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Dietary Vitamin E Intake and Risk of Prostate Cancer: A Cross-Sectional Study and a Mendelian Randomization Analysis

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Keywords: Vitamin E; Prostate cancer risk; NHANES; Mendelian randomization.

Abbreviations: NHANES: National Health and Nutrition Examination Survey; MR: Mendelian Randomization; PSA: Prostate-Specific Antigen; PCA: Prostate Cancer; BMI: Body Mass Index; NHW: Non - Hispanic White; NHB: Non-Hispanic Black.

Abstract

Background: Vitamin E is a group of antioxidant to copherols and to cotrienols that have been shown to have a potential role in chemoprophylaxis. However, whether vitamin E can reduce the risk of prostate cancer remains controversial.

Objective: To assess the causal relationship between vitamin E intake and prostate cancer risk.

Methods: Firstly, we conducted an observational study using data from National Health and Nutrition Examination Survey (NHANES) 2003-2010. Weighted multiple linear regression was applied and a model adjusted for three different covariates. Subgroups were further stratified by age, race, and BMI. Secondly, a two-sample Mendelian Randomization (MR) analysis based on publicly available genome-wide association studies was employed to infer the causal relationship. The effect estimates were calculated using the random-effects inverse-variance-weighted method.

Results: We found no significant association between vitamin E intake and prostate cancer. MR analyses with primary genetic instruments also did not support a causal association between vitamin E intake and prostate cancer risk (IVW: OR 1.001, 95% CI 0.998-1.005).

Conclusions: Therefore, our study did not support a causal association between coffee intake and prostate cancer risk. Factors such as age, race and BMI should be considered in the design of PCa preventive nutrition regimens. Further studies with a larger sample size are needed to examine if an association exists by different age, races and BMI.

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Introduction

Prostate Cancer (PCa) is the second most common type of cancer and the fifth most common cause of cancer-related death in men worldwide [1]. Globally, an estimated 1,414,259 new cases were confirmed in 2020 [2]. However, compared with other common cancers, the etiology of prostate cancer remains understudied [3]. Various environmental factors such as diet, obesity, smoking, and exercise may be associated with PCa. Vitamin E is a set of antioxidant fat-soluble micronutrients, including alpha, gamma, delta, beta birth triene phenol and alpha, gamma, delta and beta to copherol. Vegetable oils contain high amounts of vitamin E [4,5]. Particularly soy, sunflower, corn, walnut, cottonseed, palm, and wheat germ oils. Vitamin E has been identified as a potential chemoprophylaxis agent owing to its strong antioxidant, anti-inflammatory, and antithrombotic effects [6]. Studies have shown that both to copherol and tocotrienol are effective in inhibiting the growth of prostate cancer cells [7]. A meta-analysis of RCTS using interventions containing vitamin E linked vitamin E to a significant protective effect against prostate cancer risk [8]. However, several epidemiological studies have reported no association between vitamin E supplementation and prostate cancer risk [9]. In addition, a large intervention study [(Selenium and vitamin E Cancer Prevention Trial (SELECT)] found no effect of selenium + vitamin E supplementation on reducing the risk of PCa. Surprisingly, vitamin E supplementation alone was associated with an increased risk of PCa (OR 1.17, 95%CI 1.004-1.36) [10]. Still, the major limitations of these studies were that they were restricted to a particular cohort, and their results might not be representative enough. Moreover, conventional observational studies were susceptible to biases like reverse causation and residual confounding [11].

Currently, the Mendelian Randomization (MR) analysis has been widely applied to assess the potential causal relationships between various exposures and clinical outcomes. Compared with traditional observational studies, the MR analysis can overcome reverse causation bias, since allelic randomization always precedes the onset of disease. Moreover, random segregation and the independent assortment of genetic polymorphisms at conception enables the MR analysis to minimize the effect of confounding factors by introducing genetic markers as Instrumental Variables (IVs) of exposures [12,13]. The availability of Large-Scale Genome-Wide Association Studies (GWASs) further enables the exploration of causality. Therefore, by applying an MR analysis, we are determined to answer the question: is vitamin E intake negatively, neutrally, or positively associated with risk of prostate cancer?

