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Nutrition

Plasma selenium levels and risk of new-onset diabetes in hypertensive adults

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ABSTRACT

Objective: The association between plasma selenium and new-onset diabetes in hypertensive adults is still unclear. We aimed to evaluate the relationship of baseline plasma selenium with new-onset diabetes and examine possible effect modifiers in a post-hoc analysis of the China Stroke Primary Prevention Trial (CSPPT).
Methods: A total of 2367 hypertensive, non-diabetic patients with plasma selenium measurements at baseline were included. The primary outcome was new-onset diabetes, defined as physician-diagnosed diabetes or use of glucose-lowering drugs during the follow-up period, or fasting glucose (FG) ≥126.0 mg/dL at the exit visit.
Results: At baseline, higher FG levels were found among participants with plasma selenium in quartile 4 (≥94.8 μg/L) (β, 1.64 mg/dL; 95%CI: 0.54, 2.73) compared to those in quartiles 1–3. During a median follow-up duration of 4.5 years, new-onset diabetes occurred in 270 (11.4%) participants. Graphic plot showed a positive association between baseline selenium levels and risk of new-onset diabetes. This was further confirmed by adjusted regression analyses; the odds ratios (OR) for new-onset diabetes comparing quartile 4 (≥94.8 μg/L) to quartiles 1–3 was 1.36 (95%CI: 1.01, 1.83). No clear trend was evident across quartiles 1–3.
Conclusions: Our data suggest that high plasma selenium (≥94.8 μg/L) was associated with increased risk of new-onset diabetes in hypertensive patients.

1. Introduction

Selenium is an essential trace element. Selenocysteine is the key component of a number of selenoproteins with essential pleiotropic effects, ranging from antioxidant and anti-inflammatory effects to thyroid hormone metabolism [1,2]. Selenium is a component of many dietary supplements, including multivitamins. Nevertheless, despite its perceived health benefits, the unexpected detection of a strongly

Abbreviations: BMI, body mass index; BP, blood pressure; CSPPT, China stroke primary prevention trial; CI, confidence interval; DBP, diastolic blood pressure; GPx3, glutathione peroxidase 3; HDL-C, high density lipoprotein cholesterol; OR, odds ratios; ROS, reactive oxygen species; SelP, Selenoprotein P; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides

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increased risk of diabetes in the Nutritional Prevention of Cancer (NPC) trial [3] has raised concerns that high selenium exposure may be associated with an increased risk of type 2 diabetes, at least in selenium-replete populations. A recent meta-analysis [4], comprised of a combination of cross-sectional studies, case-control studies and cohort studies, also found a positive association between selenium exposure and diabetes. However, this meta-analysis only included three [5–7] previously published cohort studies investigating the prospective blood selenium-diabetes association. More importantly, although diabetes and hypertension often coexist and their coexistence substantially increases the risk of CVD [8,9], the selenium-diabetes association has not been well investigated in hypertensive populations.

As such, using data from the China Stroke Primary Prevention Trial (CSPPT) [10], we sought to examine the relationship of baseline plasma selenium with new-onset diabetes over the 4.5-year period of follow-up in hypertensive patients. In addition, we sought to examine any possible effect modifiers on the selenium-diabetes association, which has not been thoroughly evaluated in previous studies.

2. Materials and methods

2.1. Study participants, intervention and follow-up

The study design and major results of the CSPPT have been described previously [10–13]. The CSPPT was a randomized, double-blind, controlled trial conducted from May 19, 2008 to August 24, 2013 in 32 communities in China. In the CSPPT, a total of 20,702 hypertensive participants aged 45–75 years without physician-diagnosed major cardiovascular diseases, were randomly assigned to one of two treatment groups: a daily oral dose of 10 mg enalapril and 0.8 mg folic acid (the enalapril-folic acid group), or a daily oral dose of 10 mg enalapril only (the enalapril only group). Participants were followed up every three months. At the exit visit, final blood samples and diabetes status were assessed. The detailed inclusion and exclusion criteria for the CSPPT have been reported elsewhere. [10]

