
< High school	14 (2.5)	8 (1.4)	10 (1.8)
High school or GED	116 (20.3)	118 (20.7)	101 (17.7)
Some college	170 (29.7)	155 (27.2)	180 (31.6)
Bachelor's degree	118 (20.6)	126 (22.1)	119 (20.9)
Graduate/professional	154 (26.9)	164 (28.7)	160 (28.1)
Dietary intake			
Energy (kcal/d)	1859 $\pm$ 876	1883 $\pm$ 936	1849 $\pm$ 853
Protein (g/d)	75 $\pm$ 39	76 $\pm$ 39	76 $\pm$ 35
Carbohydrate (g/d)	248 $\pm$ 123	250 $\pm$ 131	247 $\pm$ 125
Total fat (g/d)	62 $\pm$ 36	63 $\pm$ 36	61 $\pm$ 33
Total fiber (g/d)	20 $\pm$ 11	21 $\pm$ 12	21 $\pm$ 12

[1]Values are means ± SDs or *n* (%). BMI, body mass index; Se, selenium. Missing data values for baseline characteristics are as follows: body mass index (*n*=1); race (*n*=2); ethnicity (*n*=2); cigarette smoking (*n*=37); education (*n*=1).

Table 3. Adjusted[1] odds ratios (95% confidence intervals) for the association between baseline plasma selenium concentration and diabetes, stratified by baseline characteristics.

	Tertile of Baseline Plasma Se (mean ± sd) Adjusted[1] Odds Ratios (95% Confidence Intervals)			
	113.5 ± 9.7	135.4 ± 5.9	168.7 ± 23.4	*P*-trend[2]
	n=572	*n*=571	*n*=571	
Total population, *n* cases (%)	43 (25.2)	55 (32.2)	73 (42.7)	
	1.00	1.25 (0.80-1.95)	1.77 (1.16-2.71)	0.007
Age at baseline, yrs, *n* cases (%)				
<63	11 (17.7)	22 (35.5)	29 (46.8)	
	1.00	2.54 (1.07-6.04)	3.04 (1.32-7.02)	0.01
≥ 63	32 (29.4)	33 (30.3)	44 (40.4)	
	1.00	0.95 (0.55-1.65)	1.41 (0.84-2.37)	0.18
P-interaction				0.15
Men, *n* cases (%)	29 (23.4)	41 (33.1)	54 (43.6)	
	1.00	1.36 (0.80-2.32)	1.91 (1.15-3.19)	0.01
Women, *n* cases (%)	14 (29.8)	14 (29.8)	19 (40.4)	
	1.00	1.30 (0.54-3.11)	2.02 (0.88-4.63)	0.09
P-interaction				0.87
BMI in kg/m^2, *n* cases (%)[1]				
<25	2 (20.0)	4 (40.0)	4 (40.0)	
	1.00	1.43 (0.18-11.16)	1.47 (0.18-11.87)	0.73
25 to <30	13 (25.5)	17 (33.3)	21 (41.2)	

	1.00	1.29 (0.58-2.84)	1.43 (0.67-3.06)	0.36
≥ 30	28 (25.5)	34 (30.9)	48 (43.6)	
	1.00	1.04 (0.59-1.85)	1.73 (1.00-2.99)	0.04
P-interaction				0.85
Smoking				
Never	14 (22.2)	24 (38.1)	25 (39.7)	
	1.00	1.66 (0.77-3.56)	1.68 (0.79-3.61)	0.20
Former	25 (28.1)	24 (27.0)	40 (44.9)	
	1.00	0.92 (0.50-1.72)	1.65 (0.94-2.91)	0.07
Current	2 (13.3)	6 (40.0)	7 (46.7)	
	1.00	3.54 (0.52-24.00)	7.04 (1.04-47.55)	0.04
P-interaction				0.43
Ethnicity, *n* cases (%)				
Non-Hispanic/Latino	38 (25.0)	51 (33.6)	63 (41.5)	
	1.00	1.37 (0.86-2.17)	1.75 (1.12-2.73)	0.01
Hispanic/Latino	5 (27.8)	3 (16.7)	10 (55.6)	
	1.00	0.13 (0.01-2.17)	0.63 (0.06-6.54)	0.80
P-interaction				0.12

[1]Models adjusted for age, sex, body mass index, race, ethnicity, smoking, education, and dietary intake of energy, protein, carbohydrate, total fat and total fiber.

[2]*P*-values are *P*-trend for continuous variables.