Materials and Methods

Data source in NHANES

Since 1960, the National Centers for Disease Control and Prevention (CDC) National Center for Health Statistics has conducted a National Health and Nutrition Examination Survey (NHANES) every two years to provide national estimates of the health and nutritional status of non-institutional populations in the United States. Data from the official website of NHANES (https://wwwn.cdc.gov/nchs/nhanes/Default.aspx) is available for free download. The National Center for Health Statistics Research Ethics Review Board reviewed and approved the NHANES protocol (NCHS Ethics Review Board (ERB) Approval: NHANES 1999-2004: Protocol # 98-12, NHANES 2005-2010: Protocol #2005-06). All the participants provided written informed consent. More detailed information about the NHANES data can be found on the official website.

Study population in NHANES

The NHANES database only has PSA data for 2003-2010, therefore we integrated data from four two-year NHANES survey cycles 2003-2004, 2005-2006, 2007-2008 and 2009-2010, and performed secondary data analysis. We restricted the population included in the analysis to men aged above 55 years old and did not have a history of prostate tumor. They provided blood samples for PSA assessment as part of NHANES. The participants were screened according to the following exclusion criteria: men with prostate cancer, prostatitis, or recent prostate surgery (a rectal exam with in 1 week and a prostate biopsy within 1 month, surgery, or cystoscopy) were not included in the study. After a series of screenings, 2965 of 41,157 participants were included in the study. A detailed flowchart of the process is shown in **Figure 1.**

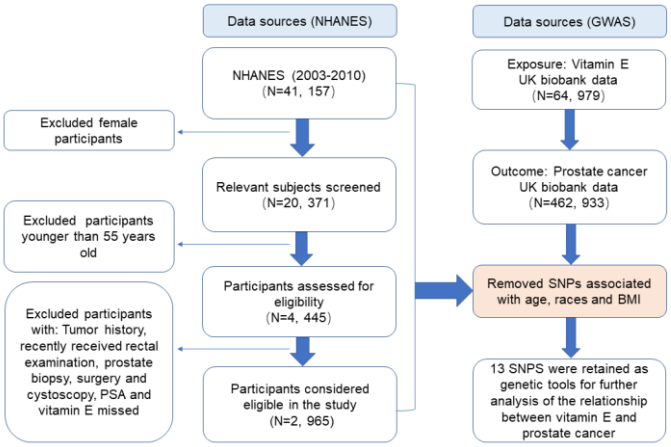

Figure 1: Flow chart of procedures from identification of eligible patients to final inclusion in NHANES 2003-2010 and suitable genetic tools used to analyze the relationship between vitamin E and prostate cancer.

Variables in NHANES

The targeted independent variable was the dietary vitamin E intake (mg). The US Department of Agriculture (USDA) Automatic Multiple Pass Method (AMPM) was used to collect dietary intake data by interviewers 24 h a day. The targeted dependent variable was the PCa risk. The risk of PCa in terms of PSA levels was the primary outcome of interest in this study. We used a combination of total PSA levels and the ratio of free PSA levels to determine the risk of PCa. Specifically, a high risk of PCa was defined as total PSA ≥10.0 (ng/ml)or when total PSA≥4.0 (ng/ml)and the ratio of free PSA was ≤25%; low risk of PCa was defined as total PSA<4.0 (ng/ml) or total PSA≥4.0 (ng/ml) and the ratio of free PSA>25% [14]. Covariates included age (years), race, living status, education level, Poverty Income Ratio (PIR), body mass index (Kg/m^2) and smoking status. The demographic information for the participants included age (55-70, ≥70), race (Non-Hispanic White, Non-Hispanic Black, Mexican American and other Hispanic and Other races), and education (less than high school, high school, and high school and above). Family PIR was defined by three consecutive levels (≤1.99, 2-2.99, and ≥3) after adjusting for state-dependent gross income vs. the total capital per house hold across the nation. Living status was defined as living alone or with partners. Based on the martial status options, a participant who selected “married” or “living with a partner” was defined as living with a partner; a

participant who selected "widowed," "divorced," "separated," or "never married" were defined as living alone [15]. BMI was classified as under/normal weight (BMI < 24), overweight (24 ≤ BMI < 27) and obese (BMI ≥ 27). Smoking status was classified as non-smoker or smoker.