Selenium deficiencies have been associated with cancer, cardiovascular disease and mortality [1]. Therefore, we selected two cohorts of study participants from the CSPPT. Study 1 included 1326 incident stroke, cancer or all-cause mortality cases matched with 1264 corresponding controls. Controls were randomly chosen from the baseline CSPPT participants who did not develop the corresponding end points during the follow-up. Controls were matched with the cases on a 1:1 ratio for age (± 1 year), sex, treatment group and study site. Study 2 included 1500 subjects randomly selected from the CSPPT. Some of the participants were included in both study 1 and study 2. The total study sample for the current analysis included those participants from both study 1 and study 2 with plasma selenium and fasting glucose measurements at baseline, as well as with physician-diagnosed diabetes or use of glucose-lowering drugs during the follow-up or fasting glucose data at the exit visit; and who were free of diabetes (physician-diagnosed diabetes or use of glucose-lowering drugs) and whose fasting glucose (FG) was < 126.0 mg/dL at baseline (Fig. S1).

As the current analysis utilized data from study 1 and study 2, participants had a range of baseline selenium levels and the analysis had enough power to examine the association between plasma selenium and new-onset diabetes. The study was approved by the Ethics Committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China (FWA assurance number: FWA00001263).

2.2. Study outcome

The major study outcome was new-onset diabetes, defined as physician-diagnosed diabetes, or use of glucose-lowering drugs during the follow-up period, or new onset FG ≥ 126.0 mg/dL at the exit visit.

2.3. Laboratory assays

Serum fasting lipids, and fasting glucose levels were measured using automatic clinical analyzers (Beckman Coulter) at the core laboratory of the National Clinical Research Center for Kidney Disease, Nanfang Hospital, Guangzhou, China. Serum folate was measured in a commercial laboratory using a chemiluminescent immunoassay (New Industrial). Plasma selenium was measured by inductively coupled plasma mass spectrometry (ICP-MS) using Thermo Fisher iCAP Q ICP-MS, and plasma vitamin E was measured by liquid chromatography with tandem quadrupole mass spectrometers (LC–MS/MS) in a commercial lab (Beijing DIAN Medical Laboratory, China).

Selenium deficiency was defined as a plasma selenium level < 20–40 μg/L [14]. Selenium insufficiency was defined as a plasma selenium level > 40–70 μg/L [15].

2.4. Statistical analysis

Baseline characteristics are listed as mean ± SD for continuous variables and proportions for categorical variables by selenium quartiles. Differences in baseline characteristics were compared using ANOVA tests, or chi-square tests, accordingly.

Logistic regression models were performed to determine the relationship of plasma selenium quartiles (< 70.8, 70.8– < 82.3, 82.3– < 94.8, and ≥ 94.8 μg/L) or tertiles (< 74.6, 74.6– < 89.8, and ≥ 89.8 μg/L) with new-onset diabetes, without and with adjustment for age, sex, study center, study treatment group, body mass index (BMI), *MTHFR* C677 T genotype, smoking, alcohol drinking, family history of diabetes, systolic blood pressure (SBP), fasting glucose, total cholesterol (TC), triglycerides, high-density lipoprotein (HDL) cholesterol, creatinine, and folate at baseline, as well as time-averaged SBP during the treatment period. Linear regression was performed to examine the relationship of plasma selenium and fasting glucose levels at baseline without and with adjustments for the above baseline covariates. Possible effect modifications of the association between plasma selenium and new-onset diabetes were investigated by stratified analyses. Interactions were examined by including interaction terms in the regression models. In addition, we explored the relation of baseline plasma selenium with baseline fasting glucose levels and new-onset diabetes using thin plate regression splines in generalized additive models implemented by the R package *mgcv*. R software (version 3.4.3, http://www.R-project.org) was used for all statistical analyses.

3. Results

3.1. Study participants and baseline characteristics

A total of 2367 participants were included in the final analysis (Fig. S1). Participant characteristics by baseline plasma selenium quartiles are presented in Table 1. The mean baseline plasma selenium level was 84.8 μg/L (SD, 21.1). The prevalence of selenium deficiency (< 20–40 μg/L) and insufficiency (> 40–70 μg/L) was 0.1% and 23.2%, respectively. Plasma selenium concentrations were directly associated with male gender, current alcohol drinking, TC, and creatinine.