Table 4. Adjusted[1] odds ratios (95% confidence intervals) for the association between baseline plasma selenium concentration and diabetes, stratified by dietary intake of other nutrients.

	Tertile of Baseline Plasma Se (mean ± sd) Adjusted[1] Odds Ratios (95% Confidence Intervals)			
Tertile of dietary intake (mean ± sd)	1 113.5 ± 9.7	2 135.4 ± 5.9	3 168.7 ± 23.4	*P*-trend[2]
Energy intake (kcal/d)				
1052 ± 244, *n* cases (%)	14 (23.3)	17 (28.3)	29 (48.3)	
	1.00	0.89 (0.40-1.98)	1.70 (0.81-3.56)	0.12
1694 ± 179, *n* cases (%)	14 (29.2)	15 (31.3)	29 (39.6)	
	1.00	1.07 (0.47-2.46)	1.37 (0.62-3.03)	0.43
2847 ± 795, *n* cases (%)	15 (23.8)	23 (36.5)	25 (39.7)	
	1.00	2.07 (0.94-4.56)	1.78 (0.82-3.90)	0.17
P-interaction				0.82
Protein (g/d)				
42.6 ± 10.5, *n* cases (%)	13 (24.5)	13 (24.5)	27 (50.9)	
	1.00	0.77 (0.32-1.83)	2.04 (0.95-4.37)	0.04
69.4 ± 7.1, *n* cases (%)	13 (27.1)	18 (37.5)	17 (35.4)	
	1.00	1.18 (0.52-2.69)	1.24 (0.55-2.80)	0.62
115.4 ± 37.2, *n* cases (%)	17 (24.3)	24 (34.3)	29 (41.4)	
	1.00	1.74 (0.83-3.62)	1.57 (0.77-3.19)	0.24
P-interaction				0.64
Carbohydrate (g/d)				
131.1 ± 33.0, *n* cases (%)	11 (20.0)	17 (30.9)	27 (49.1)	
	1.00	1.24 (0.52-2.95)	2.47 (1.11-5.50)	0.02

224.0 ± 27.4, *n* cases (%)	16 (29.1)	17 (30.9)	22 (40.0)	
	1.00	1.25 (0.57-2.72)	1.33 (0.63-2.82)	0.46
390.4 ± 108.2, *n* cases (%)	16 (26.2)	21 (34.4)	24 (39.3)	
	1.00	1.39 (0.65-3.00)	1.43 (0.67-3.05)	0.37
P-interaction				0.90
Total fat (g/d)				
31.2 ± 8.5, *n* cases (%)	17 (29.3)	18 (31.0)	23 (39.7)	
	1.00	0.94 (0.44-2.01)	1.30 (0.62-2.73)	0.47
54.8 ± 6.7, *n* cases (%)	11 (23.4)	12 (25.5)	24 (51.1)	
	1.00	0.94 (0.35-2.52)	2.40 (1.03-5.61)	0.03
99.6 ± 33.8, *n* cases (%)	15 (22.7)	25 (37.9)	26 (39.4)	
	1.00	2.26 (1.04-4.91)	2.07 (0.96-4.49)	0.08
P-interaction				
Total fiber (g/d)				
10.4 ± 2.7, *n* cases (%)	10 (20.4)	16 (32.7)	23 (46.9)	
	1.00	1.41 (0.57-3.48)	3.11 (1.33-7.24)	0.006
18.7 ± 2.5, *n* cases (%)	15 (25.9)	19 (32.8)	24 (41.4)	
	1.00	1.17 (0.54-2.51)	1.62 (0.77-3.44)	0.20
33.4 ± 11.1, *n* cases (%)	18 (28.1)	20 (31.3)	26 (40.6)	
	1.00	1.43 (0.67-3.04)	1.42 (0.69-2.92)	0.35
P-interaction				0.62
Retinol (IU/d)				
3301.0 ± 939.1, *n* cases (%)	15 (25.9)	17 (29.3)	26 (44.8)	