Study design of mendelian randomization

The schematic view of the study design, and the three key assumptions of MR are as follows: (A) Single Nucleotide Polymorphisms (SNPs) are strongly associated with vitamin E intake; (B) SNPs are independent of known confounders; (C) SNPs only affect prostate cancer via vitamin E intake (**Figure 2**).

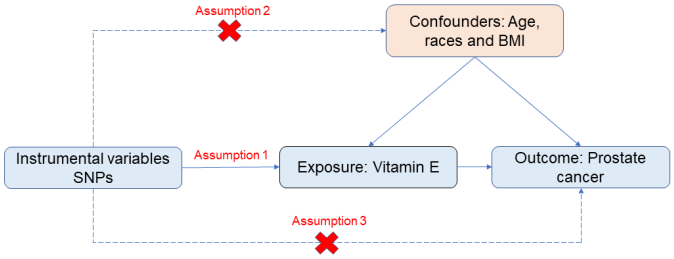

Figure 2: Flow chart for the two-sample Mendelian randomization analysis. SNPs: Single Nucleotide Polymorphisms; BMI: Body Mass Index.

Data sources of mendelian randomization

The analysis was conducted using published summary-level data from GWASs of the traits of interest in predominantly European individuals. GWAS summary statistics for vitamin E intake (n = 64,979, Dataset: ukb-b-6888) were obtained from the UK biobank study, which assessed the relationship between the quantity of vitamin E intake and SNPs. Prostate cancer (n = 462,933, Dataset: ukb-b-13348) was also obtained from UK biobank study. Ethics approval was not required for the current analysis as all included GWAS data are publicly available and had been approved by the corresponding ethical review boards (**Figure 1**).

Selection and validation of SNPs

Three criteria were applied to select suitable SNPs. First, we selected SNPs associated with vitamin E intake at the genome-wide significance threshold with $p < 1\times10^{-5}$. Second, the independence among the selected SNPs was evaluated according to the pair wise-linkage disequilibrium [16]. When $r^2 > 0.001$ (clumping window of 10,000 kb), the SNP correlated with more SNPs or with a higher p-value was deleted. Third, the F-statistic was calculated to validate the strength of individual SNPs. When F-statistics were greater than ten, SNPs were considered powerful enough to mitigate the influence of potential bias. Before performing the MR analysis, we also conducted data-harmonization steps, as the effects of an SNP on the exposure and the outcome had to correspond to the same allele (**Figure 1**).

Statistical analysis

The NHANES data was analyzed using the statistical packages R (http://www.r-project.org, The R Foundation) and Empower Stats (http://www.empower-stats.com, X&Y Solutions, Inc., Boston, MA, USA).The complex sampling design and weights were adapted to our statistical analyses, which were recommended by NHANES, and $p \leq 0.05$ was considered statistically significant. Dietary vitamin E intake was divided into four groups according to quartile levels. Participants' demographic, behavioral, and clinical features were summarized using descriptive statistics, stratified by the risk of PCa. The associations of these demographics with the risk of PCa were validated using the Rao-Scott Chi-square test for categorical variables and Fisher's exact test for small samples. One-Way Analysis Of Variance (ANOVA) was used to examine differences in continuous variables. We then constructed three multivariable linear regression models: Model 1 adjusted for no variable, which represented our crude model; Model 2 adjusted for age, race, and BMI; and Model 3 adjusted for all the covariates presented in **Table 1**. A subgroup analysis was performed. We then used the GAM model and smooth curve fitting to explore the association between dietary vitamin E intake and PCa risk.

As for MR analysis, an Inverse-Variance Weighted (IVW) meta-analysis under a random-effects model was regarded as the primary analysis. The following two methods, including weighted median and MR-Egger, were performed as sensitivity analyses. The weighted-median method can provide valid estimates if more than 50% of information comes from valid IVs [17]. The MR-Egger method can be used to assess the horizontal pleiotropy of selected IVs [18]. Cochrane's Q-value can indicate heterogeneity among selected IVs. Additionally, a leave-one-out sensitivity analysis was conducted to determine whether the overall estimates were disproportionately affected by an individual SNP. All statistical analyses were performed using the "Two Sample MR" packages in R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics of participants in NHANES