3.2. Cross-sectional association between plasma selenium and FG at baseline

At baseline, there was a positive association between plasma selenium and fasting glucose (Fig. 1A, Table 2). When plasma selenium was analyzed as quartiles, higher FG levels were found among participants in quartile 4 (≥ 94.8 μg/L) (β, 1.64 mg/dL; 95%CI: 0.54, 2.73) compared to those in quartiles 1–3.

Table 1
Characteristics of the study participants by selenium quartiles*.

Variables	Total	Selenium, μg/L				*P* value
		Quartile 1 (< 71.0)	Quartile 2 (71.0– < 82.3)	Quartile 3 (82.3– < 94.8)	Quartile 4 (≥94.8)	
N	2367	592	591	592	592	
Male, No. (%)	1108(46.8)	253 (42.7)	255 (43.1)	289 (48.8)	311 (52.5)	0.001
Age, y	61.4 ± 7.6	61.9 ± 7.8	61.5 ± 7.6	61.2 ± 7.4	60.9 ± 7.6	0.123
Body mass index, kg/m^2	24.7 ± 3.6	24.7 ± 3.6	24.9 ± 3.8	24.9 ± 3.6	24.5 ± 3.5	0.120
Current smoking, No. (%)	665 (28.1)	156 (26.4)	159 (26.9)	165 (27.9)	185 (31.2)	0.159
Current alcohol drinking, No. (%)	630 (26.6)	119 (20.1)	151 (25.6)	165 (27.9)	195 (32.9)	< 0.001
Family history of diabetes, No. (%)	80 (3.4)	17 (2.9)	24 (4.1)	20 (3.4)	19 (3.2)	0.712
Enalapril-folic acid group, No. (%)	1131(47.8)	281 (47.5)	289 (48.9)	272 (45.9)	289 (48.8)	0.712
Medication use, No. (%)						
Antihypertensive drugs,	1100 (46.5)	272 (45.9)	286 (48.4)	261 (44.1)	281 (47.5)	0.470
Lipid lowering drugs,	16 (0.7)	2 (0.3)	5 (0.8)	4 (0.7)	5 (0.8)	0.679
Antiplatelet drugs,	80 (3.4)	19 (3.2)	16 (2.7)	28 (4.7)	17 (2.9)	0.200
BP, mmHg						
Systolic BP at baseline	167.8 ± 20.2	168.7 ± 20.7	167.9 ± 20.0	167.8 ± 20.8	166.7 ± 19.3	0.427
Diastolic BP at baseline	93.9 ± 12.1	93.1 ± 12.3	93.7 ± 12.1	94.2 ± 12.3	94.6 ± 11.9	0.139
Time-averaged systolic BP	139.3 ± 10.4	139.9 ± 11.0	138.8 ± 10.7	139.1 ± 9.9	139.4 ± 10.1	0.277
Time-averaged diastolic BP	82.5 ± 7.4	82.4 ± 7.6	82.3 ± 7.3	82.6 ± 7.3	82.9 ± 7.4	0.422
Laboratory results						
Total cholesterol, mmol/L	5.5 ± 1.1	5.3 ± 1.0	5.5 ± 1.2	5.5 ± 1.1	5.7 ± 1.2	< 0.001
HDL-C, mmol/L	1.4 ± 0.4	1.3 ± 0.3	1.3 ± 0.3	1.4 ± 0.4	1.4 ± 0.4	< 0.001
Triglycerides, mmol/L	1.6 ± 0.8	1.6 ± 0.8	1.6 ± 0.8	1.5 ± 0.7	1.6 ± 0.9	0.690
Fasting glucose, mg/dL	96.4 ± 12.3	95.8 ± 11.9	96.1 ± 12.3	96.7 ± 12.1	97.1 ± 12.9	0.246
Creatinine, μmol/L	67.5 ± 17.6	66.8 ± 21.1	66.6 ± 17.1	67.5 ± 15.5	69.2 ± 16.1	0.048
Folate, ng/mL	8.3 ± 3.9	8.5 ± 4.1	8.2 ± 4.1	8.1 ± 3.8	8.4 ± 3.7	0.279
Selenium, μg/L	84.8 ± 21.1	62.8 ± 6.2	76.5 ± 3.2	87.9 ± 3.5	111.8 ± 20.8	< 0.001
Vitamin E, μg/mL	9.7 ± 3.5	9.7 ± 3.5	9.7 ± 3.4	9.4 ± 3.2	9.9 ± 3.7	0.167