	1.00	0.89 (0.40-1.96)	1.86 (0.88-3.91)	0.08
6322.7 ± 933.2, *n* cases (%)	14 (28.0)	16 (32.0)	20 (40.0)	
	1.00	0.96 (0.42-2.18)	1.50 (0.68-3.32)	0.31
14017.9 ± 12384.3, *n* cases (%)	14 (22.2)	22 (34.9)	27 (42.9)	
	1.00	2.40 (1.08-5.35)	2.08 (0.97-4.45)	0.08
P-interaction				0.74
β-carotene (μg/d)				
1173.2 ± 403.2, *n* cases (%)	15 (26.8)	16 (28.6)	25 (44.6)	
	1.00	0.79 (0.35-1.76)	1.92 (0.91-4.06)	0.07
2510.9 ± 450.5, *n* cases (%)	16 (27.1)	19 (32.2)	24 (40.7)	
	1.00	1.28 (0.59-2.77)	1.69 (0.79-3.59)	0.18
6302.7 ± 5989.8, *n* cases (%)	12 (21.4)	20 (35.7)	24 (42.9)	
	1.00	1.79 (0.78-4.13)	1.76 (0.78-3.96)	0.20
P-interaction				0.65
β-cryptoxanthin (μg/d)				
42.6 ± 17.0, *n* cases (%)	16 (25.4)	25 (39.7)	22 (34.9)	
	1.00	1.63 (0.79-3.38)	1.92 (0.92-4.00)	0.09
120.0 ± 32.3, *n* cases (%)	18 (29.5)	15 (24.6)	28 (45.9)	
	1.00	0.68 (0.31-1.48)	1.39 (0.69-2.79)	0.30
379.2 ± 174.5, *n* cases (%)	9 (19.2)	15 (31.9)	23 (48.9)	
	1.00	2.46 (0.90-6.73)	3.03 (1.15-7.98)	0.03
P-interaction				0.48
Lycopene (μg/d)				

2095.0 ± 727.3, *n* cases (%)	14 (24.1)	17 (29.3)	27 (46.6)	
	1.00	1.18 (0.54-2.57)	1.90 (0.91-3.97)	0.08
4169.3 ± 604.2, *n* cases (%)	15 (28.3)	22 (41.5)	16 (30.2)	
	1.00	1.54 (0.67-3.54)	1.18 (0.50-2.78)	0.75
8461.9 ± 3679.8, *n* cases (%)	14 (23.3)	16 (26.7)	30 (50.0)	
	1.00	1.29 (0.56-2.95)	2.66 (1.25-5.67)	0.008
P-interaction				0.25
Lutein (μg/d)				
915.9 ± 319.9, *n* cases (%)	15 (28.9)	13 (25.0)	24 (46.2)	
	1.00	0.67 (0.29-1.54)	1.77 (0.85-3.68)	0.11
1976.2 ± 354.0, *n* cases (%)	18 (28.6)	21 (33.3)	24 (38.1)	
	1.00	1.30 (0.60-2.78)	1.52 (0.73-3.16)	0.26
4774.5 ± 3453.0, *n* cases (%)	10 (17.9)	21 (37.5)	25 (44.6)	
	1.00	2.59 (1.09-6.17)	2.43 (1.03-5.72)	0.06
P-interaction				0.60
α-tocopherol (mg/d)				
3.75 ± 1.0, *n* cases (%)	15 (25.4)	18 (30.5)	26 (44.1)	
	1.00	1.03 (0.47-2.26)	1.82 (0.88-3.74)	0.09
6.5 ± 0.8, *n* cases (%)	12 (23.1)	16 (30.8)	24 (46.2)	
	1.00	1.37 (0.60-3.14)	1.95 (0.90-4.24)	0.09
12.2 ± 5.1, *n* cases (%)	16 (26.7)	21 (35.0)	23 (38.3)	
	1.00	1.83 (0.82-4.10)	1.52 (0.70-3.31)	0.34
P-interaction				0.73

γ-tocopherol (mg/d)				
1.6 ± 0.5, *n* cases (%)	16 (29.6)	15 (27.8)	23 (42.6)	
	1.00	0.91 (0.41-2.05)	1.66 (0.79-3.51)	0.17
3.3 ± 0.5, *n* cases (%)	14 (25.0)	17 (30.3)	25 (44.6)	
	1.00	1.41 (0.61-3.25)	1.95 (0.88-4.32)	0.10
7.0 ± 3.0, *n* cases (%)	13 (21.3)	23 (37.7)	25 (41.0)	
	1.00	1.78 (0.81-3.93)	2.16 (0.99-4.72)	0.06
P-interaction				0.94

[1]Models adjusted for age, sex, body mass index, race, ethnicity, smoking, education, and dietary intake of energy, protein, carbohydrate, total fat and total fiber.

[2]*P*-values are *P*-trend for continuous variables.