A total of 2965 cancer-free male adults aged > 55 years were included in NHANES 2003-2010. **Table 1** provides the weighted percentage and raw sample sizes for demographics and vitamin E intake according to the risk of high and low PCa risk. For the overall study population, people in the low PCa risk group consumed more vitamin E than people in the high PCa risk groups (7.00 ± 4.83 mg vs 6.66 ± 4.51 mg), but the association between vitamin E intake and PCa risk was not significant (p=0.160), the four quartile levels of vitamin E were not distributed differently among the two risk groups (p=0.169). The average age in the low PCa risk group was younger than that in the high PCa risk group (67.45 ± 8.27 vs 70.48 ± 8.07, p<0.001). The total PSA level and free PSA ratios were 1.54 ± 1.32 ng/ml, 31.43 ± 12.23% in the low PCa risk group and 9.68± 9.96 ng/ml, 16.63 ± 6.20% in the high PCa risk group, respectively. Although living conditions were not distributed differently among the two risk groups (p=0.066), the living alone group had more people with high PCa risk than the living with partners group (12.4 vs 10.1%). Age is strongly associated with the risk of PCa. The percentage of high PCa risk increased from the 55-70 group to the 75- group (8.4-14.2%, p<0.001). The NHB population had more people with a higher PCa risk (14.0%) than other races (p=0.027). Families with a high income (PIR ≥ 3) had the lowest PCa risk (10.0%, p=0.823). Interestingly, the obese population had a lower percentage of high-risk PCa individuals (9.5%, p=0.008).

Table 1: Characteristics of 2965 male adults with different PCa risk.

Characteristic	Overall	Low PCa Risk	High PCa Risk	P-value
Total, n (%)	2965	2647	318	
Mean total PSA ± SEM (ng/mL)	2.42±4.30	1.54 ± 1.32	9.68± 9.96	<0.001[a]
Mean free PSA ratio ± SEM (%)	29.84±12.60	31.43 ± 12.23	16.63 ± 6.20	<0.001[a]
Mean vitamin E Intake ± SEM (mg)	6.98±4.80	7.00 ± 4.83	6.66 ± 4.51	0.160[a]
Mean age ± SEM (year)	69.78 ± 8.30	67.45 ± 8.27	70.48 ± 8.07	<0.001[a]
Vitamin E intake, n (%)				0.169[b]
Q1	739 (24.9%)	644 (87.1%)	95 (12.9%)	
Q2	741 (25.0%)	671 (90.6%)	70 (9.4%)	
Q3	740 (25.0%)	664 (89.7%)	76 (10.3%)	
Q4	745 (25.1%)	668 (89.7%)	77 (10.3%)	
Age, n (%)				<0.001[b]
55-70	1772 (59.96%)	1624 (91.6%)	148 (8.4%)	
≥70	1193 (40.24%)	1023 (85.8%)	170 (14.2%)	
Race, n (%)				0.027[c]
Non-Hispanic White	1596 (53.83%)	1439 (90.2%)	157 (9.8%)	
Non-Hispanic Black	559 (18.85%)	481 (86.0%)	78 (14.0%)	
Mexican and other Hispanic	709 (23.91%)	640 (90.3%)	69 (9.7%)	
Other or multiracial	101 (3.41%)	87 (86.1%)	14 (13.9%)	
BMI, n (%)				0.008[c]
Under/normal weight	514 (17.3%)	439 (85.4%)	75 (14.6%)	
Overweight	652 (22.0%)	582 (89.3%)	70 (10.7%)	
Obese	1745 (58.9%)	1580 (90.5%)	165 (9.5%)	
Missing	54 (1.8%)	46 (85.2%)	8 (14.8%)	
Living status, n (%)				0.066[c]
Alone	804 (27.12%)	704 (87.6%)	100 (12.4%)	
With partners	2161 (72.88%)	1943 (89.9%)	218 (10.1%)	
Education level, n (%)				0.629[c]
Less than high school	1056 (35.62%)	936 (88.6%)	120 (11.4%)	
High school	655 (22.09%)	584 (89.2%)	71 (10.8%)	
More than high school	1254 (42.29%)	1127 (89.9%)	127 (10.1%)	
PIR, n (%)				0.823[b]
1.99	1193 (40.24%)	1061 (88.9%)	132 (11.1%)	
2–2.99	489 (16.49%)	434 (88.8%)	55 (11.2%)	
3	1069 (36.05%)	962 (90.0%)	107 (10.0%)	
Missing	214 (7.22%)	190 (88.8%)	24 (11.2%)	
Smoking Status, n (%)				0.246[b]
Non-smoker	1441 (48.60%)	1298 (90.1%)	143 (9.9%)	
Smoker	527 (17.77%)	472 (89.6%)	55 (10.4%)	
Missing	997 (33.63%)	877 (88.0%)	120 (12.0%)	