Abbreviations: BP, blood pressure; HDL-C, high-density lipoprotein cholesterol.
* Variables are presented as Mean ± SD or n (%).

3.3. Prospective association between baseline plasma selenium and new-onset diabetes

During a median follow-up duration of 4.5 years (IQR, 4.2–4.7 years), new-onset diabetes occurred in 270 (11.4%) participants. The association between plasma selenium and risk of new-onset diabetes were presented in Fig. 1B. When plasma selenium was analyzed as quartiles, the multivariable-adjusted odds ratios (OR) for new-onset diabetes comparing quartile 4 (≥94.8 μg/L) to quartiles 1–3 was 1.36 (95%CI: 1.01, 1.83) (Table 3). No clear trend was evident across quartiles 1–3.

The results were similar when plasma selenium was assessed as tertiles (Table S1), in participants without incident cancer or stroke or all-cause mortality during the follow-up period (Table S2), and in participants from study 1 or study 2 (Table S3).

During the treatment period, participants with higher selenium levels had a lower frequency in the use of diuretics (Table S4). However, further adjustment for the use of calcium channel blockers (CCB) or diuretics did not substantially change the results (Table S5).

3.4. Sensitivity analyses in subgroups

Stratified analyses were performed by sex, age (< 60 *vs.* ≥60 years), *MTHFR* C677 T genotypes (CC, CT, TT), BMI (< 24 *vs.* ≥24 kg/m^2), treatment group (enalapril *vs.* enalapril + folic acid), SBP (< 160 *vs.* ≥160 mmHg), TC (< 5.2 *vs.* ≥5.2 mmol/L), folate (median, < 7.7 *vs.* ≥7.7 ng/ml), fasting glucose [< 100.8 *vs.* ≥100.8 mg/dL (5.6 mmol/L)], and vitamin E (median, < 9.2 *vs.* ≥9.2 μg/mL) at baseline, and time-averaged SBP during the follow-up period (< 140 *vs.* ≥140 mmHg). A higher risk of new-onset diabetes (quartile 4 *vs.* 1–3) was observed across all subgroups (Fig. 2).

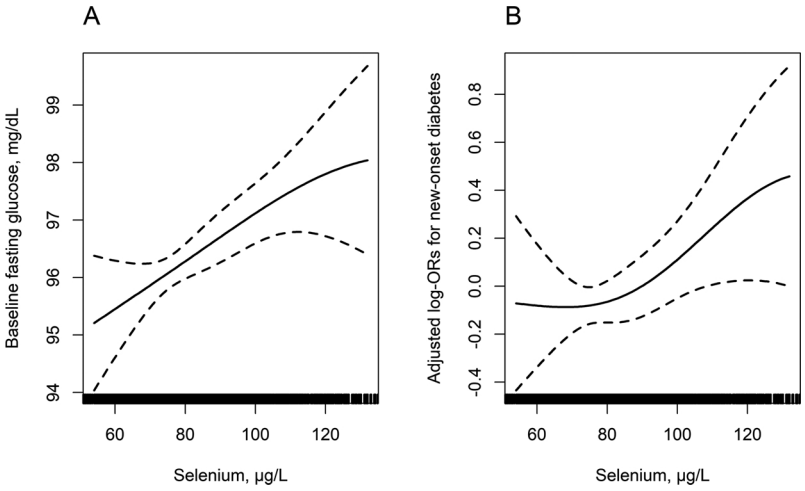

Fig. 1. The cross-sectional relationship of plasma selenium with fasting glucose at baseline (A) and the longitudinal relationship of baseline plasma selenium with risk of new-onset diabetes (B) in hypertensive patients*.
*A: Adjusted for age, sex, study center, body mass index (BMI), *MTHFR* C677 T genotype, smoking, alcohol drinking, family history of diabetes, systolic blood pressure (SBP), total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, creatinine, and folate at baseline.
B: Adjusted for age, sex, study center, study treatment group, body mass index (BMI), *MTHFR* C677 T genotype, smoking, alcohol drinking, family history of diabetes, systolic blood pressure (SBP), fasting glucose (FG), total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, creatinine, and folate at baseline, as well as time-averaged SBP during the follow-up period.

Table 2
Cross-sectional association between selenium and fasting glucose (mg/dL) at baseline.

Selenium (μg/L)	N	Mean ± SD	Unadjusted model		Adjusted model*	
			β(95%CI)	*P* value	β(95%CI)	*P* value
Quartiles						
Q1(< 71.0)	592	95.8 ± 11.9	*ref.*	–	*ref.*	–
Q2(71.0– < 82.3)	591	96.1 ± 12.3	0.32 (−1.09, 1.72)	0.659	0.14 (−1.18, 1.47)	0.830
Q3(82.3– < 94.8)	592	96.7 ± 12.1	0.90 (−0.50, 2.30)	0.209	0.88 (−0.45, 2.20)	0.195
Q4(≥94.8)	592	97.1 ± 12.9	1.33 (−0.07, 2.73)	0.063	1.99 (0.64, 3.34)	0.004
Categories						
Q1–3(< 94.8)	1775	96.2 ± 12.1	*ref.*	–	*ref.*	–
Q4(≥94.8)	592	97.1 ± 12.9	0.93 (−0.22, 2.07)	0.113	1.64 (0.54, 2.73)	0.004

* Adjusted for age, sex, study center, body mass index (BMI), *MTHFR* C677 T genotypes, smoking, alcohol drinking, family history of diabetes, systolic blood pressure (SBP), total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, creatinine, and folate at baseline.

Table 3
Prospective association between baseline plasma selenium and new-onset diabetes.

Selenium (μg/L)	N	No. of events (%)	Unadjusted model		Adjusted model*	
			OR (95%CI)	*P* value	OR (95%CI)	*P* value
Quartiles						
Q1(< 71.0)	592	63 (10.6)	*ref*	–	*ref*	–
Q2(71.0– < 82.3)	591	63 (10.7)	1.00 (0.69, 1.45)	0.992	0.99 (0.67, 1.47)	0.968
Q3(82.3– < 94.8)	592	58 (9.8)	0.91 (0.63, 1.33)	0.632	0.87 (0.59, 1.30)	0.509
Q4(≥94.8)	592	86 (14.5)	1.43 (1.01, 2.02)	0.045	1.29 (0.89, 1.89)	0.184
Categories						
Q1–3(< 94.8)	1775	184 (10.4)	*ref*	–	*ref*	–
Q4(≥94.8)	592	86 (14.5)	1.47 (1.12, 1.93)	0.006	1.36 (1.01, 1.83)	0.045

* Adjusted for age, sex, study center, study treatment group, body mass index (BMI), *MTHFR* C677 T genotype, smoking, alcohol drinking, family history of diabetes, systolic blood pressure (SBP), fasting glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, creatinine, and folate at baseline, as well as time-averaged SBP during the treatment period.

4. Discussion

This study demonstrates that among a Chinese hypertensive population, those in the top quartile of plasma selenium levels (≥94.8 μg/L) had elevated baseline fasting plasma glucose, and had an increased risk of new-onset diabetes during the 4.5 years of follow-up, compared to those in the lower quartiles.

The following factors need to be considered in order to interpret and compare our findings with previous studies in an appropriate context.