One-way ANOVA[a] test found total PSA, free PSA ratio and age are distributed differently between low and high PCa risk groups. The categorical analysis found BMI (Rao-Scott Chi-square[c] test), age (Fisher's exact[b] test) have statistically different distribution between low and high PCa risk groups. SEM: Standard Error of The Mean; NHANES: National Health and Nutrition Examination Survey; PCa: Prostate Cancer; BMI: Body Mass Index; PIR: Poverty Income Ratio.

Dietary vitamin E intake and pca risk in NHANES

The magnitude of the correlation between dietary vitamin E intake and PCa risk is presented in **Table 2**. In the fully adjusted mode, after adjusting for age (year), race, PIR, BMI (Kg/m^2), living status, educational level, and smoking, the association between dietary vitamin E intake and PCa risk was still not significant (P for trend=0.748), even though the OR (0.913, 95% CI 0.652-1.279) increased with increased vitamin E. The association between PCa risk and vitamin E was assessed using a weighted generalized additive model and a smooth curve fitting.

Table 2: Association between vitamin E intake (mg) and PCa risk.

Exposure	Model 1 OR (95% CI) *P*-value	Model 2 OR (95% CI) *P*-value	Model 3 OR (95% CI) *P*-value
Quartiles of vitamin E intake (0-55.8 mg)			
Q1 (0-13.9 mg)	Referent	Referent	Referent
Q2 (14.0-27.9 mg)	0.707 (0.510, 0.981) 0.03789	0.772 (0.553, 1.076) 0.12702	0.774 (0.553, 1.083) 0.13487
Q3 (28.0-41.8 mg)	0.776 (0.563, 1.069) 0.12076	0.876 (0.632, 1.216) 0.42983	0.876 (0.629, 1.220) 0.43348
Q4 (41.9-55.8 mg)	0.781 (0.568, 1.075) 0.13016	0.913 (0.657, 1.269) 0.58867	0.913 (0.652, 1.279) 0.59535
P for trend	0.186	0.735	0.748
Stratified by age			
<70	1.002 (0.969, 1.035) 0.91007	1.006 (0.973, 1.039) 0.73392	1.004 (0.970, 1.038) 0.83343
≥70	0.971 (0.931, 1.011) 0.15567	0.976 (0.936, 1.017) 0.23954	0.979 (0.939, 1.021) 0.32429
Stratified by race			
Non-Hispanic White	0.988 (0.954, 1.024) 0.50156	1.000 (0.965, 1.036) 0.99629	0.998 (0.962, 1.035) 0.91315
Non-Hispanic Black	0.986 (0.934, 1.041) 0.60448	1.007 (0.953, 1.063) 0.81072	1.014 (0.959, 1.072) 0.62102
Mexican and other Hispanic	0.973 (0.915, 1.036) 0.39366	0.976 (0.917, 1.038) 0.43867	0.981 (0.921, 1.044) 0.53693
Other or multiracial	1.000 (0.877, 1.139) 0.99434	1.001 (0.874, 1.146) 0.98921	0.992 (0.857, 1.148) 0.90957
Stratified by BMI			
Under/normal weight	0.984 (0.933, 1.038) 0.55177	0.994 (0.942, 1.049) 0.83067	0.984 (0.930, 1.040) 0.55910
Overweight	1.003 (0.950, 1.059) 0.91130	1.012 (0.955, 1.073) 0.68865	1.015 (0.957, 1.077) 0.61935
Obese	0.980 (0.946, 1.016) 0.28039	0.993 (0.958, 1.028) 0.68813	0.992 (0.957, 1.028) 0.66439
Missing	0.960 (0.788, 1.170) 0.68531	0.950 (0.777, 1.161) 0.61620	0.928 (0.665, 1.295) 0.66056

Model 1: No covariates were adjusted.
Model 2: Age, race and BMI were adjusted.
Model 3: Age, race, BMI, living status, education level, PIR, and smoking status were adjusted.
*In the subgroup analysis stratified by age, race and BMI, the model is not adjusted for the stratification variable itself.