4.1. First, the study design and population selenium levels should be considered

Cross-sectional and case-control studies [16,17] are more likely subject to confounding and cannot demonstrate a temporal relationship and causality. Diabetes is usually a secondary outcome in previous randomized trials. In the NPC [3] trial, oral administration of 1312 U.S. participants (mean baseline plasma selenium: 114.4 μg/L) with 200 μg/d selenium, increased the risk of type-2 diabetes by 55% (HR, 1.55; 95%CI: 1.03, 2.33). In the Selenium and Vitamin E Cancer Prevention Trial (SELECT) [18], supplementation of 200 μg/d selenium as selenomethionine increased the risk of type-2 diabetes by 7% (RR, 1.07; 99%CI: 0.94, 1.22) among 35,533 American men (median baseline serum selenium: 137.6 μg/L). In the Selenium and Celecoxib (Sel/Cel) Trial (median baseline serum selenium: 135 μg/L) [19], the hazard ratio for new-onset type-2 diabetes was 1.25 (95%CI: 0.74, 2.11) after the supplementation of 200 μg selenium daily. Of note, most studies above had a mean baseline selenium that was much higher than our study (mean plasma selenium level: 84.8 μg/L (SD, 21.1), 23.3% with selenium deficiency or insufficiency (< 20–70 μg/L)). The top quartile in our study (≥94.8 μg/L) would fall within the lower end of previous studies. On the other hand, a recent nested case control study [7] reported that compared with those in quartile 1 of plasma selenium (< 54.10 μg/L), an increased risk of diabetes was found in participants in the third quartile (61.71–72.16 μg/L; OR, 1.45; 95% CI: 1.09, 1.93), but not in the fourth quartile (72.16 μg/L; OR, 1.27; 95% CI:0.93, 1.74). However, about 70% of these participants had selenium deficiency or insufficiency (< 20–70 μg/L) and these results could not be generalized to the general population. As such, our study had an opportunity to assess the dose-response relationship between plasma selenium and new-onset diabetes at a relatively lower, but normal range (about 76.7% with a selenium level ≥70 μg/L).

4.2. Second, the sources of bio-sample for measuring selenium varied by studies

The sources of selenium need to be considered. Some studies [20–22] evaluated the relationship of toenail selenium with diabetes and had inconsistent results. It has been reported that selenium incorporation into toenails is mostly nonspecific and therefore toenail selenium levels may just be a mere bystander [1]. The randomized trials of relatively high selenium supplementation do not reflect the effects of dietary selenium intake from foods in general populations. The selenium content of foods varies by geographic regions, presenting a challenge for having a reliable estimate of Se intake. In contrast, plasma or serum selenium is considered to be a reliable biomarker for selenium status [23].

4.3. Third, the study endpoints need to be considered

A previous systematic review and meta-analysis [24] including 5 randomized controlled trials showed that selenium supplementation may result in an improvement in insulin levels and the quantitative insulin sensitivity check index (QUICKI), but had no beneficial eff ;ects on the homeostasis model assessment of insulin resistance (HOMA-IR). A recent systematic review by Retondario A et al. found that selenium