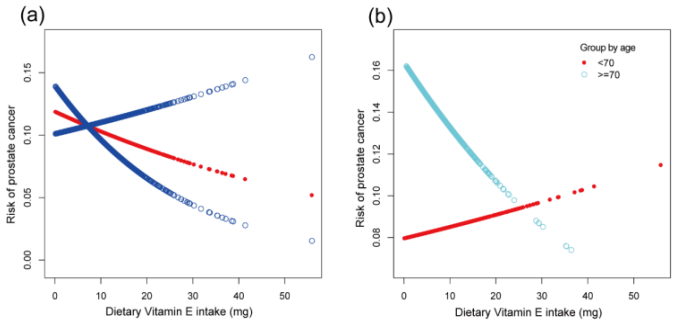

Figure 3: The association between dietary vitamin E intake and PCa risk by curve fittings in NHANES 2003-2010. (a) Solid radline represents the smooth curve fit between variables. Blue bands represent the 95% of confidence interval from the fit. Age, race, BMI, education, family PIR, living status, and smoking status were adjusted. (b) The association between dietary vitamin E intake and PCa risk, stratified by age =70 years.

To further investigate the link between vitamin E and PCa risk, we stratified the entire study population into subgroups by age, race, and BMI. We found that the OR for the subgroup of age between 55-70 was (1.004, 95%CI 0.970-1.038) in **model 3**, while the OR for the subgroup aged ≥ 70 was (0.979, 95%CI 0.939-1.021) in **model 3.** The associations between PCa risk and vitamin E stratified by age were assessed using a weighted generalized additive model and a smooth curve fitting (**Figure 3**). Similarly, the ORs for the subgroups of NHB were (1.014, 95% CI 0.959-1.072) in model 3, but the ORs for the subgroups of NHW, Mexican, and other Hispanic and other races were (0.998, 95% CI 0.962-1.035), (0.981, 95% CI 0.921-1.044) and (0.992, 95% CI 0.857-1.148) in model 3. The OR for the obese was (0.992, 95% CI 0.957-1.028) in model 3, while the OR for the under/normal weight and overweight subgroups were (0.984, 95% CI 0.930-1.040) and (1.015, 95% CI 0.957-1.077) in model 3.

Table 3: Associations between genetically predicted vitamin E and PCa in sensitivity analysis.

MR methods	OR (95% CI)	P value	Pleiotropy		Heterogeneity	
			Intercept	*p*	Q	*p*
MR Egger	0.995 (0.962,1.028)	0.758	0.0002	0.70	11	0.38
IVW	1.001 (0.998,1.005)	0.504	-	-	12	0.45
Simple mode	1.005 (0.997,1.013)	0.276	-	-	-	-
Weighted mode	1.005 (0.997,1.013)	0.260	-	-	-	-
Weighted median	1.003 (0.998,1.008)	0.314	-	-	-	-

MR analysis

The included studies were published in 2018 and were mainly based on the European population. Thirteen IVs achieved genome-wide significance levels, and all F-statistics were greater than ten. The IVW analysis revealed that, pooled OR for 1% Vitamin E intake change per allele was 1.001 (95% CI 0.998–1.005). No evidence of directional pleiotropy and heterogeneity was detected, and the Ors of MR-Egger, weighted median, simple mode and weighted mode methods were shown in **Table 3**. The forest plot of associations between vitamin E and prostate cancer of all thirteen IVs were shown in **Figure 4(a).** The scatter plot of these results was presented in **Figure 4(b).** The leave-one-out sensitivity analysis, as shown in **Figure 5(a),** revealed that the overall estimates were not disproportionately affected by any individual SNP. The funnel plot in **Figure 5(b)** indicated no evidence of horizontal pleiotropy.