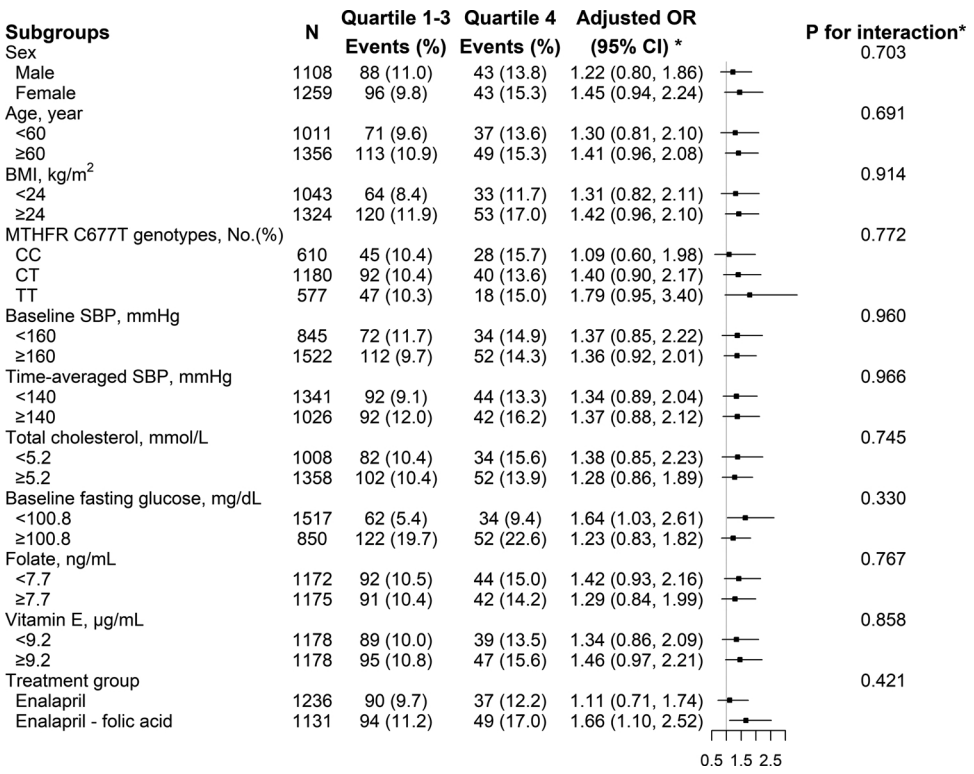

Fig. 2. Forest plots of the association between baseline plasma selenium categories (quartile 4 *vs.* 1–3) and new-onset diabetes in various subgroups*.
*Adjusted for age, sex, study center, study treatment group, body mass index (BMI), MTHFR C677 T genotype, smoking, alcohol drinking, family history of diabetes, systolic blood pressure (SBP), fasting glucose (FG), total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, creatinine, and folate at baseline, as well as time-averaged SBP during the follow-up period, if not stratified.

intake and metabolic syndrome are not clearly associated in adults and the elderly [25]. The Epidemiology of Vascular Ageing (EVA) study [26] (n = 1389, median baseline plasma selenium: 85.5 μg/L) showed an inverse association between plasma selenium and new-onset dysglycemia in men (tertile 3 *vs.* tertile 1; HR, 0.50; 95%CI: 0.24, 1.04) among an elderly French cohort. In an 8-year follow-up analysis of 445 adult males (mean baseline serum selenium: 77.5 μg/L) [27], baseline selenium status was not prospectively associated with incident diabetes; however, the incidence of diabetes was only 1.4%, thus constraining the statistical power of the analysis. Gao et al. [5] suggested that participants in the high selenium tertile had a higher trend of diabetes risk (OR, 1.25; 95%CI: 0.68, 2.27) compared with those in the low selenium tertile among a longitudinal cohort of 1925 Swedish men (mean baseline serum selenium: 75.6 μg/L). Consistently, in a Spanish cohort of 1234 non-diabetic participants (mean baseline plasma selenium: 84.2 μg/L) [6], the hazard ratio (95% CI) for incident diabetes comparing the third to the first tertile of plasma selenium levels was 1.80 (0.98, 3.31). These results suggest that although a consistent, positive selenium-diabetes association was found in previous studies, different definitions of study endpoints may possibly affect the results.

Moreover, our current study was the first of its kind to be conducted in hypertensive patients. In fact, a previous cross-sectional analysis has shown that elevated serum selenium was related to higher blood pressure levels and a higher prevalence of hypertension [28]. One possible mechanism for this is that some selenium compounds could be acting as a pro-oxidant, and the resultant reactive oxygen species (ROS) may lead to the development of hypertension [29]. Consistently, Kikuchi et al. reported that Selenoprotein P (SelP) increased the development of pulmonary hypertension [30]. Considering this, we have included both baseline SBP and time-averaged SBP during the treatment period into our regression models. Furthermore, we have conducted stratified analyses by baseline SBP (< 160 *vs.* ≥160 mmHg) and time-averaged SBP during the treatment period (< 140 *vs.* ≥140 mmHg) subgroups. However, our current study indicated that a higher risk of new-onset diabetes was found in different blood pressure subgroups. It should be noted that we did not have enough power to examine this possible interaction effect. As such, future studies are needed to further investigate the potential modifying effect of hypertension on the selenium-diabetes relation.

While biological mechanisms underlying our observed selenium-new onset diabetes association remain to be determined, our findings are biologically plausible. SelP and glutathione peroxidase 3 (GPx3) are two major selenoproteins in plasma, accounting for about 60% and 20%, respectively, of plasma selenium [31]. GPx3 has previously been implicated in the protection of pancreatic β-cells from oxidative stress [32], and increased GPx3 expression has been shown to prevent oxidative stress-induced insulin resistance [33]. However, a previous study found that treatment with physiological doses of SelP may decrease the production and secretion of insulin in normal mice [34]. Furthermore, the elevation of circulating SelP was positively connected with future onset of glucose intolerance [35]. In previous studies, the appropriate plasma selenium concentration to maximize the activity of GPx3 and SelP was found to be around 90–100 μg/L [36] and 110–125 μg/L [37], respectively. Therefore, we speculate that a high plasma selenium concentration of beyond about 95 μg/L, at which GPx3 may have been optimized in our current study, may induce major detrimental effects on glucose metabolism. Additionally, it has been shown that glutathione peroxidase 1 (GPX1) overexpression may contribute to the development of insulin resistance or obesity in selenium-adequate diet mice [38], which results suggest that GPX1 may also be implicated in the etiology of diabetes following selenium overexposure. GPX1 might be induced by increased circulating levels of SelP [35]. Finally, selenium may be involved in generating oxidative stress, *via* evidence of increased production of ROS under conditions of high concentrations of selenite, which may adversely affect pancreatic β cells [39]. Additional future studies are needed to verify these results and further examine the underlying mechanisms.

There are some limitations to our study. First, our current study was conducted in hypertensive patients, thus the generalizability of the results to adults without hypertension remains to be examined. Second, our study is a post hoc analyses of the CSPPT. While a broad set of covariates has been included in the regression models, residual confounding effects from unmeasured or incompletely measured factors cannot be excluded. Further confirmation of our findings in an

independent study is necessary. Third, we did not measure glycosylated hemoglobin A1c or perform glucose tolerance tests. However, our definition of diabetes was similar to that of previous randomized trials [3,18] or observational studies [40]. In addition, a glucose tolerance test is difficult to perform in practice, particularly in rural China. Fourth, it should be noted that with the current study's existing sample size, the power for detecting an interaction effect may have been limited. Therefore, a negative finding does not necessarily confirm an absence of interaction. For instance, Fig. 2 clearly suggests a possible enhanced effect of selenium exposure in females. Consistently, Vinceti M et al. [4] found that selenium supplementation increased diabetes risk by 11% (RR, 1.11; 95% CI: 1.01, 1.22) compared with a placebo-allocated group, with a higher RR in women than in men. However, the role of sex as a potential effect modifier is still uncertain. Another limitation of the CSPPT is the lack of classification of subtypes of diabetes. However, as the current study's population was between 45–75 years of age, we speculate that most, if not all of the patients who developed diabetes, have type 2 diabetes. Overall, our findings were just hypothesis-generating. All reported results should be further investigated and confirmed in future studies.

In conclusion, our analyses of the CSPPT data indicate that high plasma selenium ($\geq$94.8 μg/L) was associated with increased risk of new-onset diabetes in hypertensive patients. In light of the wide variation of selenium content in foods and soils, and the presence of selenium in many dietary supplements, our findings lend further support that excessive selenium intake may be harmful and if further confirmed, would offer a novel strategy to modulate diabetes risk by optimizing individual blood selenium levels.

Authors' contributions

Yuanyuan Zhang, Xiping Xu, Xianhui Qin and Hao Zhang designed the research; Yuanyuan Zhang, Xianhui Qin, Chongfei Jiang and Chengzhang Liu analyzed the data; Yuanyuan Zhang and Xiaobin Wang wrote the paper. All authors contributed to data collection and reviewed/edited the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jtemb.2019.07.003.

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