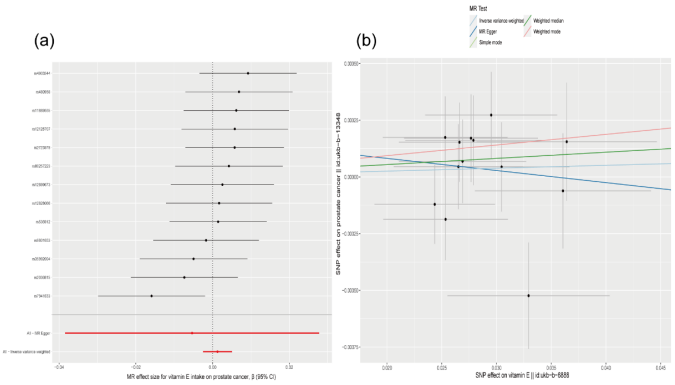

Figure 4: (a): Forest plot of the association of vitamin E intake with prostate cancer. **(b)** Scatter plot of the association of vitamin E intake with prostate cancer.

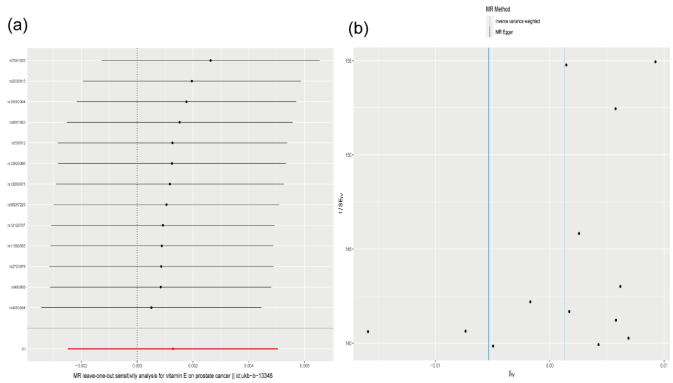

Figure 5: (a): Leave-one-out sensitivity analysis of the association of vitamin E intake with prostate cancer. **(b)** Funnel plot of the association of vitamin E intake with prostate cancer.

Discussion

This study investigated the association between daily dietary vitamin E intake and prostate cancer risk by using the NHANES dataset. Our study showed no statistically significant difference in vitamin E levels between high - and low-risk prostate cancer groups (7.00 ± 4.83 vs 6.66 ± 4.51 mg, p=0.160). Although the risk of prostate cancer was significantly higher in the group with the lowest vitamin E score than in the other three groups (12.9% vs 9.4%, 10.3%, and 10.3%), the difference was not statistically significant (p=0.169). This means that high dietary vitamin E intake may not explain the negative association reported in the literature between serum/plasma vitamin E (especially alpha-tocopherol) and prostate cancer risk. In addition to dietary intake, serum/plasma concentrations of alpha-tocopherol may be influenced by other factors, including age, race, genetics, obesity, endocrine disorders such as diabetes, supplement use, seasonality, ethnicity, and place of residence [19,20]. In our study, men aged ≥ 70 years and black adult men were at a significantly higher risk for prostate cancer. Interestingly, we found that as BMI increased, the proportion of prostate cancer risk decreased gradually, which may be related to increased BMI leading to lower PSA concentrations [21,22]. A recent systematic review and meta-analysis found that for every 5 kg/m^2 increase in BMI, PSA concentration decreased by 5.88% [23].

Weighted multiple linear regression analysis and curve fitting showed that dietary vitamin E intake slightly reduced the risk of prostate cancer, however, there was no statistical evidence of benefit. After adjusting for various covariates, there was no significant statistical correlation between vitamin E and prostate cancer risk, P for trend=0.186 (**Model 1**), 0.735 (**Model 2**), 0.748 (**Model 3**), and with the increase in vitamin E intake, its possible protective effect against prostate cancer decreased gradually, and in **Model 3**, OR=0.774 (Q2), 0.876 (Q3),0,913 (Q4).

Considering that this variation in the association of vitamin E with prostate cancer may be influenced by age, race and body mass index, we further investigated the association of vitamin E with prostate cancer in subgroups. The results showed that if the age of 70 years was the threshold, the risk of prostate cancer increased with increased vitamin E intake in men younger than 70 years, and vitamin E may be a risk factor for prostate cancer. In men aged ≥ 70 years, the greater the intake of vitamin E, the greater its protective effect. We believe that this difference may be due to the decreased absorption of vitamin E in men with age, as well as the closely related roles and mechanisms of vitamin E in men of different ages. Vitamin E absorption follows the same pathway as cholesterol and other fats, with rates ranging from 20% to 80% depending on the food substrate [24]. The ability of the intestinal cavity to absorb vitamin E changes with age, and the expression of some intestinal mucosal receptors, such as scavenger receptor Type BI (SR-BI), significantly affects vitamin E uptake. It is still being investigated whether the expression of these intestinal mucosal receptors differs in different age groups [25]. The relationship between human diet, gut microbiome, and physical and mental health has become a hot topic [26]. Recent studies have demonstrated the effect of different intakes of vitamin E (mainly α-tocopherol isomers) on the gut microbiome of mice [27]. The increased risk of prostate cancer may be related to vitamin E metabolism altering gut microbes, and this cancer-promoting effect may outweigh its antioxidant and anti-inflammatory anticancer effects. In our study, men over the age of 70 may maintained their vitamin E levels to play an anticancer role because their ability to absorb vitamin E decreased. In racial subgroups, we found that vitamin E had a weak protective effect on prostate cancer risk in Caucasians and Hispanics, while the opposite was true in blacks, and this difference may be related to genetic differences among different racial groups. Several studies in European populations have observed a significant negative association between vitamin E supplementation and prostate cancer risk [28]. In addition, in the BMI subgroup, vitamin E intake was associated with an increased risk of prostate cancer in overweight men, but had the opposite protective effect in normal and obese men. We hypothesized that vitamin E would have been a risk factor as body mass index increased, but obese people were an exception. The deficiency or underutilization of vitamin E may be due to the characteristics of endocrine or metabolic capacity of obese individuals. Therefore, higher intake of vitamin E may play a role in preventing the risk of prostate cancer in obese men.

Still, the major concern with existing conventional observational studies is bias caused by unmeasured or uncontrolled confounding. Previously, many findings from observational studies have been doubted. For example, higher circulating vitamin D used to be correlated with a higher prostate cancer risk according to conventional observational studies (OR 1.15, 95% CI 1.06-1.24) [29]. However, in one latest MR, after analyzing genetic data from 79,148 cases and 61,106 controls, researchers pointed out that circulating vitamin D was not causally related to prostate cancer (OR 1.00, 95% CI 0.93-1.07) [30].To our knowledge, no Mendelian randomization study of association between vitamin E and prostate cancer has been reported. However, different from previous meta-analyses mainly based on observational studies, our results derived from the MR anal-

ysis may provide a more solid conclusion, as the MR analysis is not influenced by confounders or reverse causality. We used 13 vitamin E intake-associated SNPs in our analyses, and no evidence of directional pleiotropy was detected in our study, making our results more robust. The results of MR analysis in our study showed that there was no clear causal association between vitamin E and prostate cancer, which validates our previous conclusion from the NHANES database in terms of causality.

This study has some limitations. First, the actual effect of vitamin E intake on prostate cancer risk may be influenced by other nutrients, and more advanced analytical methods are needed to address this issue in further studies. Second, there are eight isoforms of vitamin E, and these subtypes vary in function and activity, as well as in bioavailability in humans [31]. Our data were not able to assess or compare the effects of different vitamin E sub types on prostate cancer risk. Finally, completely excluding the influence of potential directional pleiotropy is difficult in any MR study and the examined GWASs were primarily conducted in individuals of European ancestry, which might limit the generalization of our findings to other ethnicities.

Conclusion

Our study did not support a causal association between vitamin E intake and prostate cancer. Further studies with a larger sample size are needed to examine if an association exists by different age, races and BMI.

Declaration

Ethical approval and consent to participate: Ethical review and approval were waived for this study, since all the data from National Health and Nutrition Examination Survey and Mendelian randomization is publicly accessible. Informed consent was obtained from all subjects in the original genome-wide association studies and National Health and Nutrition Examination Survey.

Author contributions and consent for publication: Conceptualization, Zhilong Dong and Long Cheng; methodology, Long Cheng and Chengyu You; datacuration, Zeming Qiu; writing-original draft preparation, Long Cheng; writing-review and editing, Zhilong Dong. All authors have read and agreed to the published version of the manuscript.

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Availability of data and material: Data available in a publicly accessible repository that does not issue DOIs. Publicly available datasets were analyzed in this study. This data can be found here: [https://gwas.mrcieu.ac.uk/datasets/].

Conflict of interest statement: The authors declare no potential conflicts of interest.

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